INDONESIAN DANONE INSTITUTE FOUNDATION

ANNUAL REPORT 2020

LIST OF ATTACHMENTS

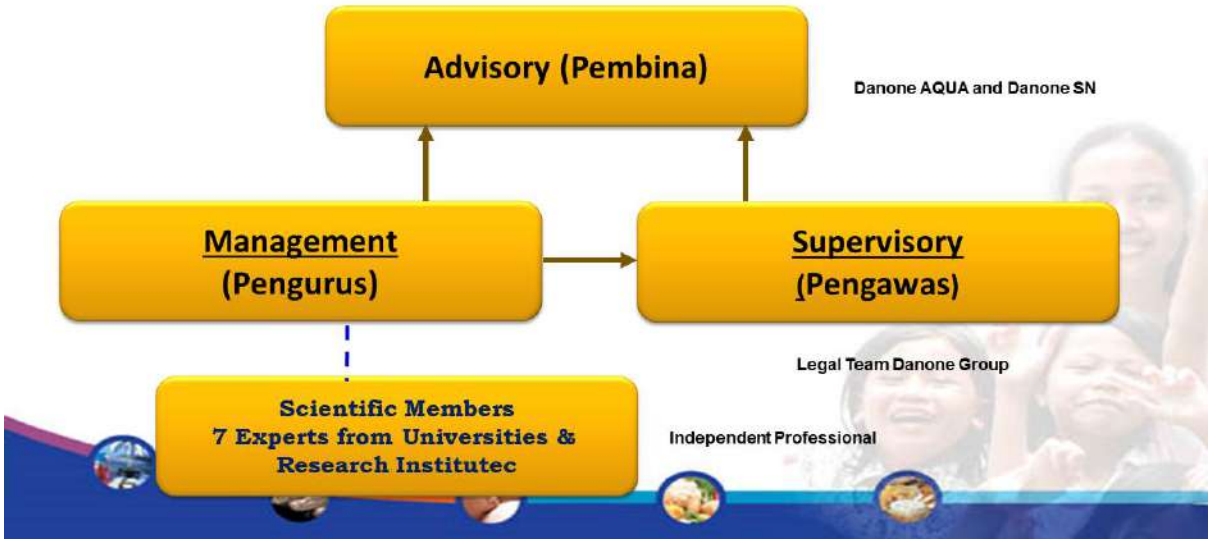
ATTACHMENT 1

Organizational Structures

- Organizational Structures 2020
- Deed of Appointment of Anindita Saraswati Dwiwinata as the General Representative
- Circular Decision of the Supervisor of the Indonesian Danone Institute Foundation

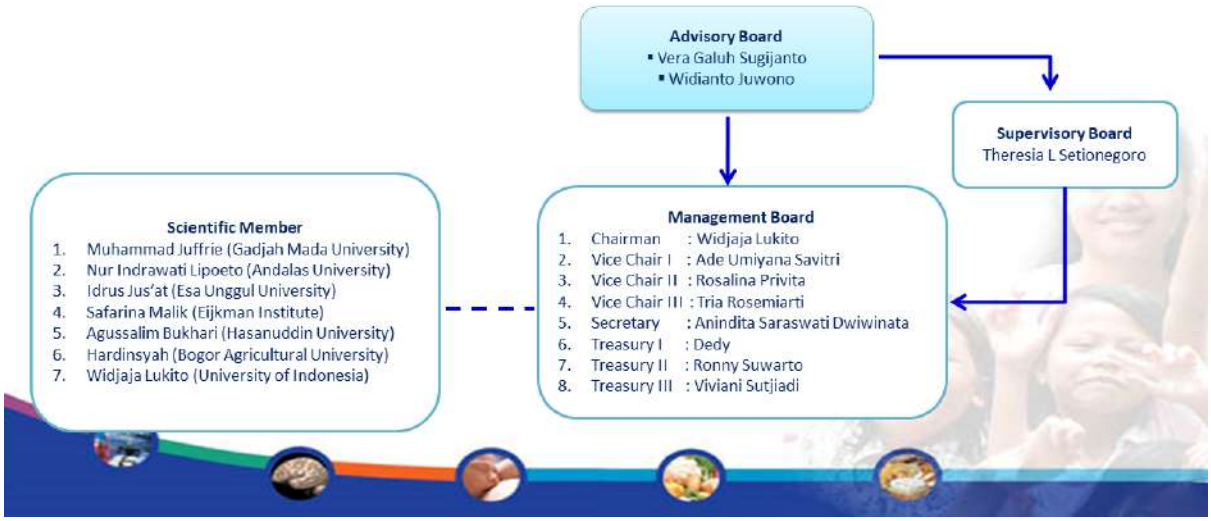
Yayasan INSTITUT DANONE Gizi untuk Anak Bangsa

Organizational Structure



Yayasan INSTITUT DANONE Gizi untuk Anak Bangsa

Organizational Structure : DANONE INSTITUTE INDONESIA 2020



KANTOR NOTARIS
Ny. BERTHA S. IHALAUW H., S.H.
Jl. Alaydrus No. 16 A
Telp. (021) 6349622 - 6343310
JAKARTA PUSAT

PERNYATAAN KEPUTUSAN PEMBINA

YAYASAN INSTITUT DANONE INDONESIA

dalam bahasa Inggris

INDONESIAN DANONE INSTITUTE FOUNDATION

Nomor : 01.-

-- Pada hari ini, hari Jum'at, tanggal 04-09-2020 ----
(empat September dua ribu dua puluh).----------
Pukul 11.00 W.I.B (sebelas Waktu Indonesia bagian ----
Barat).----------

-- Berada dihadapan saya, **Nyonya BERTHA SURIATI IHALAUW HALIM**, Sarjana Hukum, Notaris berkedudukan di Jakarta Pusat, dengan wilayah jabatan seluruh wilayah Propinsi Daerah Khusus Ibukota Jakarta, dengan dihadiri oleh -- saksi-saksi yang akan disebut pada akhir akta ini dan telah dikenal oleh saya, Notaris :----------

BERTHA SURIATI IHALAUW HALIM, SH
NOTARIS KOTA JAKARTA PUSAT

-- Nyonya **THERESIA LIANAWATY SETIONEGORO**, lahir di --- Jakarta pada tanggal 10-12-1958 (sepuluh Desember ---- seribu sembilan ratus lima puluh delapan), Warga Negara Indonesia, swasta, bertempat tinggal di Jakarta, Jalan Pulo Asem Utara Raya nomor 8, Rukun Tetangga 008, Rukun Warga 002, Kelurahan Jati, Kecamatan Pulo Gadung, ---- Jakarta Timur, pemegang Kartu Tanda Penduduk Republik Indonesia Nomor Induk Kependudukan 3175025012580018;--

-menurut keterangannya dalam hal ini bertindak ---- berdasarkan kuasa yang diberikan kepadanya oleh --- Pembina **"YAYASAN INSTITUT DANONE INDONESIA"** dalam - bahasa Inggris **INDONESIAN DANONE INSTITUTE** -------- **FOUNDATION**, berkedudukan dan berkantor pusat di --- Jakarta Selatan, Cyber 2 Tower lantai 16, Jalan --- H.R. Rasuna Said blok X-5 nomor 13, Jakarta 12950,-

yang anggaran dasarnya telah :----------

a. mendapat pengesahan dari Menteri Hukum dan Hak - Asasi Manusia Republik Indonesia dengan surat -- keputusannya tertanggal 10-10-2007 (sepuluh ---- Oktober dua ribu tujuh) nomor ---------- C-3394.HT.01.02.TH.2007 dan telah diumumkan dalam Berita Negara Republik Indonesia tertanggal ---- 29-04-2008 (dua puluh sembilan April dua ribu -- delapan) nomor 35 Tambahan nomor 432;----------

b. diberitahukan, diterima dan dicatat di dalam --- daftar yayasan Kementerian Hukum dan Hak Asasi - Manusia Republik Indonesia tertanggal 02-12-2013 (dua Desember dua ribu tiga belas) nomor ------- AHU-AH.01.03-1162;----------

-dan susunan anggota Pembina, Pengurus, dan Pengawas Yayasan terakhir sebagaimana ternyata dari akta --- tertanggal 14-02-2020 (empat belas Pebruari dua ribu dua puluh) nomor 08, yang aslinya dibuat dihadapan saya, notaris dan telah diberitahukan, diterima dan dicatat di dalam Sistem Administrasi Badan Hukum -- Kementerian Hukum dan Hak Asasi Manusia Republik -- Indonesia tertanggal 13-03-2020 (tiga belas Maret - dua ribu dua puluh) nomor AHU-AH.01.06-0012697;---- -selanjutnya **YAYASAN INSTITUT DANONE INDONESIA** dalam bahasa Inggris **INDONESIAN DANONE INSTITUTE** -------- **FOUNDATION** tersebut dalam akta ini cukup disebut -- "Yayasan".----------

-- Penghadap dikenal oleh saya, notaris dari identitas yang disampaikan kepada saya, notaris.----------

-- Penghadap mana senantiasa bertindak seperti tersebut

menerangkan terlebih dahulu :----------

-- Bahwa, Pembina Yayasan telah menyetujui/mengambil - keputusan, satu dan lain sebagaimana itu ternyata dari surat Keputusan Sirkuler Pembina Yayasan Institut ---- Danone Indonesia, yang dibuat dibawah tangan dan ----- bermeterai cukup efektif pada tanggal 03-09-2020 (tiga September dua ribu dua puluh) serta dijahitkan pada -- asli akta ini (selanjutnya cukup disebut "Keputusan -- Pembina Yayasan".----------

-- Bahwa sesuai dengan ketentuan Pasal 11 ayat 8 juncto ayat 9 dari anggaran dasar Yayasan, Pembina Yayasan -- dapat juga mengambil keputusan yang sah tanpa -------- mengadakan Rapat Pembina, dengan ketentuan semua ----- anggota Pembina telah diberitahu secara tertulis dan - semua anggota Pembina memberikan persetujuan mengenai usul yang diajukan secara tertulis serta menandatangani persetujuan tersebut. Keputusan yang diambil dengan -- cara demikian, mempunyai kekuatan yang sama dengan --- keputusan yang diambil secara sah dalam Rapat Pembina dan karenanya keputusan yang diambil dalam "Keputusan Pembina Yayasan" dapat juga dianggap sama dengan ----- keputusan yang diambil dalam Rapat Pembina.----------

-- Bahwa menurut keterangan penghadap, Pembina Yayasan yang telah menandatangani "Keputusan Pembina Yayasan" adalah segenap Pembina dalam Yayasan hingga hari dan - tanggal "Keputusan Pembina Yayasan" ditandatangani.---

-- Bahwa Pembina Yayasan telah memberi kuasa kepada -- penghadap sebagaimana tercantum dalam "Keputusan ----- Pembina Yayasan" untuk menyatakan keputusan tersebut - dalam suatu akta notaris, hal mana hendak dinyatakan -

dalam akta ini.----------

-- Sehubungan dengan apa yang diuraikan di atas, -----
penghadap senantiasa bertindak berdasarkan kuasa yang diberikan kepadanya menerangkan dengan ini menyatakan keputusan yang telah diambil tersebut adalah sebagai - berikut :----------

1. Menyetujui pengunduran diri nona **NADHILA RENALDI** -- dari jabatannya sebagai Sekretaris Pengurus Yayasan efektif sejak tanggal 31-08-2020 (tiga puluh satu - Agustus dua ribu dua puluh) dan memberikan -------- pembebasan dan pelunasan sepenuhnya (acquit et de - charge) kepada nona **NADHILA RENALDI** dari segala --- tindakan selama masa jabatannya sepanjang tindakan-tindakan tersebut tercermin dalam laporan keuangan Yayasan.----------

2. Mengangkat nona **ANINDITA SARASWATI DWIWINATA** sebagai Sekretaris Pengurus Yayasan yang baru menggantikan nona **NADHILA RENALDI**, efektif sejak tanggal ------- 31-08-2020 (tiga puluh satu Agustus dua ribu dua -- puluh) sampai dengan sisa masa jabatan yang ------- digantikannya. Oleh karena itu, terhitung sejak --- tanggal 31-08-2020 (tiga puluh satu Agustus dua ribu dua puluh) susunan Pengurus Yayasan menjadi sebagai berikut:----------

PENGURUS :----------

- Ketua : tuan **WIDJAJA LUKITO**;-------
- Wakil Ketua I : nyonya **ADE UMIYAMA** (dalam - Kartu Tanda Penduduk ------ tertulis **UMIYANA SAVITRI** -- **AKIL**);----------

- Wakil Ketua II : nyonya **ROSALINA PRIVITA**;---
- Wakil Ketua III : nyonya **Dokter TRIA ROSEMIARTI**;----------
- Sekretaris : nona **ANINDITA SARASWATI DWIWINATA**;----------
- Bendahara I : tuan **DEDI SUWARTONO** (dalam Kartu Tanda Penduduk ------ tertulis **DEDY**)----------
- Bendahara II : tuan **RONNY SUWARTO**;--------
- Bendahara III : nyonya **VIVIANI SUTJIADI**;---

3. Menegaskan kembali susunan Pembina, Pengurus dan -- Pengawas Yayasan terhitung sejak tanggal 31-08-2020 (tiga puluh satu Agustus dua ribu dua puluh) adalah sebagai berikut :----------

PEMBINA :----------

- Ketua : nyonya **VERA GALUH SUGIJANTO**, lahir di Jakarta pada ----- tanggal 22-08-1975 (dua --- puluh dua Agustus seribu -- sembilan ratus tujuh puluh - lima), Warga Negara ------- Indonesia, swasta, -------- bertempat tinggal di ------ Jakarta, Jalan Ruby 1 Blok - F2 nomor 4 Permata Hijau, - Rukun Tetangga 008, Rukun - Warga 013, Kelurahan Grogol Utara, Kecamatan Kebayoran - Lama, Jakarta Selatan, ---- pemegang Kartu Tanda ------

Penduduk Republik Indonesia Nomor Induk Kependudukan -- 3174056208750002;----------

- Anggota : tuan **Insinyur WIDIANTO ---- JUWONO**, lahir di Mojokerto - pada tanggal 23-02-1967 (dua puluh tiga Pebruari seribu - sembilan ratus enam puluh - tujuh), Warga Negara ------ Indonesia, swasta, -------- bertempat tinggal di Kota - Bogor, Jalan Sektor ------- Pertukangan nomor 1, Rukun - Tetangga 003, Rukun Warga - 001, Kelurahan Sempur, ---- Kecamatan Kota Bogor Tengah, pemegang Kartu Tanda ------ Penduduk Republik Indonesia Nomor Induk Kependudukan -- 3271032302670002;----------

PENGURUS :----------

- Ketua : tuan **WIDJAJA LUKITO**, lahir - di Surabaya pada tanggal -- 29-08-1958 (dua puluh ----- sembilan Agustus seribu --- sembilan ratus lima puluh - delapan), Warga Negara ---- Indonesia, swasta, -------- bertempat tinggal di Kota - Tangerang, Taman Golf XVIII-

EG.3/26, Rukun Tetangga 002, Rukun Warga 014, Kelurahan - Poris Plawad Indah, ------- Kecamatan Cipondoh, ------- pemegang Kartu Tanda ------ Penduduk Republik Indonesia Nomor Induk Kependudukan -- 3671052908580003;----------

- Wakil Ketua I : nyonya **ADE UMIYAMA** (dalam - Kartu Tanda Penduduk ------ tertulis **UMIYANA SAVITRI** -- **AKIL)**, lahir di Bandung pada tanggal 21-12-1969 (dua --- puluh satu Desember seribu - sembilan ratus enam puluh - sembilan), Warga Negara --- Indonesia, swasta, -------- bertempat tinggal di ------ Jakarta, Jalan Tebet Timur - Dalam nomor 151, Rukun ---- Tetangga 014, Rukun Warga - 009, Kelurahan Tebet Timur, Kecamatan Tebet, Jakarta -- Selatan, pemegang Kartu --- Tanda Penduduk Republik --- Indonesia Nomor Induk ----- Kependudukan ---------- 3174016112690002;----------

- Wakil Ketua II : nyonya **ROSALINA PRIVITA**, -- lahir di Jakarta pada -----

tanggal 07-10-1977 (tujuh - Oktober seribu sembilan --- ratus tujuh puluh tujuh), - Warga Negara Indonesia, --- swasta, bertempat tinggal di Jakarta, Jalan Bendungan -- Hilir Raya nomor 90, Rukun - Tetangga 005, Rukun Warga - 003, Kelurahan Bendungan -- Hilir, Kecamatan Tanah ---- Abang, Jakarta Pusat, ----- pemegang Kartu Tanda ------ Penduduk Republik Indonesia Nomor Induk Kependudukan -- 3173024710770003;----------

- Wakil Ketua III : nyonya **Dokter TRIA** -------- **ROSEMIARTI**, lahir di ------ Yogyakarta pada tanggal --- 25-04-1968 (dua puluh lima - April seribu sembilan ratus enam puluh delapan), Warga - Negara Indonesia, swasta, - bertempat tinggal di Kota - Tangerang, Jalan Anggrek -- C.II/6, Rukun Tetangga 001, Rukun Warga 005, Kelurahan - Larangan Indah, Kecamatan - Larangan, pemegang Kartu -- Tanda Penduduk Republik --- Indonesia Nomor Induk -----

Kependudukan ----------
3671136504680002;----------

- Sekretaris : nona **ANINDITA SARASWATI** --- **DWIWINATA**, lahir di Jakarta pada tanggal 29-06-1995 (dua puluh sembilan Juni seribu - sembilan ratus sembilan --- puluh lima), Warga Negara - Indonesia, swasta, -------- bertempat tinggal di Kota - Denpasar, Jalan Permata --- Gatsu II DPS, BR/Link ----- Tengah, Kelurahan Ubung, -- Kecamatan Denpasar Utama, - pemegang Kartu Tanda ------ Penduduk Republik Indonesia Nomor Induk Kependudukan -- 5171046906950006;----------

- Bendahara I : tuan **DEDI SUWARTONO** (dalam - Kartu Tanda Penduduk ------ tertulis **DEDY)**, lahir di -- Purwokerto pada tanggal --- 16-10-1986 (enam belas ---- Oktober seribu sembilan --- ratus delapan puluh enam), - Warga Negara Indonesia, --- swasta, bertempat tinggal di Kota Tangerang Selatan, --- Jalan Kucica 2 Blok J G 6/2 Bintaro Jaya Sektor IX, ---

Rukun Tetangga 003, Rukun - Warga 011, Kelurahan Pondok Pucung, Kecamatan Pondok -- Aren, pemegang Kartu Tanda - Penduduk Republik Indonesia Nomor Induk Kependudukan -- 3173081610860006;----------

- Bendahara II : tuan **RONNY SUWARTO** lahir di Malang pada tanggal ------- 10-01-1985 (sepuluh Januari seribu sembilan ratus ----- delapan puluh lima), Warga - Negara Indonesia, swasta, - bertempat tinggal di ------ Jakarta, Jalan Duri Permai - III nomor 9, Rukun Tetangga 013, Rukun Warga 007, ----- Kelurahan Duri Kepa, ------ Kecamatan Kebon Jeruk, ---- Jakarta Barat, pemegang --- Kartu Tanda Penduduk ------ Republik Indonesia Nomor -- Induk Kependudukan -------- 3573041001850013;----------

- Bendahara III : nyonya **VIVIANI SUTJIADI**, -- lahir di Jakarta pada ----- tanggal 16-11-1969 (enam -- belas Nopember seribu ----- sembilan ratus enam puluh - sembilan), Warga Negara ---

		Indonesia, swasta, -------- bertempat tinggal di ------ Jakarta, Jalan Kembang Indah II Blok G 3 nomor 51, Rukun Tetangga 007, Rukun Warga - 006, Kelurahan Kembangan -- Selatan, Kecamatan -------- Kembangan, Jakarta Barat, - pemegang Kartu Tanda ------ Penduduk Republik Indonesia Nomor Induk Kependudukan -- 3173055611690009;----------
- **PENGAWAS**	:	nyonya **THERESIA LIANAWATY - SETIONEGORO**, lahir di ----- Jakarta pada tanggal ------ 10-12-1958 (sepuluh ------- Desember seribu sembilan -- ratus lima puluh delapan), - Warga Negara Indonesia, --- swasta, bertempat tinggal di Jakarta, Jalan Pulo Asem -- Utara Raya nomor 8, Rukun - Tetangga 008, Rukun Warga - 002, Kelurahan Jati, ------ Kecamatan Pulogadung, ----- Jakarta Timur, pemegang --- Kartu Tanda Penduduk ------ Republik Indonesia Nomor -- Induk Kependudukan -------- 3175025012580018;----------

-- Penghadap bertindak sebagaimana tersebut di atas -- menyatakan dengan ini menjamin kebenaran identitas --- penghadap sesuai dengan tanda pengenal yang disampaikan kepada saya, notaris dan bertanggung jawab sepenuhnya atas hal tersebut serta membebaskan notaris dari segala tuntutan sehubungan dengan hal tersebut.----------

-- Selanjutnya penghadap bertindak sebagaimana tersebut di atas menyatakan telah mengerti dan memahami isi akta ini serta menyatakan bahwa isi akta ini telah sesuai - dengan apa yang dikehendaki oleh penghadap.----------

-- Dari segala apa yang tersebut diatas, maka -------- dibuatlah:----------

---------- A K T A I N I. ----------

-- Dibuat sebagai minuta, dibacakan serta ditanda ---- tangani di Jakarta, pada hari dan tanggal tersebut pada awal akta ini, dengan dihadiri oleh nona ELITAWATI, -- lahir di Bukit Maraja pada tanggal 29-01-1965 (dua --- puluh sembilan Januari seribu sembilan ratus enam puluh lima), Warga Negara Indonesia, swasta, bertempat ----- tinggal di Jakarta, Jalan Cideng Timur, nomor 31, Rukun Tetangga 015, Rukun Warga 005, Kelurahan Petojo Utara, Kecamatan Gambir, Kota Administrasi Jakarta Pusat, --- pemegang Kartu Tanda Penduduk Republik Indonesia Nomor Induk Kependudukan : 3171011691650003 dan tuan ------- FAKHRIZAL ZUHRI ATMA, lahir di Medan pada tanggal ---- 25-04-1992 (dua puluh lima April seribu sembilan ratus sembilan puluh dua), Warga Negara Indonesia, swasta, - bertempat tinggal di Medan, Jalan Bhayangkara Gang --- Buntu nomor 502 B, Kelurahan Indra Kasih, Kecamatan -- Medan Tembung, pemegang Kartu Tanda penduduk Republik

Indonesia Nomor Induk Kependudukan : 1271142504920001, untuk sementara berada di Jakarta;----------

-keduanya sebagai saksi-saksi.----------

-- Segera setelah akta ini dibacakan oleh saya, notaris kepada penghadap dan para saksi, maka seketika ditanda tanganilah akta ini oleh penghadap, para saksi dan --- saya, notaris, sedangkan penghadap disamping menanda - tangani akta ini juga telah membubuhkan sidik jari --- jempol tangan kanan dan sidik jari jempol tangan kiri pada lembar kertas tersendiri yang dijahitkan pada --- minuta akta ini.----------

-- Dilangsungkan dengan tidak ada perubahan.----------

-- Asli akta ini telah ditanda tangani dengan -------- semestinya.----------

DIBERIKAN SALINAN YANG SAMA BUNYINYA.

Notaris Kota Jakarta Pusat.

(Nyonya BERTHA SURIATI IHALAUW HALIM, S.H.)

KEPUTUSAN SIRKULER PEMBINA
YAYASAN INSTITUT DANONE INDONESIA

Yang bertandatangan dibawah ini, Pembina Yayasan Institut Danone Indonesia, suatu yayasan yang didirikan berdasarkan hukum yang berlaku di Indonesia dan berdomisili di Jakarta Selatan (selanjutnya disebut sebagai "**Yayasan**"), yaitu:

- Nyonya VERA GALUH SUGIJANTO, bertindak dalam jabatannya selaku Ketua Pembina Yayasan; dan
- Nona Ir. WIDIANTO JUWONO, bertindak dalam jabatannya selaku Anggota Pembina Yayasan

menerangkan terlebih dahulu bahwa:

I. Sesuai dgn akta No. 08 tertanggal 14 Februari 2020 yang aslinya dibuat dihadapan BERTHA SURIATI IHALAUW HALIM, SH., notaris di Jakarta, Pembina Yayasan adalah Nyonya VERA GALUH SUGIJANTO dan Tuan Ir. WIDIANTO JUWONO;

II. Nona NADHILA RENALDI telah mengundurkan diri dari jabatannya sebagai Sekretaris Yayasan terhitung efektif sejak tanggal 31 Agustus 2020, sebagaimana disebutkan dalam Surat Pengunduran Diri yang dibuat dibawah tangan dan bermeterai cukup, tertanggal 31 Juli 2020, sesuai dengan ketentuan Pasal 14 Ayat 6 Anggaran Dasar Yayasan.

III. Sesuai dengan ketentuan Pasal 11 Ayat 8 dan Ayat 9 dari Anggaran Dasar Yayasan, Pembina dapat mengambil keputusan yang sah tanpa mengadakan Rapat Pembina, dengan ketentuan semua anggota Pembina telah diberitahu secara tertulis dan semua anggota Pembina memberikan persetujuan mengenai usul yang diajukan secara tertulis serta menandatangani persetujuan tersebut dan keputusan yang diambil dengan cara demikian mempunyai kekuatan yang sama dengan keputusan yang diambil dengan sah dalam Rapat Pembina.

Selanjutnya, Pembina Yayasan menerangkan bahwa sehubungan dengan pengunduran diri sebagaimana tersebut diatas, maka berdasarkan ketentuan Pasal 14 Ayat 1 dan Ayat 2 dari Anggaran Dasar Yayasan, sesuai dengan Surat Penunjukan yang dibuat di bawah tangan dan bermeterai cukup dari Pendiri Yayasan tertanggal 19 Agustus 2020 dengan ini:

- Mengangkat Nona ANINDITA SARASWATI DWIWINATA sebagai Sekretaris Yayasan yang baru sebagai pengganti Nona NADHILA RENALDI, berlaku efektif terhitung tanggal 31 Agustus 2020 untuk sisa masa jabatan yang digantikannya;

Berdasarkan hal-hal tersebut diatas, Pembina Yayasan memutuskan sebagai berikut:

1. Menyetujui pengunduran diri Nona NADHILA RENALDI dari jabatannya sebagai Sekretaris Pengurus Yayasan efektif sejak tanggal 31 Agustus 2020 dan memberikan pembebasan dan pelunasan sepenuhnya *(acquit et de charge)* kepada Nona NADHILA RENALDI dari segala tindakan selama masa jabatannya sepanjang tindakan-tindakan tersebut tercermin dalam laporan keuangan Yayasan.

2. Mengangkat Nona ANINDITA SARASWATI DWIWINATA sebagai Sekretaris Pengurus Yayasan yang baru menggantikan Nona NADHILA RENALDI, efektif sejak tanggal 31 Agustus 2020 sampai dengan sisa masa jabatan yang digantikannya. Oleh karena itu, terhitung sejak tanggal 31 Agustus 2020 susunan Pengurus Yayasan menjadi sebagai berikut:

   PENGURUS:
   - Ketua : Tuan Widjaja Lukito
   - Wakil Ketua I : Nyonya Ade Umiyama
   - Wakil Ketua II : Nyonya Rosalina Privita
   - Wakil Ketua III : Nyonya Dr. Tria Rosemiarti
   - Sekretaris : Nona Anindita Saraswati Dwiwinata
   - Bendahara I : Tuan Dedi Suwartono
   - Bendahara II : Tuan Ronny Suwarto
   - Bendahara III : Nyonya Viviani Sutjiadi

3. Menegaskan kembali susunan Pembina, Pengurus dan Pengawas Yayasan terhitung sejak tanggal 31 Agustus 2020 adalah sebagai berikut:

   PEMBINA:
   - Ketua : Nyonya Vera Galuh Sugijanto
   - Anggota : Tuan Ir. Widianto Juwono

   PENGURUS:
   - Ketua : Tuan Widjaja Lukito
   - Wakil Ketua I : Nyonya Ade Umiyama
   - Wakil Ketua II : Nyonya Rosalina Privita
   - Wakil Ketua III : Nyonya Dr. Tria Rosemiarti
   - Sekretaris : Nona Anindita Saraswati Dwiwinata
   - Bendahara I : Tuan Dedi Suwartono
   - Bendahara II : Tuan Ronny Suwarto
   - Bendahara III : Nyonya Viviani Sutjiadi

   PENGAWAS:
   - Nyonya Theresia L. Setionegoro

4. Memberi kuasa dengan hak substitusi kepada Tuan Widjaja Lukito atau Nyonya Theresia L. Setionegoro untuk menyatakan Keputusan Sirkuler Pembina Yayasan ini dalam suatu akta notaris, untuk itu menghadap notaris dan/atau pejabat yang berwenang, menandatangani surat atau akta dan semua persyaratan administratif serta melaporkan kepada instansi pemerintah yang berwenang guna pelaksanaan dari Keputusan Sirkuler Pembina ini dan lebih lanjut mengambil tindakan-tindakan lain yang perlu dan/atau harus dilakukan guna mencapai tujuan tersebut tidak ada dikecualikan.

Demikian Keputusan Sirkuler Pembina ini dibuat dan berlaku efektif sejak tanggal dari tanda tangan terakhir yang dicantumkan dalam asli Keputusan Sirkuler Pembina ini

Yayasan Institut Danone Indonesia
Pembina:

Nama: VERA GALUH SUGIJANTO
Jabatan: Ketua
Tanggal: 3 September 2020

Nama: Ir. WIDIANTO JUWONO
Jabatan: Anggota
Tanggal: 3 September 2020

ATTACHMENT 2

Publication and Research Grants

- Journal Publication by Safarina G. Malik titled “Maternal Biomarker Patterns for Metabolism and Inflammation in Pregnancy Are Influenced by Multiple Micronutrient Supplementation and Associated with Child Biomarker Patterns and Nutritional Status At 9-12 Years of Age.”
- Journal Publication by Arif Sabta Aji titled “A Genetic Approach to Study the Relationship Between Maternal Vitamin D Status and Newborn Anthropometry Measurements: The Vitamin D Pregnant Mother (VDPM) Cohort Study.”
- Journal Publication by Arif Sabta Aji titled “Pre-Pregnancy Maternal Nutritional Status and Physical Activity Levels During Pregnancy Associated with Birth Size Outcomes in Minangkabau Women, Indonesia.”

PLOS ONE

RESEARCH ARTICLE

Maternal biomarker patterns for metabolism and inflammation in pregnancy are influenced by multiple micronutrient supplementation and associated with child biomarker patterns and nutritional status at 9-12 years of age

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Abstract

Maternal nutritional status influences fetal development and long-term risk for adult non-communicable diseases. However, the underlying mechanisms remain poorly understood. We examined whether biomarkers for metabolism and inflammation during pregnancy were associated with maternal health and with child biomarkers and health at 9–12 years of age in 44 maternal-child dyads from the Supplementation with Multiple Micronutrients Intervention Trial (SUMMIT, ISRCTN34151616) in Lombok, Indonesia. Archived blood for each dyad from maternal enrollment, later in pregnancy, postpartum, and from children at 9–12 years comprised 132 specimens. Multiplex microbead immunoassays were used to quantify vitamin D-binding protein (D), adiponectin (A), retinol-binding protein 4 (R), C-reactive protein (C), and leptin (L). Principal component analysis (PCA) revealed distinct variance patterns, i.e. principal components (PC), for baseline pregnancy, bp.pc1.D↓A↓R↓ and bp.pc2.C↓L↑; combined follow-up during pregnancy and postpartum, dp-pp.pc1.D↑↓A↑R↑↓L↓ and dp-pp.pc2.A↑C↑L↑; and children, ch.pc1.D↑R↑C↑ and ch.pc2.D↓A↑L↑. Maternal multiple micronutrient (MMN) supplementation led to an association of baseline maternal bp.pc2.C↓L↑ with decreased post-supplementation maternal dp-pp.pc2.A↑C↑L↑ ($p = 0.022$), which was in turn associated with both increased child ch.pc1.D↑R↑C↑ ($p = 0.036$) and decreased child BMI z-score (BMIZ) ($p = 0.022$). Further analyses revealed an association between maternal dp-pp.pc1.D↑↓A↑R↑↓L↓ and increased child BMIZ ($p = 0.036$). Child ch.pc1.D↑R↑C↑ was associated with decreased birth weight ($p = 0.036$) and increased child BMIZ ($p = 0.002$). Child ch.pc2.D↓A↑L↑ was associated with increased child BMIZ ($p = 0.005$), decreased maternal height ($p = 0.030$) and girls ($p = 0.002$). A pattern of elevated maternal adiponectin and leptin in pregnancy was associated with increased C-reactive protein,

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vitamin A, and D binding proteins pattern in children, suggesting biomarkers acting in concert may have qualitative as well as quantitative influence beyond single biomarker effects. Patterns in pregnancy proximal to birth were more associated with child status. In addition, child patterns were more associated with child status, particularly child BMI. MMN supplementation affects maternal biomarker patterns of metabolism and inflammation in pregnancy, and potentially in the child. However, child nutrition conditions after birth may have a greater impact on metabolism and inflammation.

Introduction

Emerging epidemiological evidence has shown that the risk for non-communicable diseases (NCDs) during childhood or as an adult is mediated in part by maternal nutrition in pregnancy and fetal growth [1–3]. Studies in animal models indicate that alterations in nutritional, metabolic, immune and hormonal milieu *in-utero* profoundly affect long-term health of the offspring, including increased risk for NCDs such as diabetes, obesity or cardiovascular disease [4,5]. Knowledge of the underlying mechanisms of these effects remains limited, although evidence is growing for the pivotal roles of metabolism-related hormones and inflammatory mediators [6,7].

Adipocytokines, including leptin, adiponectin, and retinol binding protein 4 (RBP4), play an important role in regulating metabolism, energy homeostasis and inflammatory responses [8–11]. Leptin is involved in body weight control by acting on the satiety center in the hypothalamus [12]. Leptin also promotes fetal growth and regulates fetal adipose tissue development [13]. Adiponectin plays a role in the catabolism of fatty acids and carbohydrates, improvement of insulin sensitivity and reduction of inflammation [14]. RBP4, previously thought to act as a specific transport protein for retinol, has been added to the family of adipocytokines given its role in obesity-induced insulin resistance [15]. Increased concentrations of both leptin and RBP4 have been associated with increased body mass index (BMI) [16,17], while adiponectin concentration was negatively associated with BMI [18]. Morevover, elevated concentrations of these adipocytokines during pregnancy have also been associated with adverse conditions, including gestational diabetes, preeclampsia and intrauterine growth restriction (IUGR) [19–22]. A previous study reported that maternal leptin and adiponectin concentrations were correlated with fetal leptin and adiponectin concentrations [23].

Inflammatory markers have been associated with increased risk of cardiovascular disease [24]. Specifically, higher C-reactive protein (CRP) concentrations in pregnant women were associated with increased risks for preterm birth and low birth weight (LBW) newborns [25,26], as well as elevated BMI in children [27]. Vitamin D binding protein (VDBP), previously known as a transport protein for vitamin D and as a regulator of vitamin D metabolism [28], has recently been shown to mediate inflammation and macrophage activation [29]. Maternal vitamin D status was reported to have an impact on birth weight and offspring immunity [30,31].

Multiple dietary factors, including micronutrients, have been reported to modulate leptin, adiponectin, RBP4, CRP, and VDBP concentrations [32–37]. Maternal expression patterns for these biomarkers may be associated with expression patterns in their children. To examine these relationships, we studied mother-child dyads from the Supplementation with Multiple Micronutrients Intervention Trial (SUMMIT) in Lombok, Indonesia wherein blood specimens and the relevant data were available from pregnancy as well as their children 9–12 years after birth. The SUMMIT, a randomized trial comparing maternal multiple micronutrients (MMN) supplementation to iron and folic acid (IFA), showed that maternal MMN reduced

early infant mortality and LBW [38]. The study also identified multiple risk factors for poor fetal development [39]. A follow-up study of children at 9–12 years of age indicated long term effects of MMN on child cognitive development. We hypothesized that in this cohort: 1. Maternal nutritional status is associated with maternal biomarkers; 2. Maternal MMN supplementation influenced maternal biomarkers; 3. Maternal biomarkers are associated with child biomarkers; 4. Child biomarkers are associated with child health outcomes (Fig 1).

Materials and methods

Data collection

The SUMMIT (ISRCTN34151616) was approved by the National Institute of Health Research and Development of the Ministry of Health of Indonesia, the Provincial Planning Department of Nusa Tenggara Barat Province, and the Johns Hopkins Joint Committee on Clinical Investigation, Baltimore, USA; the ten-year follow-up study was approved by the University of Mataram Ethical Research Committee as a certified Institutional Review Board of the National Institute of Health Research and Development of the Ministry of Health of Indonesia; the current study of SUMMIT archived materials was also approved by the Eijkman Institute Research Ethics Commission. Plasma specimens from pregnant women were collected at enrolment before supplementation (baseline) and follow-up specimens at one of four

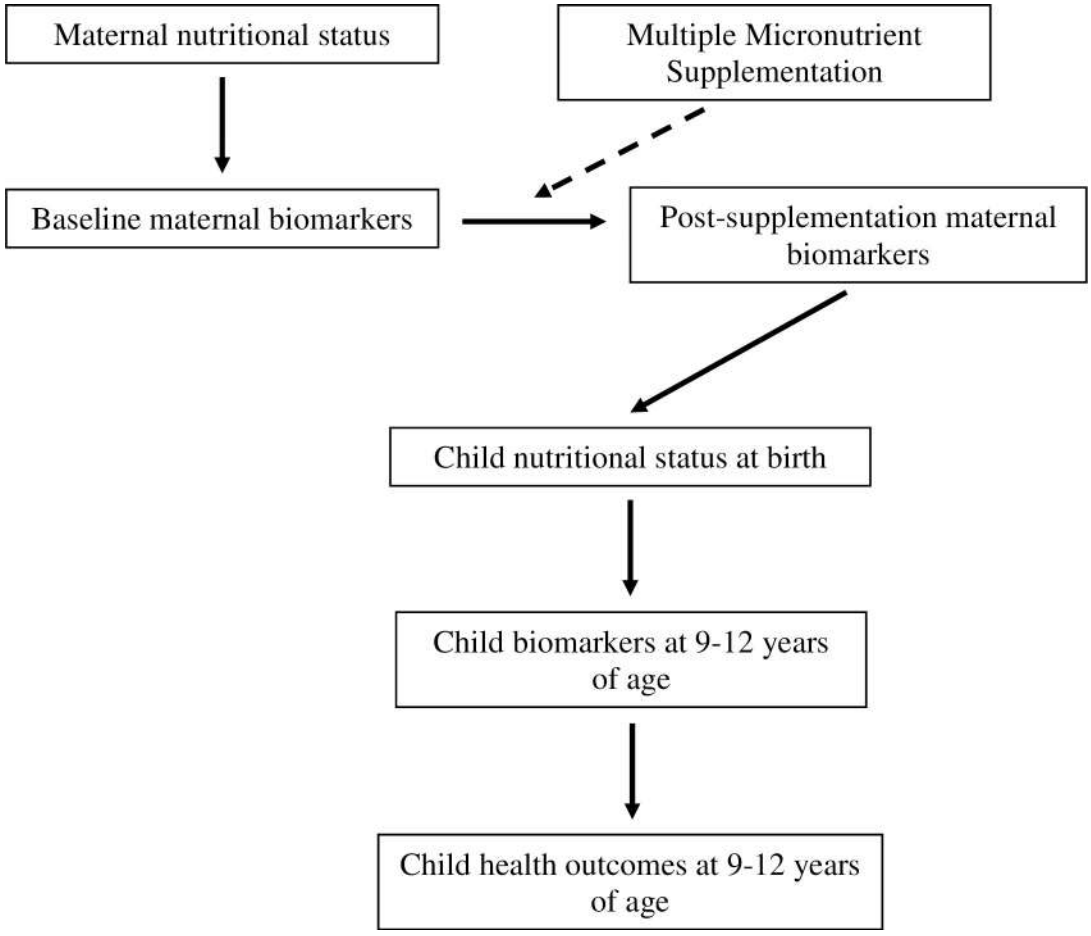

Fig 1. Conceptual framework.

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subsequent time points: one month after enrolment, 36 weeks of gestation, one week postpartum, and 12 weeks postpartum (post-supplementation) [40]. Maternal nutritional status was measured at enrollment by mid-upper arm circumference (MUAC), maternal height and maternal hemoglobin (Hb). Child status at age 9–12 years was characterized by height and weight which were converted to BMI-for-age z-score (BMIZ) following World Health Organization norms [41], and by systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Sample selection

We selected 414 mother-child dyads from the SUMMIT with plasma samples from three time points: maternal pre-supplementation, maternal post-supplementation, and the child at age 9–12 years. From these, we further selected 44 dyads, consisting of 22 each of the MMN and the IFA groups, who had participated in the studies on maternal cognition [40], cognition at pre-school age [40], and cognition at 9–12 years [42]. This was to optimize the spectrum of outcomes over time that could be included in analyses. Within these 44 dyads, maternal plasma consisted of baseline pre-supplementation samples paired with post-supplementation samples. The post-supplementation samples were collected during pregnancy (either four weeks after enrolment or at 36 weeks gestational age) or postpartum (either one week or 12 weeks postpartum). The post-supplementation during pregnancy group consists of 18 samples (9 from MMN and 9 from IFA groups) and the post-supplementation postpartum group consists of 23 samples (13 from MMN and 13 from IFA groups). A total of 132 maternal and child plasma specimens were analyzed for VDBP, adiponectin, RBP4, CRP, and leptin (Fig 2).

Multiplex immunoassay

Quantification of leptin, adiponectin, RBP4, CRP, and VDBP was conducted using Luminex® Magnetic Screening Assays (Catalogue number LXSAHM-8, R&D System, Minneapolis, MN, USA) following the manufacturer's instructions. Plasma samples were diluted according kit requirements and incubated with antibody-coated microspheres, followed by biotinylated detection antibody, and phycoerythrin-labeled streptavidin. The bead immuno-complexes were read using a MagPix CCD Imager (Luminex, Austin, TX, USA) set to the following parameters: events (beads) = 50, sample size = 50 μl. Biomarker concentrations were calculated based on the average of the median fluorescence intensity (MFI) of each duplicate sample.

Statistical analysis

Data normality for biomarkers was assessed by the Shapiro Wilk test and QQ plots. Biomarkers concentrations were log-transformed to normalize distributions as needed. Normally distributed variables were presented as the mean (±standard deviation). Non-normally distributed variables were presented as the median (interquartile range). Principal component analysis (PCA) was performed to identify specific components of correlation between the five biomarkers as putative composite biomarkers. A component was retained following cross validation by meeting at least two of three criteria: (1) eigenvalue cutoffs defined by Horn's parallel analysis [43], (2) being robust to outlier prediction based on the squared residual distance Q and Hotelling T^2 distance as well as pattern of variance explained, (3) frequency of associations in regression analyses that exceeds what would be expected as assessed by the Fisher Exact test. These criteria yielded two retained components for all PCA conducted. Factor loadings greater than absolute value of 0.40 were used to identify biomarkers that loaded on each component as this threshold would imply the observed variable shares more than 15% of its variance ($0.40^2 = 0.16$) with the component [44].

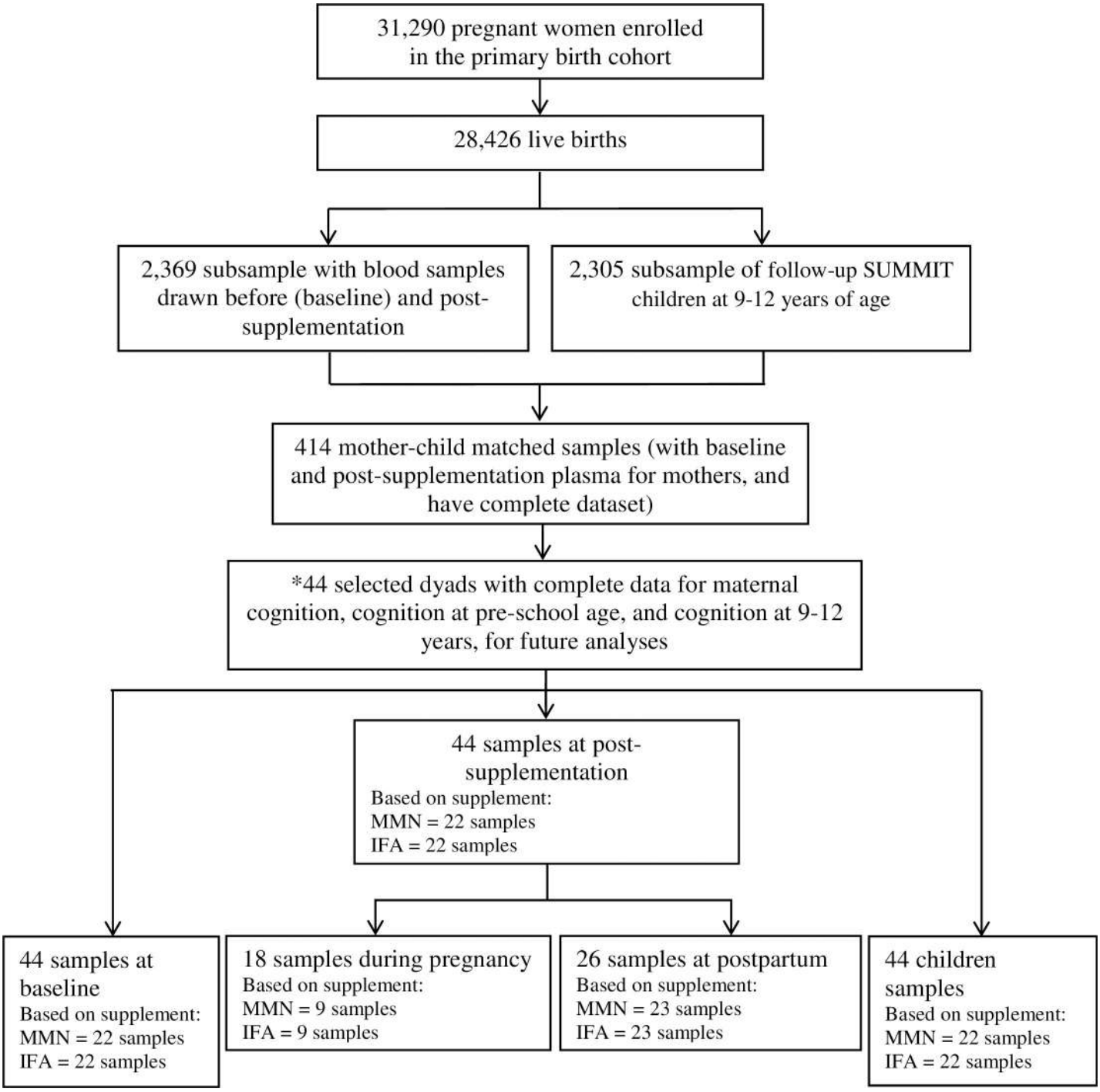

Fig 2. Participant and specimen selectionflow chart. IFA = iron folic acid; MMN = multiple micronutrients. *44 paired maternal-child plasma specimens were selected, consisting of 22 each of the MMN and the IFA groups, with data for maternal cognition, cognition at pre-school age, and cognition at 9–12 years [40].

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The principal component (PC) scores for retained components were computed for each specimen type (baseline, post-supplementation, and child), then normalized to a mean of 0 and standard deviation of 1 and used as either the independent or dependent variable in regression models. To include post-supplementation PC scores in regression analyses, we merged the

normalized scores from samples collected during pregnancy and postpartum. Multiple linear regression was used to determine the association of the following variables: maternal PC scores at baseline with maternal nutritional status (association 1), maternal PC scores at baseline with post-supplementation (association 2), maternal PC scores at each time point with child PC scores (association 3), and PC scores of each group with child health outcomes (association 4). Analyses for association 1 were a regression model with maternal PCs at baseline as the dependent variable and baseline maternal hemoglobin, maternal height, maternal mid-upper arm circumference (MUAC), and gestational age at enrolment as independent variables. Association 2 modeled maternal PCs at post-supplementation as the dependent variable and baseline maternal PCs, maternal hemoglobin, maternal height, maternal mid-upper arm circumference (MUAC), and type of supplement (MMN or IFA) as the independent variables. We analyzed the interaction of MMN supplementation with maternal PCs at baseline and maternal PCs at post-supplementation. In the regression model for association 3, the dependent variables were child PCs, while the independent variables were maternal PCs at baseline and post-supplementation, and baseline maternal hemoglobin, maternal height, maternal MUAC, birth weight, child gender (boy or girl), and type of supplement (MMN or IFA). Association 4 modeled maternal and child PCs, baseline maternal hemoglobin, maternal height, maternal MUAC, birth weight, child gender (boy or girl), and type of supplement (MMN or IFA) as the independent variables when the BMIZ was the dependent variable, with additional adjustment for child BMIZ when the systolic blood pressure (SBP) and diastolic blood pressure (DBP) were the dependent variables. All regression analyses were performed using R-Project for Statistical Computing version 3.4.0 and SAS 9.4. A p-value of less than 0.05 was considered significant.

Results

Baseline characteristics of subjects

The baseline characteristics of mother-child dyads were collected during the SUMMIT and its follow up studies, as shown in Table 1. Pregnant women who received MMN supplementation had similar characteristics to those receiving IFA. The characteristics of the children at 9–12 years of age whose mothers received MMN or IFA supplementation were also similar to the overall SUMMIT enrollees, as were the general characteristics of women in this study [38,45].

Biomarker concentrations of women and children

The median values of the selected biomarkers are summarized in Table 2. The biomarker concentrations for each supplement are presented in S1 Table.

Principal Component Analysis (PCA) to identify composite biomarker components

Table 3 shows the results of principal component analysis. The first two PCs were retained for further analyses based on the criteria detailed in Materials and Methods. For maternal PCA, the first two PCs explained 60% (PC1 = 39.5%, PC2 = 20.5%), 77.6% (PC1 = 52.1%, PC2 = 25.5%), and 60.5% (PC1 = 36.9%, PC2 = 23.6%) of the total variance for baseline, post-supplementation during pregnancy and post-supplementation postpartum groups, respectively. For child PCA, the first two PCs explained 63.2% (PC1 = 40.0%, PC2 = 23.2%). Each group had distinctive component patterns based on biomarker loadings. For the maternal baseline pregnancy (bp) group, PC1 consisted of negative loadings for VDBP (D), adiponectin (A), and RBP4 (R) (bp.pc1.D↓A↓R↓), while PC2 consisted of negative loadings for CRP (C) and positive for leptin (L) (bp.pc2.C↓L↑). The PC1 for post-supplementation during pregnancy (dp) was

Table 1. Baseline characteristics of mother-child dyads.

Characteristics	MMN (N = 22)	IFA (N = 22)	*p*-value
Mothers			
Age (years) ¶	25.0 (20.0–26.5)	25.5 (20.5–30.0)	0.251
Parity (number of births) ‡			
0	8 (36)	5 (23)	0.509
≥ 1	14 (64)	17 (77)	
Height (cm) ¶	151.4 (149.3–153.6)	149.8 (148.7–152.6)	0.231
Mid-upper arm circumference (mm) ¶	239.5 (228.2–253.0)	245.0 (230.2–253.1)	0.503
Haemoglobin at enrolment (g/dL) ¶	11.1 (10.3–12.0)	11.3 (10.4–11.9)	0.842
Gestational age at enrolment (weeks) ¶	16.5 (9.5–24.1)	14.6 (12.3–18.7)	0.734
Children			
Gender (M/F)	13/9	10/12	0.546
BMI-for-age z-scores †	−0.7x (±1.0x)	−0.8x (±1.1x)	0.678
Systolic blood pressure (mmHg) †	110.0 (±11.3)	104.4 (±7.8)	0.525
Diastolic blood pressure (mmHg) †	65.0 (±9.8)	63.4 (±5.3)	0.067
Birth weight (g) ¶	3300 (2925–3500)	3000 (2825–3450)	0.350
Gestational age at birth (weeks) ¶	39.1 (36.9–40.1)	39.6 (38.1–40.9)	0.231

¶: median (interquartile range).

†: mean (±standard deviation).

‡: n (percentage). MMN: multiple micronutrients supplement. IFA: iron and folic acid supplement.

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comprised of positive loadings for VDBP, adiponectin, and RBP4 (dp.pc1.D↑A↑R↑), while PC2 was comprised of positive loadings for adiponectin and leptin (dp.pc2.A↑L↑). For the post-supplementation postpartum group (pp), PC1 was characterized by negative loadings for VDBP, RBP4, and leptin (pp.pc1.D↓R↓L↓), and PC2 by positive loadings for adiponectin, CRP and leptin (pp.pc2.A↑C↑L↑). The child (ch) PC1 consisted of positive loadings for VDBP, RBP4 and CRP (ch.pc1.D↑R↑C↑), while the PC2 consisted of negative loadings for VDBP, and positive for adiponectin and leptin (ch.pc2.D↓A↑L↑). The complete principal component analysis results of maternal biomarkers and child biomarkers are presented in S2–S5 Tables.

Associations of maternal baseline nutrition characteristics with maternal baseline pregnancy components

Linear regression analyses between maternal PCs at baseline and maternal nutrition status showed that PC1 bp.pc1.D↓A↓R↓ had a mild negative association with reduced MUAC in both unadjusted (β = −0.017, $p = 0.036$) and adjusted (β = −0.020, $p = 0.025$) models. Meanwhile, PC2 bp.pc2.C↓L↑ displayed a mild positive association with increased MUAC in

Table 2. Biomarker concentrations of women during baseline, post-supplementation during pregnancy, post-supplementation at postpartum, and in children.

Biomarker	Baseline (N = 44)	Post-supplementation during pregnancy (N = 18)	Post-supplementation at postpartum (N = 26)	Children (N = 44)
VDBP (μg/mL)	52.8 (32.6–86.0)	34.1 (21.3–49.0)	39.5 (29.4–102.4)	19.1 (15.9–24.7)
Adiponectin (μg/mL)	3.0 (2.0–4.1)	2.5 (2.1–2.9)	3.3 (2.3–4.3)	5.2 (4.6–6.5)
RBP4 (μg/mL)	27.3 (22.1–35.9)	20.3 (16.6–32.3)	39.4 (28.8–47.1)	24.2 (19.6–28.9)
CRP (μg/mL)	2.0 (0.6–3.4)	1.3 (0.4–2.2)	0.5 (0.1–1.2)	0.2 (0.1–0.6)
Leptin (ng/mL)	8.2 (4.8–13.8)	15.0 (10.5–21.4)	3.5 (2.1–5.7)	3.1 (2.4–5.8)

VDBP: vitamin D binding protein. RBP4: retinol binding protein. CRP: C-reactive protein. Data in median (interquartile range).

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Table 3. Principal component analysis of biomarkers for maternal baseline, maternal follow-up, and for children.

	Baseline (N = 44)		Post-supplementation during pregnancy (N = 18)		Post-supplementation at postpartum (N = 26)		Children (N = 44)	
	PC1	PC2	PC1	PC2	PC1	PC2	PC1	PC2
Eigenvalues	1.974	1.026	2.607	1.277	1.846	1.181	1.997	1.163
% variance accounted for	39.484	20.518	52.134	25.540	36.927	23.620	39.950	23.268
Loadings								
Log VDBP	**−0.407**	0.056	**0.586**	−0.057	**−0.585**	0.170	**0.464**	**−0.529**
Log Adiponectin	**−0.569**	−0.222	**0.427**	**0.533**	0.310	**0.536**	0.157	**0.609**
Log RBP4	**−0.519**	0.368	**0.496**	0.303	**−0.609**	−0.077	**0.600**	0.086
Log CRP	−0.390	**−0.679**	0.389	−0.397	0.111	**0.689**	**0.497**	−0.226
Log Leptin	−0.299	**0.592**	−0.280	**0.680**	**−0.422**	**0.452**	0.391	**0.540**

PC: principal component. VDBP: vitamin D binding protein. RBP4: retinol binding protein. CRP: C-reactive protein. Principal component analysis (PCA) was performed to identify composite biomarker components. Components were retained based on criteria described in Materials and Methods. Loadings >0.40, in bold, were used to define and characterize the component [44].

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unadjusted analysis (β = 0.013, $p = 0.023$), and tendency, though not significant, for association in adjusted analysis (β = 0.012, $p = 0.068$) (Table 4). Regression analyses between individual maternal biomarkers and maternal nutritional status are presented in S6 Table.

Associations of maternal baseline pregnancy components, maternal nutrition, and multiple micronutrient supplementation with post-supplementation components

Regression analyses for the associations between maternal PCs at baseline and at post-supplementation are presented in Table 5. Baseline maternal PC1 bp.pc1.D↓A↓R↓ was negatively associated with the post-supplementation maternal PC2 dp-pp.pc2.A↑C↑L↑ (β = −0.315, $p = 0.028$). A negative association was also found between the baseline maternal PC2 bp.pc2.C↓L↑ and the post-supplementation maternal PC1 dp-pp.pc1.D↑↓A↑R↑↓L↓ (β = −0.518, $p = 0.022$). Of particular interest were analyses incorporating an interaction term between

Table 4. Associations of maternal baseline nutrition characteristics with maternal baseline pregnancy components.

	bp.pc1.D↓A↓R↓ (n = 44)				bp.pc2.C↓L↑ (n = 44)			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	B	*p*	B	*p*	B	*p*	B	*p*
Hb at baseline	0.005	0.975	0.036	0.835	0.162	0.148	0.065	0.617
Height (cm)	-0.075	0.263	-0.053	0.400	-0.008	0.865	-0.016	0.732
MUAC (mm)	-0.017	**0.036**	-0.02	**0.025**	0.013	**0.023**	0.012	0.068
Gestational age (weeks)	-0.043	0.146	-0.052	0.095	-0.014	0.499	-0.001	0.964

PC: principal component; bp.pc1.D↓A↓R↓: baseline maternal PC1; bp.pc2.C↓L↑: baseline maternal PC2; D: vitamin D binding protein; A: adiponectin; R: retinol binding protein 4; C: C-reactive protein; L: leptin; ↓: decrease; ↑: increase; B: coefficient of regression; Hb: hemoglobin; MUAC: mid-upper arm circumference. Association analyses were performed using unadjusted and adjusted linear models. For adjusted regressions, the dependent variables were baseline maternal PCs and the independent variables were maternal Hb at baseline, maternal height, maternal MUAC at baseline, and gestational age at enrolment. Significant p values <0.05 are in bold.

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Table 5. Associations of maternal baseline pregnancy components, maternal nutrition, and multiple micronutrient supplementation with and post-supplementation components.

	dp-pp.pc1.D↑↓A↑R↑↓L↓ (n = 44)				dp-pp.pc2.A↑C↑L↑ (n = 44)			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	B	*p*	B	*p*	B	*p*	B	*p*
bp.pc1.D↓A↓R↓	-0.269	0.088	-0.29	0.083	-0.284	**0.015**	-0.315	**0.028**
bp.pc2.C↓L↑	-0.516	**0.016**	-0.518	**0.022**	0.084	0.616	0.066	0.719
Hb at baseline (g/dL)	-0.241	0.132	-0.132	0.421	0.062	0.61	0.042	0.762
Height (cm)	-0.07	0.312	-0.111	0.100	-0.015	0.772	-0.026	0.646
MUAC (mm)	-0.011	0.204	-0.003	0.731	0.009	0.166	0.001	0.889
MMN supplementation	0.648	0.14	0.723	0.100	-0.121	0.718	-0.279	0.445
Interaction model:								
bp.pc1.D↓A↓R↓*MMN	-0.281	0.376	−0.257	0.395	-0.121	0.604	−0.149	0.531
bp.pc2.C↓L↑*MMN	0.240	0.558	0.315	0.438	-0.799	**0.016**	−0.761	**0.022**

PC: principal component; bp.pc1.D↓A↓R↓: baseline maternal PC1; bp.pc2.C↓L↑: baseline maternal PC2; dp-pp.pc1.D↑↓A↑R↑↓L↓: post-supplementation maternal PC1; dp-pp.pc2.A↑C↑L↑: post-supplementation maternal PC2; D: vitamin D binding protein; A: adiponectin; R: retinol binding protein 4; C: C-reactive protein; L: leptin; ↓: decrease; ↑: increase; ↑↓: increased post-supplementation during pregnancy and decreased post-supplementation at postpartum; B: coefficient of regression; Hb: hemoglobin; MUAC: mid-upper arm circumference; MMN: multiple micronutrients. Analysis were performed using unadjusted and adjusted linear models. For adjusted regressions, the dependent variables were post-supplementation maternal PCs, and the independent variables were baseline maternal PCs, maternal Hb at baseline, maternal height, maternal MUAC at baseline, and MMN/IFA supplementation. For interaction (*) we added the terms baseline maternal PC1*MMN/IFA supplementation and baseline maternal PC2*MMN/IFA supplementation. Significant *p* values <0.05 are in bold.

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each PC and supplementation type (IFA or MMN), which revealed that MMN caused baseline bp.pc2.C↓L↑ to be negatively associated with post-supplementation maternal PC2 dp-pp.pc2.A↑C↑L↑, whereas these components were positively associated for the IFA group (*p* interaction = 0.022) (Fig 3A), Analysis of maternal baseline and post-supplementation biomarkers is shown in S7 Table.

Associations of maternal components and child characteristics with child biomarker components

We found that post-supplementation maternal PC2 dp-pp.pc2.A↑C↑L↑ was positively associated with child PC1 ch.pc1.D↑R↑C↑ (β = 0.439, *p* = 0.036) (Fig 3B). As shown in Table 6, the child PC1 ch.pc1.D↑R↑C↑ was also negatively associated with birth weight (β = −0.826, *p* = 0.036). The child PC2 ch.pc2.D↓A↑L↑ showed a mild negative association with maternal height (β = −0.097, *p* = 0.030), and strong negative association with male gender (β = −0.958, *p* = 0.002) (Table 6). The association of individual child biomarkers with maternal biomarkers at baseline and post-supplementation are shown in S8 Table and S9 Table.

Association of child health outcomes with maternal and child biomarker components

We then analyzed the association of maternal and child biomarker PC scores with child health outcomes (BMIZ, SBP, and DBP) as seen in Table 7. We found that child BMIZ was negatively associated with the maternal dp-pp.pc2.A↑C↑L↑ (β = −0.302, *p* = 0.022), and positively associated with maternal pp.pc1.D↑↓A↑R↑↓L↓ (β = 0.224, *p* = 0.036), ch.pc1.D↑R↑C↑ (β = 0.347, *p* = 0.002), and ch.pc2.D↓A↑L↑ (β = 0.515, *p* = 0.005) (Fig 4). With respect to maternal characteristics, we observed that child BMIZ was negatively associated with baseline maternal Hb (β = −0.280, *p* = 0.010), and mildly positively associated with maternal MUAC (β = 0.014, *p* = 0.027). No significant associations were found with child SBP and DBP. The association of

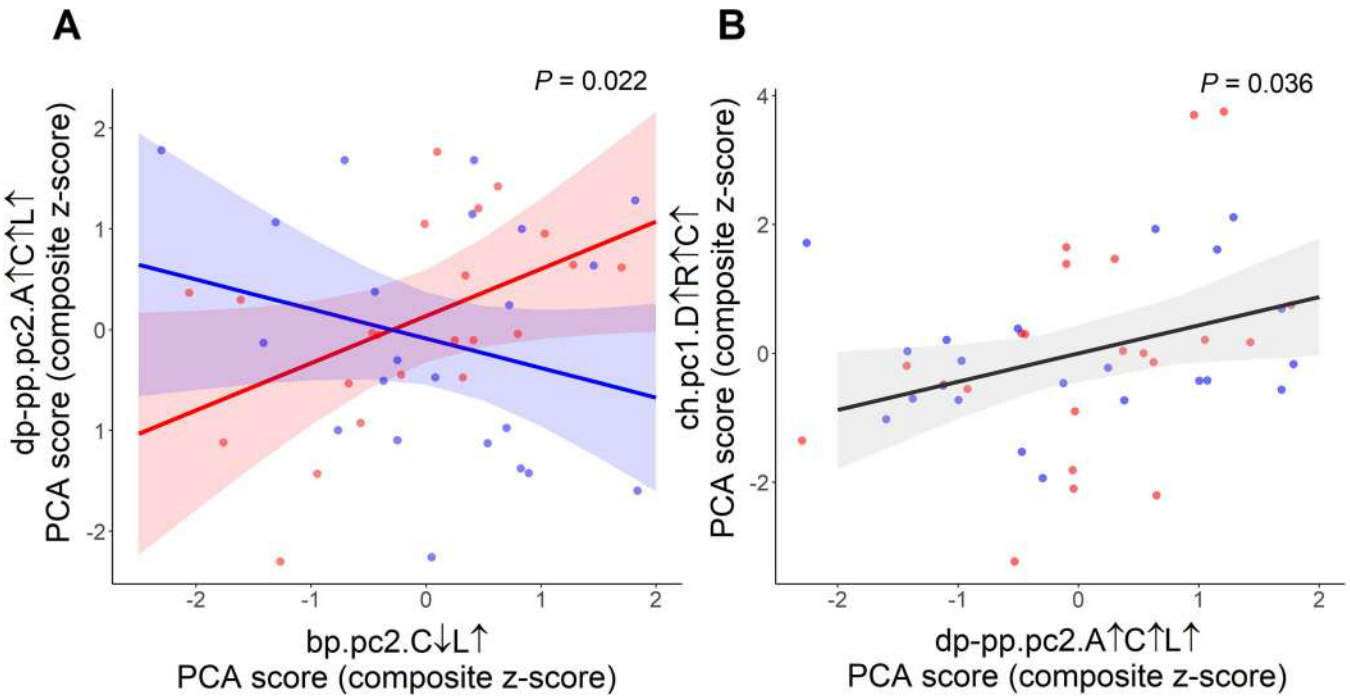

Fig 3. A. Maternal multiple micronutrient supplementation affects associations between maternal biomarker components. Interaction between baseline maternal PC2 bp.pc2.C↓L↑ and supplementation type with post-supplementation maternal PC2 dp-pp.pc2.A↑C↑L↑. B. Effect of maternal biomarker component on child biomarker component. Association of maternal PC2 dp-pp.pc2.A↑C↑L↑ and child PC1 ch.pc1.D↑R↑C↑. Blue line and blue dots: MMN supplementation; Red line and red dots: IFA supplementation.

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Table 6. Association of maternal components and child characteristics with child biomarker components.

	ch.pc1.D↑R↑C↑ (n = 44)				ch.pc2.D↓A↑L↑ (n = 44)			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	B	*p*	B	*p*	B	*p*	B	*p*
bp.pc1.D↓A↓R↓	-0.094	0.546	0.243	0.195	0.041	0.732	-0.010	0.932
bp.pc2.C↓L↑	0.303	0.156	0.292	0.237	0.230	0.160	-0.043	0.774
dp-pp.pc1.D↑↓A↑R↑↓L↓	0.011	0.939	0.204	0.242	-0.040	0.727	-0.103	0.330
dp-pp.pc2.A↑C↑L↑	0.392	**0.046**	0.439	**0.036**	0.189	0.214	0.168	0.182
Hb at baseline (g/dL)	0.220	0.158	0.015	0.932	-0.124	0.301	-0.072	0.511
Height (cm)	0.066	0.324	0.090	0.204	-0.125	**0.012**	-0.097	**0.030**
MUAC (mm)	0.018	**0.023**	0.018	0.091	0.005	0.441	0.001	0.925
Birth weight (kg)	-0.685	0.074	-0.826	**0.036**	0.203	0.496	0.347	0.142
Gender: Boy	-0.035	0.936	0.496	0.299	-0.566	0.082	-0.958	**0.002**
MMN supplementation	-0.073	0.866	-0.092	0.841	0.006	0.986	0.328	0.249

PC: principal component; bp.pc1.D↓A↓R↓: baseline maternal PC1; bp.pc2.C↓L↑: baseline maternal PC2; dp-pp.pc1.D↑↓A↑R↑↓L↓: post-supplementation maternal PC1; dp-pp.pc2.A↑C↑L↑: post-supplementation maternal PC2; ch.pc1.D↑R↑C↑: child PC1; ch.pc2.D↓A↑L↑: child PC2; D: vitamin D binding protein; A: adiponectin; R: retinol binding protein 4; C: C-reactive protein; L: leptin; ↓: decrease; ↑: increase; ↑↓: increased post-supplementation during pregnancy and decreased post-supplementation at postpartum; B: coefficient of regression; Hb: hemoglobin; MUAC: mid-upper arm circumference; MMN: multiple micronutrients. Analysis was performed using unadjusted and adjusted linear models. For adjusted regressions, the dependent variables were child PCs, and the independent variables were baseline maternal PCs, post-supplementation maternal PCs, maternal Hb at baseline, maternal height, maternal MUAC at baseline, birth weight, child's gender (boy/girl), and MMN/IFA supplementation. Significant p values <0.05 are shown in bold.

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Table 7. Associations of maternal and child components and nutritional characteristics with child body mass index and blood pressure.

	Child's outcome											
	BMIZ (n = 44)				SBP (n = 43)				DBP (n = 43)			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	B	*p*	B	*p*	B	*p*	B	*p*	B	*P*	B	*p*
bp.pc1.D↓A↓R↓	-0.063	0.581	0.088	0.424	0.564	0.609	1.100	0.445	0.486	0.571	0.853	0.438
bp.pc2.C↓L↑	0.081	0.610	0.114	0.429	1.272	0.415	1.050	0.606	0.186	0.879	-0.427	0.783
dp-pp.pc1.D↑↓A↑R↑↓L↓	0.144	0.191	0.224	**0.036**	1.352	0.201	1.968	0.185	1.222	0.136	1.369	0.227
dp-pp.pc2.A↑C↑L↑	-0.067	0.649	-0.302	**0.022**	-1.954	0.164	-2.788	0.126	-0.432	0.695	-0.605	0.658
ch.pc1.D↑R↑C↑	0.368	**0.001**	0.347	**0.002**	1.991	0.064	2.123	0.199	1.696	**0.042**	0.894	0.474
ch.pc2.D↓A↑L↑	0.163	0.269	0.515	**0.005**	1.113	0.441	2.097	0.428	2.289	**0.037**	2.403	0.237
Hb at baseline (g/dL)	-0.155	0.176	-0.280	**0.010**	0.273	0.807	0.594	0.692	-0.042	0.962	1.073	0.352
Height (cm)	0.061	0.210	0.063	0.165	0.314	0.509	0.328	0.592	0.042	0.909	0.402	0.392
MUAC (mm)	0.009	0.125	0.014	**0.026**	0.030	0.612	0.018	0.842	0.027	0.558	-0.013	0.851
Birth weight (kg)	0.000	0.540	-0.046	0.852	0.476	0.864	2.667	0.415	-2.179	0.309	-0.912	0.714
Gender: Boy	-0.277	0.381	0.540	0.104	-1.077	0.728	-0.715	0.875	-2.988	0.211	-2.332	0.503
MMN supplementation	0.132	0.678	-0.080	0.766	5.637	0.063	3.684	0.322	1.592	0.508	0.587	0.835
Child BMIZ					4.064	**0.007**	1.035	0.670	3.444	**0.003**	1.990	0.288

PC: principal component; bp.pc1.D↓A↓R↓: baseline maternal PC1; bp.pc2.C↓L↑: baseline maternal PC2; dp-pp.pc1.D↑↓A↑R↑↓L↓: post-supplementation maternal PC1; dp-pp.pc2.A↑C↑L↑: post-supplementation maternal PC2; ch.pc1.D↑R↑C↑: child PC1; ch.pc2.D↓A↑L↑: child PC2; D: vitamin D binding protein; A: adiponectin; R: retinol binding protein 4; C: C-reactive protein; L: leptin; ↓: decrease; ↑: increase; ↑↓: increased post-supplementation during pregnancy and decreased post-supplementation at postpartum; B: coefficient of regression; Hb: hemoglobin; MUAC: mid-upper arm circumference; MMN: multiple micronutrients; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure. Analysis was performed using unadjusted and adjusted linear models. For adjusted regressions, the dependent variables were BMIZ, SBP, DBP, and the independent variables were baseline maternal PCs, post-supplementation maternal PCs, child PCs, maternal Hb at baseline, maternal height, maternal MUAC at baseline, birth weight, child's gender (boy/girl), MMN/IFA supplementation, and child BMIZ for models with SBP and DBP as dependent variables. Significant *p* values <0.05 are indicated in bold.

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child health outcome with maternal biomarkers and child biomarkers are shown in S10 Table (maternal biomarkers at baseline) and S11 Table (maternal biomarkers at post-supplementation) and S12 Table (child biomarkers).

Discussion

To our knowledge, few studies have explored the association of maternal metabolic biomarkers during pregnancy and postpartum with child metabolic biomarkers at age 9–12 years. Moreover, because biomarkers may not work independently, but in concert, potential interactions between composite biomarker components and outcomes may better represent the complexity of their effects. We therefore utilized PCA to construct composite components of biomarkers that represented their covariance structure and analyzed the associations of the resulting components and other characteristics, with downstream components and health indicators.

PCA showed that maternal biomarkers at baseline and post-supplementation during pregnancy and postpartum had distinctive component structures, indicating that gestational age may influence the maternal biomarker patterns. We found that increased maternal MUAC was associated with lower baseline maternal PC1 bp.pc1.D↓A↓R↓. This is consistent with previous reports where nutritional status measured by BMI was positively correlated with leptin, adiponectin, and RBP4 concentrations [46–48], though these studies were not done in pregnant women.

We also found that maternal biomarker PCs at baseline were associated with biomarker PCs at post-supplementation, although associations at these timepoints between individual

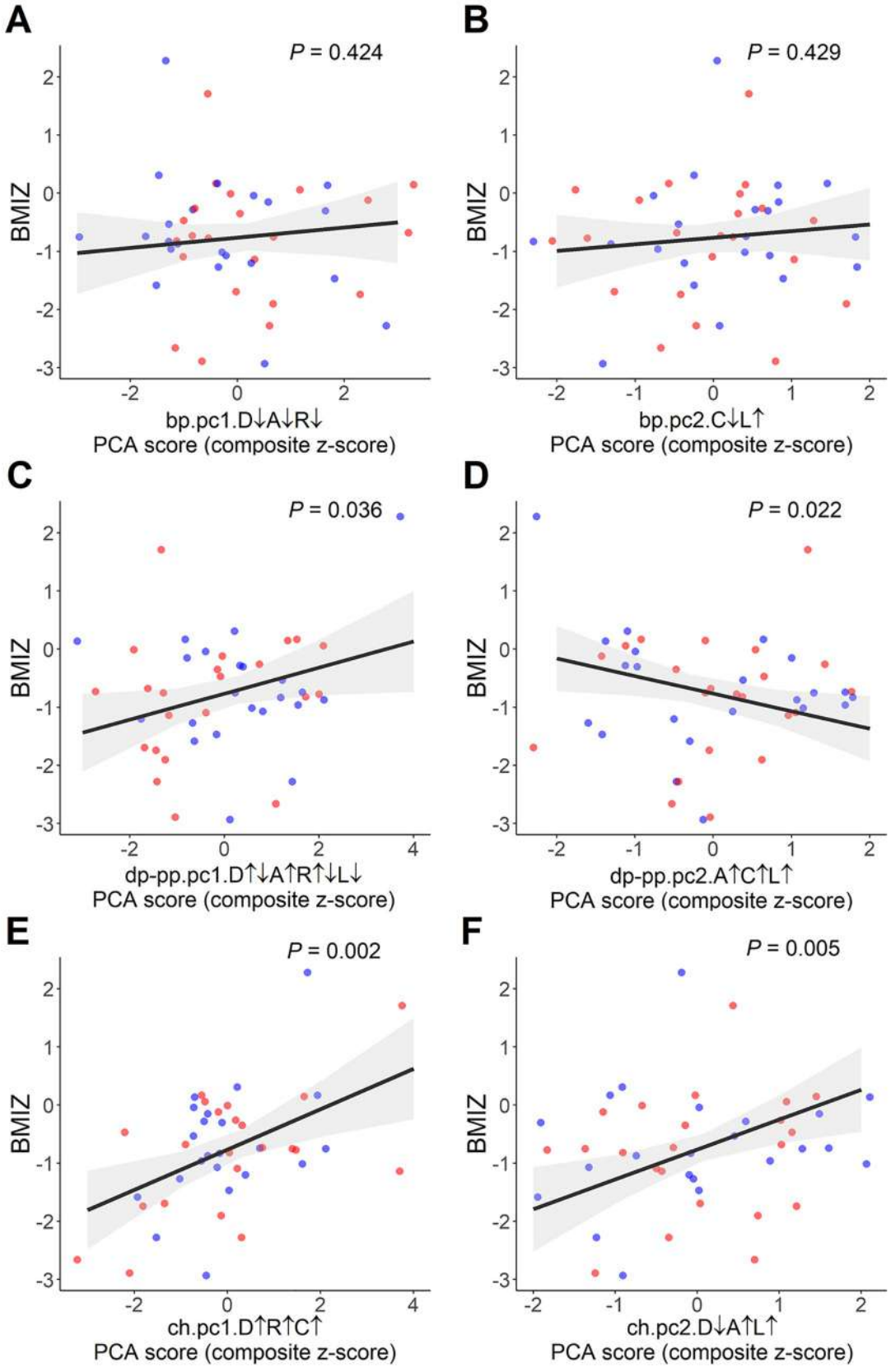
A
P = 0.424
BMIZ
bp.pc1.D↓A↓R↓
PCA score (composite z-score)
B
P = 0.429
BMIZ
bp.pc2.C↓L↑
PCA score (composite z-score)
C
P = 0.036
BMIZ
dp-pp.pc1.D↑↓A↑R↑↓L↓
PCA score (composite z-score)
D
P = 0.022
BMIZ
dp-pp.pc2.A↑C↑L↑
PCA score (composite z-score)
E
P = 0.002
BMIZ
ch.pc1.D↑R↑C↑
PCA score (composite z-score)
F
P = 0.005
BMIZ
ch.pc2.D↓A↑L↑
PCA score (composite z-score)

Fig 4. Association of maternal and child biomarker components with child BMIZ. A-B. Maternal baseline PC1 bp.pc1.D↓A↓R↓ and PC2 bp.pc2.C↓L↑. **C-D**. Maternal PC1 dp-pp.pc1.D↑↓A↑R↑↓L↓ and PC2 dp-pp.pc2. A↑C↑L↑. **E-F**. Child PC1 ch.pc1.D↑R↑C↑ and PC2 ch.pc2.D↓A↑L↑. Blue dots: MMN supplementation; Red dots: IFA supplementation.

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biomarkers were observed only for adiponectin and RBP4 (S8 Table). This suggests that biomarkers may indeed have stronger influence working in concert as components in a networked biological system. In this context it is intriguing that maternal MMN supplementation interacted with maternal baseline PC bp.pc2.C↓L↑ to strongly decrease post-supplementation PC dp-pp.pc2.A↑C↑L↑. This is consistent with reports of vitamin C and E supplementation reducing CRP concentrations [36,49], and vitamin D supplementation reducing serum leptin [50].

We observed that maternal PC dp-pp.pc2.A↑C↑L↑ was associated with higher child PC ch.pc1.D↑R↑C↑ at 9–12 years of age and with lower child BMIZ. This suggests co-elevation of adiponectin, CRP, and leptin in pregnancy may lead to co-elevation of VDBP, RBP4, and CRP in the child. Moreover, maternal MMN might therefore tend to decrease VDBP, RBP4, and CRP in the child, which could favor lower BMIZ, as we observed in Table 7, and possibly leaner growth. However, we note that a decrease in PC dp-pp.pc2.A↑C↑L↑ as shown in Table 7 might also favour higher BMIZ.

Previous studies showed that maternal leptin concentration was correlated with child leptin concentration in cord blood [23,51] and serum of 9-years old children [52]. Postpartum maternal biomarkers may be associated with child biomarkers through breast milk, in agreement with a previous study that reported a correlation between leptin concentration in breast milk with its concentration in maternal serum and infant weight gain [53]. Although genetics was also reported to have moderate influence on variation of biomarkers concentration [54,55], environmental factors such as nutrition, including micronutrients, and infection have been reported to more strongly modulate adipocytokines and inflammatory markers [32–37,56]. Our analysis did not include the influence of dietary intake on biomarkers concentrations, which could reveal additional associations. Daily nutrient-dense food intake should remain the principal source of micronutrients. In this study, we did not include analysis of dietary intake, and further analyses of SUMMIT dietary data in this context may yield additional insights.

BMI-for-age z-score represents nutritional and health conditions in children and adolescents [57]. Our study showed that maternal and child biomarker PCs were associated with child BMIZ. This is in line with previous studies that reported BMIZ in children was correlated with biomarkers concentrations, such as leptin [58] and RBP4 concentrations [59]. In our study, the average BMIZ was below the WHO standard for a healthy population [41], which means the children tended to be underweight. However, BMIZ is a modifiable factor which can be improved by nutritional and behavioral interventions [60]. Thus, maternal MMN supplementation during pregnancy might indirectly influence child BMIZ considering that our results indicated that MMN modified the association between maternal baseline and maternal post-supplementation biomarker PC scores, while maternal post-supplementation PC scores were associated with child biomarker PC scores and BMIZ.

It has been suggested that pre-pregnancy and pregnancy nutritional status have long term effects on health outcomes of children. Both maternal height and MUAC were positively associated with child PC scores, although these were not significant. Maternal Hb during pregnancy and height were also associated with child BMIZ. These results support the potential influence of maternal nutritional status on long term child metabolism and health. This notion has been previously reported wherein maternal BMI was correlated with child BMI [61] and

weight for height z-score (WHZ) [62]. Maternal BMI was also reported to be associated with infant serum leptin values [48]. Therefore, our findings also highlight the importance of optimal macronutrient intake during pregnancy that would improve maternal nutritional status and child health later in life [63]. In this context, the reported greater impact of maternal MMN on birth weight in well-nourished women is noteworthy [38].

We proposed that maternal biomarkers of adipocytokines and inflammatory markers could influence the same biomarkers in the child through the interactions of immunologic and metabolic factors. Adiponectin, RBP4, CRP, and leptin play important roles in regulating metabolism, energy homeostasis, and inflammatory responses, while VDBP has a role in modulating immune and inflammatory response. The immune and metabolic system have co-evolved to signal each other and form complex networks in response to environmental exposures, such as the secretion of leptin and adiponectin that are contra-regulated [64,65]. Transfer of immune and metabolic properties between mother and child occurs through the placenta [23,66], and through breast milk during the neonatal period [53]. Together, these immune-metabolic signals provide innate and adaptive immunity, and influencing the metabolic homeostasis of the newborn. The transmission of these cross-generational immune and metabolic properties may be modified via optimal macronutrient and micronutrient intake during pregnancy and postpartum. Maternal adverse conditions, such as malnutrition or infection may modify these signals and alter newborn immunity, consequently influencing newborn and infant health, and possibly later life [67,68].

It is remarkable that despite the relatively small set of specimens analyzed in this study, significant and interpretable associations were observed, suggesting that the biomarker components exhibit strong influence. We also note that the overall associations identified through components tended, although not always, to be more frequent and stronger than for individual biomarkers alone. Replication of this study's findings would be warranted. In addition, due to the multiple hypotheses tested, the multiple comparisons in the study were unavoidable, but again we note the frequency of associations exceeds that which would be expected by chance as assessed by the Fisher Exact test on PCs not retained for analyses which would represent random data. To our knowledge, this is the first study suggesting an effect of maternal MMN supplementation on the child outcomes via modulation of the mother's biomarkers. We suggest that specific effects of a particular micronutrient or of MMN overall cannot be determined based on a single biomarker, as there would be many pathways involved. Therefore, analyzing the effect of a composite biomarker component may be more relevant, as conducted here.

While the above findings suggest associations between maternal and child biomarker status as well as a role of MMN in this relationship, there are several limitations of the study. First, the limited sample size yielded limited statistical power, precluding more detailed analyses. For example, we could not assess the outcome of gestational age at birth. Similarly, in some cases the distribution of predictors in regression models may not have adequately represented the full spectrum of values. The impact of this in many cases was greater variance, thereby limiting associations. In addition, other potentially important covariates were not included, such as dietary intake or recent infections, or blood samples from children at younger ages that could be analyzed. Finally, while we utilized PCA to discern components, this approach would not be able to identify localized clustering of biomarkers in the n-dimensional space. Other techniques such as k-means clustering or uniform manifold approximation and projection (UMAP) may also be useful and would require greater sample size. Nevertheless, the results herein are suggestive, and additional confirmation would be warranted.

In the SUMMIT, MMN supplementation compared to IFA improved birth and health outcomes [38]. The IFA contained 30 mg iron and 400 μg folic acid, and the MMN followed the UNIMMAP formulation that contained 30 mg iron and 400 μg folic acid along with 800 μg

retinol, 200 IU vitamin D, 10 mg vitamin E, 70 mg ascorbic acid, 1.4 mg vitamin B1, 1.4 mg vitamin B2, 18 mg niacin, 1.9 mg vitamin B6, 2.6 μg vitamin B12, 15 mg zinc, 2 mg copper, 65 μg selenium, and 150 μg iodine. Deficiencies of these micronutrients have been associated with adverse pregnancy outcomes. For example, vitamin A deficiency may lead to night blindness [69], vitamin D deficiency is associated with preeclampsia, insulin resistance, and gestational diabetes mellitus [70]. Vitamin E and C are antioxidants to prevent pre-eclampsia [71]. Vitamin B1 deficiency may cause of IUGR [72]. Vitamins B6 and B12 play important roles in maternal health as well as fetal development and physiology [73]. Deficiencies of minerals such as zinc, selenium, copper and iodine have also been associated with complications in pregnancy, childbirth or fetal development [74–76]. We recently showed that increases in mitochondrial DNA copy number during pregnancy are associated with LBW, and that maternal MMN supplementation stabilized mitochondrial DNA copy number in peripheral blood mononuclear cells of SUMMIT women, indicating its effects on improved energy efficiency and reduced oxidative damage [77,78].

In conclusion, the results herein suggest that biomarkers of adipocytokines and inflammatory mediators during pregnancy comprise components that may influence downstream biomarker components in pregnancy and in children 9–12 years later, along with child BMIZ. Moreover, MMN supplementation may affect the relationship between components, and further influence child BMIZ score. Improving maternal nutritional status may improve child health not only at birth, but also during childhood, and into adulthood.

Supporting information

S1 Checklist. STROBE statement—checklist of items that should be included in reports of *cross-sectional studies*.
(DOCX)

S1 Fig. Screeplot of maternal baseline PCA.
(DOCX)

S2 Fig. Screeplot of maternal post-supplementation during prengancy PCA.
(DOCX)

S3 Fig. Screeplot of maternal post-supplementation at post-partum PCA.
(DOCX)

S4 Fig. Screeplot of children PCA.
(DOCX)

S5 Fig. Cross validation of cumulative variance. Cross validation was performed using 'mdatools' package. Blue line: cumulative variance of PCA result. Red line: cumulative variance of cross validation result.
(DOCX)

S6 Fig. Correlation map between principle components and all variables.
(DOCX)

S1 Table. Biomarker concentrations of pregnant women during baseline, post-supplementation during pregnancy, post-supplementation at post-partum, and in children.
(DOCX)

S2 Table. Principal component analysis results of maternal biomarkers at baseline.
(DOCX)

S3 Table. Principal component analysis results of maternal biomarkers post-supplementation during pregnancy.
(DOCX)

S4 Table. Principal component analysis results of maternal biomarkers post-supplementation at post-partum.
(DOCX)

S5 Table. Principal component analysis results of children's biomarkers.
(DOCX)

S6 Table. Association between maternal biomarkers at baseline and maternal nutritional status.
(DOCX)

S7 Table. Association between maternal biomarkers at baseline and post-supplementation.
(DOCX)

S8 Table. Association between child biomarkers and maternal biomarkers at baseline.
(DOCX)

S9 Table. Association between child biomarkers and maternal biomarkers at post-supplementation.
(DOCX)

S10 Table. Association between child's outcome and maternal biomarkers at baseline.
(DOCX)

S11 Table. Association between child's outcome and maternal biomarkers at post-supplementation.
(DOCX)

S12 Table. Association between child's outcome and child's biomarkers.
(DOCX)

S13 Table. Spearman correlation of maternal biomarkers at baseline and post-supplementation during pregnancy.
(DOCX)

S14 Table. Spearman correlation of maternal biomarkers at baseline and post-supplementation at post-partum.
(DOCX)

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RESEARCH ARTICLE

A genetic approach to study the relationship between maternal Vitamin D status and newborn anthropometry measurements: the Vitamin D pregnant mother (VDPM) cohort study

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Abstract

Purpose Adverse effects of maternal vitamin D deficiency have been linked to adverse pregnancy outcomes. We investigated the relationship between maternal vitamin D status and newborn anthropometry measurements using a genetic approach and examined the interaction between genetic variations in involved in vitamin D synthesis and metabolism and maternal vitamin D concentrations on newborn anthropometry.

Methods The study was conducted in 183 pregnant Indonesian Minangkabau women. Genetic risk scores (GRSs) were created using six vitamin D–related single nucleotide polymorphisms and their association with 25-hydroxyvitamin D [25(OH)D] levels and newborn anthropometry (183 infants) were investigated.

Results There was no significant association between maternal 25(OH)D concentrations and newborn anthropometry measurements ($P > 0.05$, for all comparisons). After correction for multiple testing using Bonferroni correction, GRS was significantly associated with 25(OH)D in the third trimester ($P = 0.004$). There was no association between GRS and newborn anthropometric measurements; however, there was an interaction between GRS and 25(OH)D on head circumference ($P = 0.030$), where mothers of neonates with head circumference < 35 cm had significantly lower 25(OH)D if they carried ≥4 risk alleles compared to those who carried ≤3 risk alleles.

Conclusion Our findings demonstrate the impact of vitamin D-related GRS on 25(OH)D and provides evidence for the effect of vitamin D-related GRS on newborn anthropometry through the influence of serum 25(OH)D levels among Indonesian pregnant women. Even though our study is a prospective cohort, before the implementation of vitamin D supplementation programs in Indonesia to prevent adverse pregnancy outcomes, further large studies are required to confirm our findings.

Keywords Vitamin D · Single nucleotide polymorphisms · 25-hydroxyvitamin D · Pregnancy · Newborn anthropometry · Genetic risk score, West Sumatra

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Introduction

As one of the tropical countries in Southeast Asia located at the equator, Indonesia has an abundant sunlight all year round. According to recent studies, vitamin D deficiency in Indonesian women ranges between 60 and 95% [1–5]. Adequacy of maternal vitamin D status is important for the development of bone, teeth, immune system and general growth of the foetus [5]. Vitamin D insufficiency during pregnancy have been shown to be associated with adverse pregnancy outcomes such as small-for-gestational-age (SGA), neurodevelopment and cognitive impairment, high blood pressure in women and infants, respiratory infections, increased incidence of infants treated in neonatal intensive care unit, and health outcomes in infants such as asthma, atopic allergy, and autoimmune disorders such as type 1 diabetes mellitus [6–11].

Hereditary factors have been shown to affect 29% to 80% of serum 25-hydroxyvitamin D [25(OH)D] concentrations [11]. Candidate gene studies have identified twelve genes based on the genome-wide association studies (GWAS) for 25(OH)D *(GC, CYP24A1, CYP2R1, DHCR7)* [12], GWAS for skin colour/tanning (interferon regulatory factor 4 *(IRF4)*; melanocortin 1 receptor *(MC1R)*; oculocutaneous albinism type 2 *(OCA2)*; solute carrier family 45, member 2 *(SLC45A2)*; tyrosinase (oculocutaneous) *(TYR)*) [13–15], and candidate gene studies for vitamin D pathway genes *(VDR,* cytochrome P450, family 27, subfamily A, polypeptide 1 *(CYP27A1)*; cytochrome P450, family 27, subfamily B, polypeptide 1 *(CYP27B1))* [16]. Recent GWASs have confirmed the association of six genetic variants in the following genes *(*short/branched chain acyl-CoA dehydrogenase *(ACADSB), GC, DHCR7, CYP2R1, and CYP24A1)* with 25OHD levels [12, 17], and these variants were found near genes involved in cholesterol synthesis, hydroxylation, and vitamin D transport that affects vitamin D status. The metabolic pathways and synthesis of vitamin D are regulated by the specific genes present in the pathway and the pathway is initiated by the exposure to UVB rays (vitamin D_3) and dietary intake of vitamin D sources (vitamin D_2).

Previous GWASs [12, 17] have identified common genetic variations that influence vitamin D status in western populations; however, very few studies have investigated the influence of common genetic variations on vitamin D status in populations within Southeast Asia, especially in Indonesian population. In this study, we explored the association between maternal vitamin D status and newborn anthropometry measurements using a genetic approach. Given the high level of confounding factors that exists between maternal vitamin D status and newborn anthropometry measurements, we used genetic variants as markers of maternal vitamin D status and tested for their association with newborn anthropometry measurements as genetic associations are less prone to confounding. In addition, we also investigated whether the association between genetic variants and newborn anthropometry measurements were modified by 25(OH)D concentrations in Indonesian pregnant women from West Sumatra.

Methodology

Study population

The study was conducted among singleton pregnant women of West Sumatran Vitamin D Pregnant Mother (VDPM) cohort study in West Sumatra, from July 2017 to April 2018. The study was performed at community health centres in five cities (Padang, Pariaman, Payakumbuh, Padang Pariaman, and Lima Puluh Kota) in West Sumatra, Indonesia. In this study, participants were followed up from the first trimester (T1) to third trimester (T3) of pregnancy and at delivery to determine newborn anthropometry measurements (birth weight, birth length and head circumference). This study was conducted in accordance with the declaration of Helsinki and approved by the Ethics Committees of Medical Faculty, Andalas University (No. 262/KEP/FK/2016). All women provided written informed consent prior to the start of the data collection.

All participants were pregnant women who were recruited during their first antenatal care checks at the public health centres. Inclusion criteria included: 1) pregnant women willing to visit public health care at each site, 2) those who were in the T1 (<13 weeks) of their singleton pregnancy, 3) those who were healthy based on medical examination, and 4) those who were willing to participate by signing the informed consent and following the research procedures. Stratified random sampling was applied for the data collection that took place at two research locations: mountainous and coastal areas. Public health centers that had high numbers of the first-trimester pregnant mothers were chosen for the data collection. Women were excluded from the study if they had multiple pregnancies, some common complications of pregnancy such as preeclampsia, miscarriage or pregnancy loss, stillbirth, and they had chronic illness like diabetes, hypertension, cardiovascular disease, or hypothyroidism. Women who were taking drugs that can interfere with vitamin D metabolism such as antiepileptic agents, glucocorticoids, anti-oestrogens or antiretroviral drugs during pregnancy were excluded. Out of 239 women, 53 were dropped out for different reasons, including pregnancy loss, change of residence, not willing to continue research, and those who could not be contacted again. The number of pregnancy loss due to complications of pregnancy such as foetal inflammation, stillbirth, and abnormal foetal development was 25 (13.44%). There were

3 cases of preterm birth, 8 cases of stillbirth, and 14 cases of miscarriage. Finally, we obtained 186 pregnant women who completed all requirements and attended follow-ups from T1 to delivery. After excluding three samples due to low DNA yield, a total of 183 mother and infant pairs were used for the present study. Participant's recruitment process is shown in detail in Fig. 1.

Study Participant's characteristics

Maternal sociodemographic factors were assessed using a standardized questionnaire administered by trained field data collector (enumerator, i.e., a registered nutritionist). The questionnaire included information on demographics, maternal occupation, education, and pregnancy profile. These data were prospectively collected from medical records or interviews. Maternal sociodemographic characteristics included age, education level (primary, secondary, and tertiary levels), maternal working status (working and not working), and geographical status (mountainous and coastal area). Maternal health status included pre-pregnancy BMI, and mid-upper arm circumference (MUAC). Maternal lifestyle included the outdoor activity to measure the sun exposure status during pregnancy and maternal vitamin D and calcium supplementation during pregnancy.

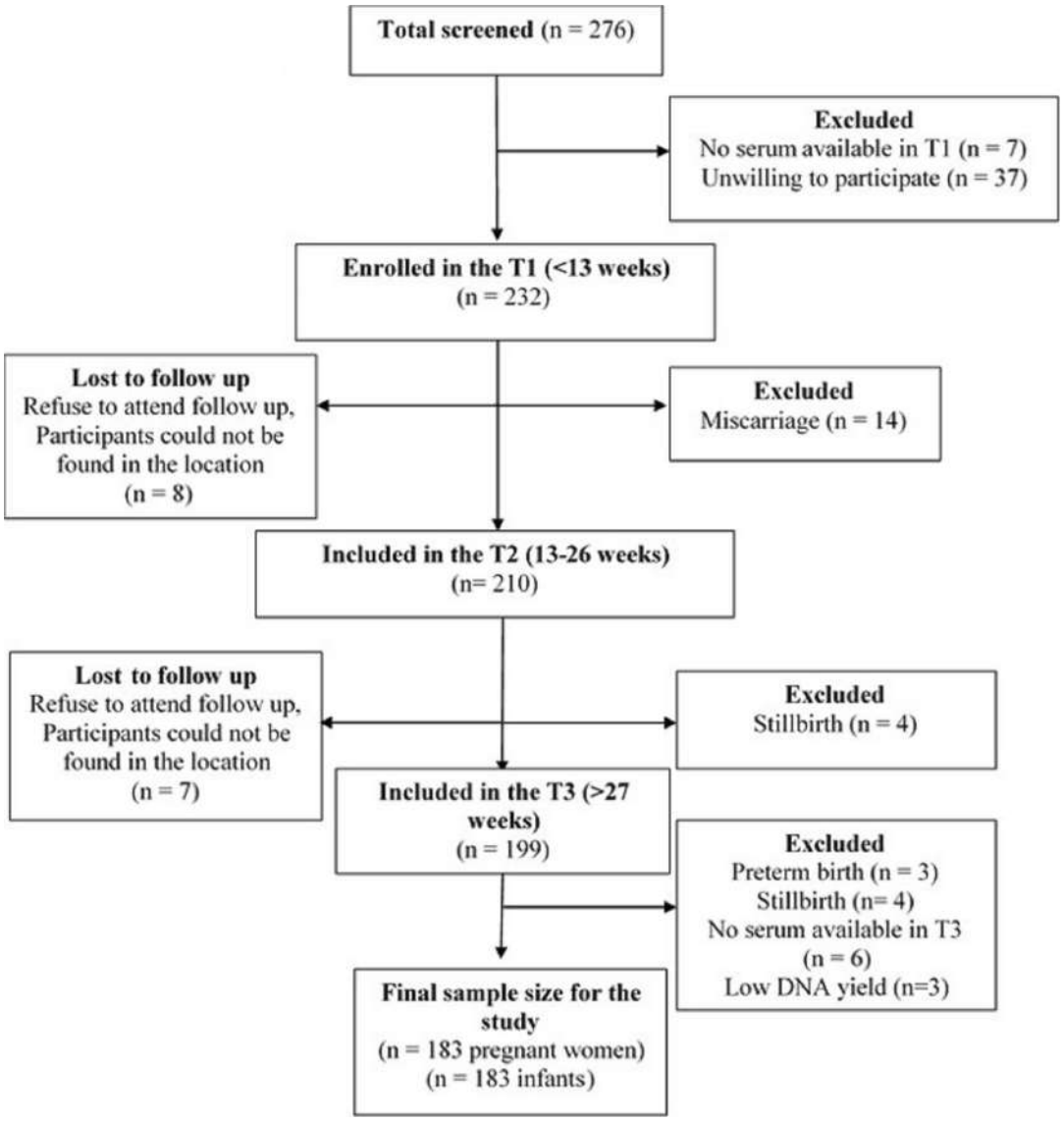

Fig. 1 Flowchart showing the selection of study participants. Pregnant women who were < 13 weeks of gestation were recruited and followed up until the delivery to determine newborn anthropometry measurements. Out of 276 women, 90 were dropped out because of pregnancy loss, change of residence, not willing to continue research, and those who could not be contacted again. Out of 186 pregnant women who completed all requirements and attended follow-ups from the T1 to delivery, three individuals were excluded due to low DNA yield and hence a total of 183 mother and infant pairs were used for analysis. T1: first trimester; T2: second trimester; T3: third trimester

Anthropometric measurements

Maternal anthropometric measurements (height, weight, and MUAC) were determined at enrolment and followed up during pregnancy. Pre-pregnancy BMI was calculated based on the height routinely measured at the clinic visit and pre-pregnancy body weight obtained at interview through maternal and child monitoring book. Maternal body weight was measured to the nearest 100 g using an electronic scale (Seca 815, Seca GmbH. Co. kg, Germany) and height was measured to the nearest millimeter using a stadiometer (Seca 217, Seca GmbH. Co. kg, Germany). The BMI calculation was based on the body weight (kg) divided by the square of body height (m). Pre-pregnancy BMI was classified according to World Health Organization guidelines for Asian populations (underweight, <18.5 kg/m^2; normal, 18.5–23.49 kg/m^2; overweight, 23.5–24.99 kg/m^2; Pre-obese, 25–29.99 kg/m^2; Obese, ≥30 kg/m^2) [18].

Measuring serum 25-hydroxyvitamin D levels

Maternal blood was collected two times under non-fasting conditions at <13 and > 27 weeks of gestation. Serum samples were stored at -70 °C until they were analyzed for 25(OH)D concentrations. Serum levels of 25(OH)D were assessed using Enzyme-linked immunosorbent assay (ELISA) from Diagnostic Biochemistry Canada (DBC) 25-Hydroxyvitamin D ELISA kit (DBC, London, Ontario Canada) and measured using xMark Microplate Spectrophotometer (Bio-Rad Laboratories Inc., Hercules, California, USA). The assay had a sensitivity of 5.5 ng/mL and an intra and inter-assay coefficient of variation of 5% and 8.1%, respectively. The vitamin D status was defined as serum 25(OH)D < 12 ng/mL (vitamin D deficient), 12–19 ng/mL (vitamin D insufficient), ≥20 ng/mL (vitamin D sufficient) according to Institute of Medicine (IOM) guidelines [19].

SNP selection and genetic analysis

We selected six candidate SNPs according to the following criteria: (1) biological importance in vitamin D synthesis, metabolism, transportation, or degradation; (2) SNPs with minor allele frequency of >5%, and (3) evidence of a significant association in previous GWASs. The selected genes were *DHCR7* (rs12785878), *CYP2R1* (rs12794714), *GC* (rs2282679), *CYP24A1* (rs6013897), and *VDR* (rs2228570 and rs7975232) [12, 17, 20] and the roles of these genes in the vitamin D cascade are shown in Supplementary Fig. 1.

Blood samples were collected from all the study participants. Genomic DNA was isolated from peripheral blood leukocytes using PureLink Genomic DNA Mini Kit (Invitrogen, Carlsbad, USA). The DNA concentration was determined using a NanoDrop spectrophotometer (Isogen Life Science, De Meern, the Netherlands). Genotyping was performed at LGC Genomics, UK (http://www.lgcgroup.com/services/genotyping). Genotype frequencies were tested against the Hardy-Weinberg equilibrium (HWE) using the χ^2 test. Genotype frequencies of all SNPs were in Hardy Weinberg equilibrium and the minor-allele frequencies of the SNPs ranged from 0.18 to 0.39 (Supplementary Table 1).

Pregnancy outcomes

Gestational age at birth was calculated from estimated gestational age examined by obstetricians or midwives using transabdominal ultrasound performed or date of last menstrual period in the absence of ultrasound at the Maternal Clinic or Hospital. Infants' birth weight, birth length, and head circumference were recorded at birth using Seca mechanical measuring scales (Seca 803, Seca GmbH. Co. kg, Hamburg, Germany). We classified newborn anthropometry status according to World Health Organization Child Growth Standards for head circumference-for-age (small head circumference, <35 cm and normal head circumference, ≥35 cm), weight-for-age (low birth weight, <2500 g and normal birth weight ≥ 2500 g), and length-for-age (short birth length, <50 cm and normal birth length, ≥50 cm) [21].

Sample size and power calculation

The sample size was calculated for investigating the association between vitamin D levels and birth weight, which was the main objective of the VDPM study. Previous study found that 13.08 ng/mL difference of maternal vitamin D level between mothers of low birth weight neonate and those of normal birth weight neonate with standard deviation ranging from 18.50 to 20.16 ng/mL [22]. The sample size was calculated using the following formula [23].

$$n = \frac{2(Z\alpha + Z\beta)^2 S^2}{(U1-U2)^2}$$

n	Sample size of each group.
Zα	Value of standard normal distribution that is equal to $\alpha = 0.05$ is 1.96.
Zβ	Value of standard normal distribution (90%) that equal to $\beta = 0.10$ is 1,28.
S	Outcome standard deviation based on the study by Khalessi et al. 2015 [23] is 18.5.
(U1-U2)	Difference of mean outcome in low birthweight and normal birthweight status (13.08)
n	2 (1,96 + 1,28)2 × 18.52/(13.08)2 = 41.96 ≈ 42.

Based on the above formula, the minimum number of samples required for each group is 42 to achieve a

statistical power of 90% to test for the association between vitamin D levels and birth weight. Hence, we aimed to recruit a total sample size with minimum of 100 participants to account for a 20% drop-out. Given that there are no studies, to date, that have examined the association between genetic variants and vitamin D levels and adverse pregnancy outcomes in Indonesia, we were unable to calculate the power for the genetic analysis. Furthermore, genetic analysis was conducted as a retrospective post hoc analysis and hence the power calculation was not performed for the genetic study.

Statistical analysis

Data were analysed using the IBM SPSS Statistics for Windows (version 23.0; SPSS, Inc., Chicago, IL, USA). Continuous variables with normal distribution were presented as mean ± SD. Categorical variables were presented as frequency and percentage. The normality of distribution of outcome variables (maternal serum 25(OH)D levels) was tested by Kolmogorov-Smirnov test.

Bivariate Pearson correlation was established to examine the correlation of serum 25(OH)D levels in the first trimester with serum 25(OH)D levels in the third trimester. A multinomial logistic regression model was used to identify the association between vitamin D status during pregnancy and newborn anthropometry status such as birth weight status, head circumference status, and birth length status. A multivariate analysis using general linear model (GLM) was conducted to determine the association between vitamin D status and newborn anthropometry. Significant factors associated with vitamin D status were entered into the GLM to adjust for covariate variables such as age, pre-pregnancy BMI, gestational age birth, infant gender, and supplement intake during pregnancy.

Genetic risk score (GRS), which was the sum of risk alleles from the SNPs rs12785878 (*DHCR7*), rs12794714 (*CYP2R1*), rs2282679 (*GC*), rs6013897 (*CYP24A1*), and rs2228570 and rs7975232 (*VDR*) [12, 17, 20], was created. Furthermore, GRS was divided into three groups as "vitamin D-GRS", "synthesis-GRS" and "metabolism-GRS". "Vitamin D-GRS" was obtained from all the six SNPs that play a role in the synthesis and metabolism of vitamin D. Two SNPs in genes encoding proteins involved in 25(OH)D synthesis (*DHCR7* and *CYP2R1*) were included in the "synthesis-GRS" [12] and four SNPs in genes encoding proteins involved in 25(OH)D metabolism (*GC*, *CYP24A1*, *VDR*) were included in the "metabolism-GRS" [20].

The effect of GRSs on 25(OH)D levels and newborn anthropometry was assessed using univariate general linear models after adjustment for potential confounders (age, pre-pregnancy BMI, geography status, vitamin D and calcium supplement consumption during pregnancy and sunlight exposure status). The associations of GRSs with vitamin D status and newborn anthropometry (birth weight, birth length, head circumferences) were analysed using logistic regression analysis. The interaction between GRS and 25(OH)D levels during pregnancy (T1 and T3) on newborn anthropometry measurements was determined by including interaction terms [GRS*25(OH)D] in the model and adjusting for age, pre-pregnancy BMI, gestational age at birth, and infant's gender. The study objectives are shown in Fig. 2.

Correction for multiple testing was performed using Bonferroni correction. Corrected *P* value for association analysis was ≤0.006 [3 GRS * 3 maternal 25(OH)D level outcomes (T1, T3, and changes in 25(OH)D during pregnancy) = 9 tests]. For the interaction analysis, corrected P value was ≤0.003 [3 GRS * 2 maternal 25(OH)D outcomes (T1 and T3) * 3 newborn anthropometry outcomes (birth weight, birth length, and head circumference) = 18 tests].

Results

Characteristic of the study population

The characteristics of the study participants stratified based on maternal vitamin D status at T1 and T3 are shown in Table 1. There was a significant difference in diastolic blood pressure (DBP), and body weight during the third trimester and there was a significant difference in outdoor activity (hours/day) during the first trimester between those who were vitamin D deficient (VDD) and those with normal vitamin D status (NVD) ($p < 0.05$). In Table 1, there was a significant difference in systolic blood pressure, bodyweight, and MUAC between T1 and T3 ($p < 0.05$, for all comparisons). Systolic blood pressure, bodyweight, and MUAC were significantly higher in T3 compared to T1. However, there was no significant difference in the levels of hemoglobin and diastolic blood pressure ($p > 0.05$, for all comparisons). The study participants were enrolled at an average age of 29.7 ± 5.68 years. The average of pre-pregnancy Body Mass Index (BMI) was 23.45 ± 4.56 kg/m^2. The average gestational duration was 38.88 ± 1.91 weeks and 73.30% of deliveries were normal. Mean birth weight, birth length, and head circumference were 3204.87 ± 494.99 g, 48.56 ± 2.87 cm, and 33.89 ± 2.52 cm, respectively. Approximately 6.80% ($n = 12$) of newborn babies had low birth weight (LBW) status, while 5.40% ($n = 10$) were diagnosed with macrosomia. There were < 10% of cases who had adverse pregnancy outcomes such as LBW, SGA, and preterm birth (PTB). However, a higher number of women had babies with a small head circumference

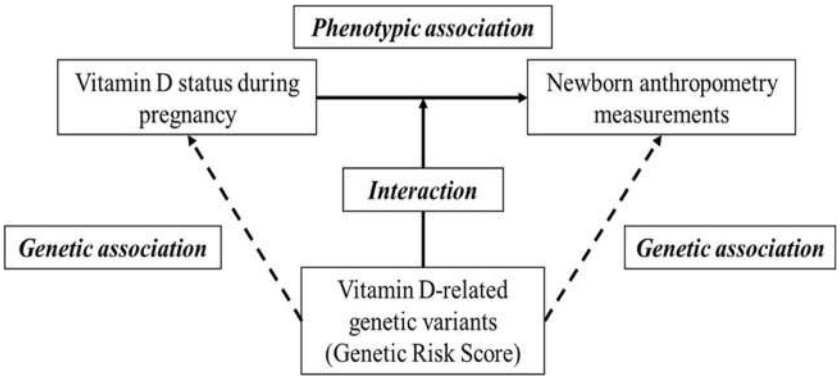

Fig. 2 Diagram representing the study objectives. Three possible associations and one possible interaction were examined. Broken lines represent genetic associations and unbroken lines represent phenotypic association and interaction between genetic risk score (GRS) and vitamin D status on newborn anthropometry measurements, respectively. Phenotypic association between vitamin D status and newborn anthropometry measurements and the genetic associations between GRS and vitamin D status and newborn anthropometry measurements were investigated

(<35 cm) and short birth length (<50 cm) (57.30% and 64.10%, respectively).

Vitamin D status during pregnancy

Average maternal serum 25(OH)D level in T1 was 14.00 ± 6.97 ng/mL. Approximately 82.80% ($n = 154$) of women were deficient (47.30%, $n = 88$) and insufficient (35.50%, $n = 66$) for vitamin D. The serum 25(OH)D levels increased significantly during pregnancy ($P = 0.0001$, R = 0.425). In the T3, average maternal serum 25(OH)D level was 21.21 ± 10.16 ng/mL. A total of 46.80% ($n = 87$) of women were vitamin D sufficient, 34.40% ($n = 64$) were insufficient and 18.80% ($n = 35$) were deficient. The prevalence of vitamin D deficiency and insufficiency in the T1 lowered from 82.80% ($n = 154$) to 53.20% ($n = 99$) in the T3.

Association between maternal Vitamin D status during pregnancy and newborn anthropometry

We found no significant association between 25(OH)D level during T1 and T3 and newborn anthropometric measurements ($P > 0.05$ for all comparisons). There was also no significant association between changes in vitamin D status during pregnancy and newborn anthropometry (P > 0.05 for all comparisons) (Table 2).

Association between GRS and serum 25(OH)D levels during pregnancy

There was a significant association between vitamin D-GRS and 25(OH)D levels in T3 (P = 0.004) and changes in 25(OH)D levels during pregnancy ($P = 0.018$), but not with T1 25(OH)D levels ($P = 0.157$). The synthesis-GRS and metabolism-GRS had no effect on 25(OH)D levels and changes in 25(OH)D levels during pregnancy ($P > 0.05$ for all comparisons). The association between GRSs and serum 25(OH)D levels during pregnancy are shown in Table 3 and Fig. 3.

Association between GRSs and newborn anthropometry

We observed no statistically significant association of the vitamin D-GRS, synthesis-GRS, and metabolism-GRS with newborn anthropometry measurements ($P > 0.05$ for all comparisons). Similar finding was observed even after classifying newborn anthropometry measurements into categorical variables (P > 0.05 for all comparisons) (Supplementary Tables 2 and 3).

Interaction between GRS and 25(OH)D during pregnancy on newborn anthropometry

None of the interactions were statistically significant except for the interaction between vitamin D-GRS and 25(OH)D concentrations in T3 on newborn head circumference measurement ($P = 0.030$). Further stratification of study participants based on head circumference cut-off points (small heads, <35 cm and normal head, ≥35 cm) [18] showed that mothers of neonates with head circumference < 35 cm had significantly lower 25(OH)D levels if they carried ≥4 risk alleles compared to those who carried ≤3 risk alleles (Fig. 4). However, after correction for multiple testing, this interaction was not considered statistically significant (Table 4).

Association between SNPs and 25(OH)D during pregnancy

Besides exploring the impact of GRS on 25(OH)D levels during pregnancy, the individual effect of the SNPs on 25(OH)D levels was also examined. Under a dominant genetic model, *ApaI* (rs7975232) SNP showed a significant association with 25(OH)D levels in both T1 (0.047) and T3 ($p = 0.043$), where A allele carriers had significantly lower 25(OH)D concentrations. In addition, A allele carriers of the *CYP2R1*

Table 1 Characteristics of study participants

Variables	T1					T3					T1		T3		
	n	VDD Status	n	NVD Status	P	n	VDD Status	n	NVD Status	P	n	Mean ± SD	n	Mean ± SD	P
Age, years	192	29.60 ± 5.51	40	30.53 ± 6.48	0.412	87	29.05 ± 5.21	99	30.36 ± 6.13	0.122					
Systolic, mmHg	192	110.94 ± 11.16	40	107.75 ± 11.87	0.124	87	111.36 ± 10.88	99	111.44 ± 9.79	0.962	186	107.08 ± 10.84	186	111.51 ± 10.26	**0.005**
Diastolic, mmHg	192	75.57 ± 7.08	40	74.63 ± 7.28	0.455	87	77.62 ± 8.61	99	75.37 ± 6.80	**0.047**	186	72.86 ± 7.36	186	76.60 ± 7.88	0.553
GA, weeks	192	9.67 ± 2.32	40	9.48 ± 2.53	0.661	87	30.49 ± 3.18	99	30.15 ± 2.93	0.442					
Hb, g/dL	192	11.62 ± 1.39	40	10.34 ± 1.15	0.180	87	10.82 ± 1.51	99	11.19 ± 1.50	0.650	186	11.58 ± 1.39	186	11.81 ± 1.36	0.413
Height, cm	192	154.51 ± 5.91	40	153.59 ± 6.47	0.409	87	154.68 ± 5.78	99	153.78 ± 6.65	0.228					
Bodyweight, Kg	192	56.61 ± 11.68	40	54.81 ± 11.70	0.380	87	63.67 ± 11.58	98	64.21 ± 10.71	**0.016**	186	56.32 ± 11.63	186	63.93 ± 11.15	**0.001**
BMI, kg/m^2	192	23.54 ± 4.37	40	23.04 ± 5.42	0.590	87	23.23 ± 4.56	99	23.77 ± 4.56	0.842					
MUAC, cm	192	27.04 ± 3.78	40	26.81 ± 3.94	0.740	87	24.65 ± 3.66	99	27.90 ± 3.82	0.994	186	27.02 ± 3.81	186	27.82 ± 3.80	**0.001**
Outdoor activity, hours/day	192	59.22 ± 51.90	40	73.88 ± 38.02	**0.042**	87	60.35 ± 48.65	99	64.31 ± 54.51	0.604					
Birth weight, g						86	3244.90 ± 469.51	98	3147.09 ± 458.73	0.155					
Birth length, cm						86	48.59 ± 3.43	98	48.53 ± 3.05	0.890					
Head circumference, cm						86	34.10 ± 2.98	98	33.55 ± 1.89	0.128					
GA at birth, weeks						86	39.08 ± 1.81	98	38.73 ± 1.94	0.209					

VDD vitamin D deficient, *NVD* normal vitamin D, *GA* gestational age, *BMI* body mass index, *25(OH)D* 25-hydroxyvitamin D, *T1* first trimester, *T3* third trimester, *MUAC* mid-upper arm circumference. Data provided are mean ± standard deviation. Bold number presented as $P < 0.05$

Table 2 Association between Vitamin D Status during Pregnancy and Newborn Anthropometry

Variables	Newborn Anthropometries		
	Birth weight (g)	Birth length (g)	Head circumference (cm)
Sufficiency ($n = 86$)	3147.09 ± 458.73	48.53 ± 2.87	33.55 ± 1.89
Insufficiency ($n = 63$)	3246.03 ± 403.14	48.86 ± 1.89	34.21 ± 1.98
Defficiency (n = 35)	3242.86 ± 576.65	48.11 ± 5.17	33.91 ± 4.25
P value	0.301	0.618	0.386

Vitamin D status during pregnancy defined based on Institute of Medicine (IOM): sufficient (≥20 ng/mL), insufficient (12–19.99 ng/mL), and deficient (<12 ng/mL) [17]

P values were adjusted for age, pre-pregnancy BMI, preterm status, vitamin D intake, sun exposure status and consumption of vitamin D and calcium supplements

(rs12794714) SNP had significantly lower levels of 25(OH)D in both T1 ($p = 0.001$) and T3 ($p <= 0.0001$). There was also a significant association between *GC* (rs22282679) SNP and 25(OH)D concentrations in T3 and changes in 25(OH)D levels during pregnancy ($P < 0.001$), but not in T1 ($P = 081$). None of the other associations were statistically significant (Supplementary Table 4).

Discussion

To our knowledge, this is the first study of its kind to investigate whether maternal vitamin D status was associated with newborn anthropometry measurements using a genetic approach. Our study demonstrated a high prevalence (82.80%) of vitamin D deficiency among Indonesian pregnant mothers. Women who had ≥4 vitamin D-decreasing risk alleles had significantly lower levels of serum 25(OH)D during pregnancy. Even though there was no direct association between GRS and newborn anthropometric measurements, mothers of neonates with head circumference < 35 cm had significantly lower 25(OH)D levels if they carried ≥4 risk alleles suggesting that vitamin D deficiency during pregnancy can increase the genetic risk of adverse newborn anthropometry outcomes. Considering that more than half of the study participants were vitamin D deficient (83%), establishing a vitamin D prevention program for pregnant women may be considered to maintain optimal foetal growth and development. Our findings, if replicated in future studies, may have a significant public health impact on initiating strategy to raise the awareness on the importance of vitamin D during pregnancy to prevent vitamin D deficiency and its adverse pregnancy outcomes.

Recent studies have shown a significant phenotypic association between serum 25(OH)D levels during pregnancy and adverse pregnancy outcomes such as gestational diabetes mellitus, pre-eclampsia, SGA, LBW and PTB [22, 24–26]. Evidence from observational studies have suggested that lower maternal 25(OH)D concentrations are associated with LBW

Table 3 Association pregnancy

Variables	25(OH)D T1 (ng/mL)		25(OH)D T3 (ng/mL)		Changes 25(OH)D (ng/mL)	
	Mean ± SD	P	Mean ± SD	P	Mean ± SD	P
Vitamin D-GRS total score*						
less than or equal 3 (n = 99)	14.77 ± 8.22	0.157	23.35 ± 10.65	0.004	8.58 ± 9.54	0.018
greater than or equal 4 ($n = 85$)	12.98 ± 5.40		18.74 ± 8.95		5.76 ± 9.50	
Synthesis GRS score**						
less than 2 ($n = 137$)	14.37 ± 7.65	0.182	21.80 ± 10.46	0.287	7.43 ± 9.64	0.724
greater than or equal 2 ($n = 46$)	12.72 ± 5.03		19.65 ± 9.06		6.93 ± 9.62	
Metabolism GRS score***						
less than or equal 3 ($n = 147$)	14.07 ± 7.55	0.655	21.63 ± 10.45	0.482	6.57 ± 9.53	0.643
greater than or equal 4 ($n = 37$)	13.44 ± 4.96		19.56 ± 8.73		6.11 ± 9.90	

Bold number indicate $P < 0.05$; 25(OH)D, 25-Hydroxyvitamin D levels; T1, First trimester; T3, Third trimester

P values were adjusted for age, BMI, vitamin D supplements, sun exposure status, and geographical status

*All six SNPs in genes involved in the synthesis and metabolism of vitamin D

**Two SNPs in genes encoding proteins involved in 25(OH)D synthesis (*DHCR7 and CYP2R1*) included in the "Synthesis score"

***Four SNPs in genes encoding proteins involved in 25(OH)D metabolism (*GC, CYP24A1, VDR*) are included in the "Metabolism score"

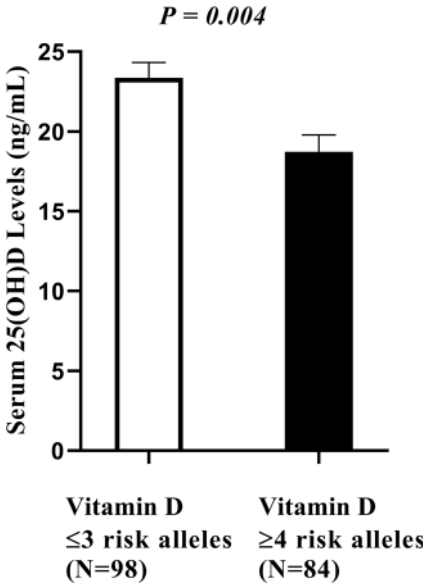

Fig. 3 Association between vitamin D-GRS and serum 25(OH)D levels in T3. Among those who carried ≥4 risk alleles had lower serum 25(OH)D levels in T3 compared to women with ≤3 risk alleles ($P = 0.004$)

[7, 27, 28]. A recent prospective cohort study in 3658 Chinese mother-and-singleton-offspring pairs demonstrated that vitamin D deficiency during pregnancy was associated with neonatal birth size and estimated to double the risk of LBW [28]. In addition, two other studies that examined serum 25(OH)D levels during pregnancy found no association between first trimester vitamin D status and neonatal length but found a significant association in the third trimester [29, 30]. However, a few studies failed to show an association between maternal 25(OH)D levels and adverse pregnancy outcomes [29, 31–33]. These inconsistencies in findings could be due to confounding by unknown factors and the differences in cut-points of vitamin D status used, sample size, population characteristics, skin pigmentation, exposure to sunlight, vitamin D supplementation and methods to measure 25(OH)D [24–26, 29, 31–35]. Given these limitations, we used a genetic approach, which is less prone to confounding, to explore the association between serum 25(OH)D levels during pregnancy and adverse pregnancy outcomes.

One of the main findings of our study was the significant association between GRS (≥4 risk alleles) and lower serum 25(OH)D levels in the third trimester ($P = 0.004$) and changes in serum 25(OH)D levels during pregnancy. Our finding was similar to a study in 759 Chinese Han pregnant women from Zhoushan Pregnant Women Cohort (ZPWC) which also showed that individuals with >3 risk alleles had significantly lower 25(OH)D levels compared to those with 1 risk allele [36]. These findings are suggestive of the fact that the vitamin D-related genetic variants might have additive or synergistic effects in influencing 25(OH)D concentrations in pregnant mothers.

Very few studies have assessed the association of vitamin D-related genotypes with 25(OH)D and newborn anthropometry (birth weight, birth length, head circumferences). A few recent studies have shown that *VDR* gene variants influence birth weight and risk for SGA in black and white women [7, 27]. A recent Mendelian randomization study has also shown that polymorphisms in vitamin D-related genes, *CYP2R1* [rs10741657] and *DHCR7* [rs12785878], were associated with LBW suggesting a causal link between maternal vitamin D deficiency and neonatal birth weight [37]. Conversely, our study found no association between GRS and newborn anthropometry measurements (birth weight, birth length, head circumferences); however, mothers of neonates with small head circumference group (<35 cm) had significantly lower 25(OH)D levels if they carried ≥4 risk alleles suggesting that vitamin D deficiency could increase the genetic risk of adverse neonatal outcomes. Our finding is in line with a previous

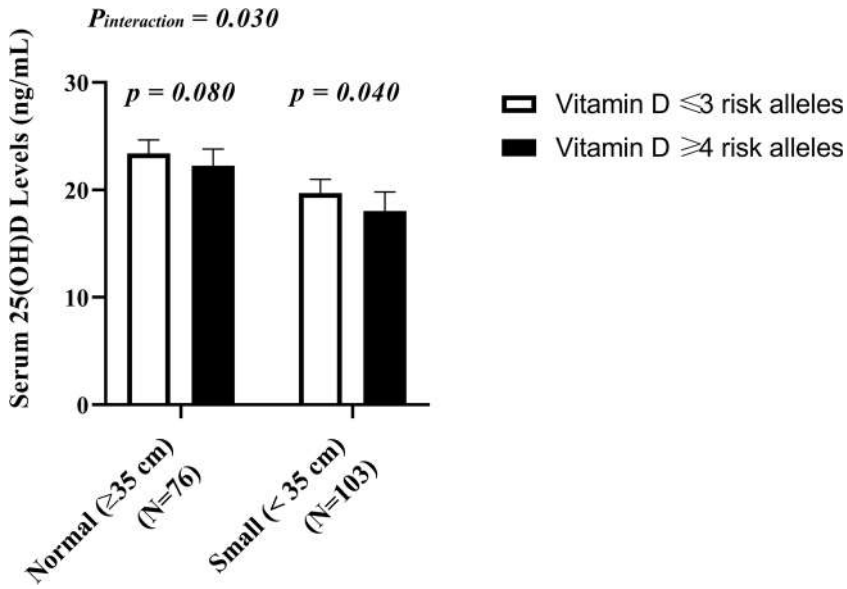

Fig. 4 Interaction between vitamin D-GRS and 25(OH)D levels in T3 (ng/mL) on Head circumference. Mothers of neonates with head circumference < 35 cm had significantly lower 25(OH)D levels if they carried ≥4 risk alleles compared to those who carried ≤3 risk alleles ($P = 0.040$)

Table 4 Interaction between GRS and 25(OH)D on Newborn Anthropometry

Interaction between the GRS and 25(OH)D T1 on newborn anthropometry measurements		
Interaction between vitamin D-GRS*25(OH)D T1 on birth weight	Interaction between vitamin D-GRS*25(OH)D T1 on birth length	Interaction between vitamin D-GRS*25(OH)D T1 on head circumference
2.72 ± 10.55	0.04 ± 0.06	0.09 ± 0.05
(0.797)	(0.510)	(0.098)
Interaction between synthesis-GRS*25(OH)D T1 on birth weight	Interaction between synthesis-GRS*25(OH)D T1 on birth length	Interaction between synthesis-GRS*25(OH)D T1 on head circumference
−0.23 ± 14.19	−0.11 ± 0.08	0.07 ± 0.07
(0.472)	(0.897)	(0.312)
Interaction between metabolism-GRS*25(OH)D T1 on birth weight	Interaction between metabolism-GRS*25(OH)D T1 on birth length	Interaction between metabolism-GRS*25(OH)D T1 on head circumference
−5.31 ± 15.85	0.121 ± 0.10	0.02 ± 0.08
(0.738)	(0.214)	(0.799)
Interaction between the GRS and 25(OH)D T3 on newborn anthropometry measurements		
Interaction between vitamin D-GRS*25(OH)D T3 on birth weight	Interaction between vitamin D-GRS*25(OH)D T3 on birth length	Interaction between vitamin D-GRS*25(OH)D T3 on head circumference
9.56 ± 6.80	0.06 ± 0.04	0.08 ± 0.03
(0.162)	(0.199)	(0.031)
Interaction between synthesis-GRS*25(OH)D T3 on birth weight	Interaction between synthesis-GRS*25(OH)D T3 on birth length	Interaction between synthesis-GRS*25(OH)D T3 on head circumference
7.39 ± 8.14	0.04 ± 0.05	0.08 ± 0.04
(0.366)	(0.426)	(0.075)
Interaction between metabolism-GRS*25(OH)D T3 on birth weight	Interaction between metabolism-GRS*25(OH)D T3 on birth length	Interaction between metabolism-GRS*25(OH)D T3 on head circumference
5.99 ± 9.16	0.04 ± 0.056	0.08 ± 0.05
(0.514)	(0.475)	(0.105)

T1 first trimester, *T3* third trimester, *25(OH)D* 25-hydroxyvitamin D

Values are beta coefficients ±standard errors. P values are provided within brackets

P values were adjusted for age, pre-pregnancy BMI, supplement consumption, gestational age at birth, and gender of the infants

study which had also shown that mothers of neonates with small head circumference (<35 cm) had significantly lower levels of 25(OH)D [22]; but the previous study did not explore the genetic susceptibility of the pregnant mothers. Future studies investigating the genetic basis of the associations between vitamin D status during pregnancy and newborn anthropometry measurements are required to confirm or refute our findings.

While most of the genetic variants chosen for our study have not been studied previously in relation to the risk of adverse pregnancy outcomes, *VDR* gene variants (rs2228570 and rs7975232) have been shown to be associated with the risk of adverse pregnancy outcomes such as PTB, LBW, and SGA status [27, 38–42]. However, there are also a few studies which failed to provide evidence for the relationship between rs7975232 (*VDR)* and PTB risk [38, 39]. We were unable to explore the association between *VDR* variants and PTB risk in the present study as the PTB variable was not available for all study participants; however, we examined other newborn anthropometry measurements such as birth weight, birth length and head circumference. *VDR* is required for the vitamin D metabolic pathway where its activation regulates the expression of genes involved in cell proliferation and differentiation [43]. Studies have shown the expression of *VDR* in placental tissues suggesting the role of vitamin D in reproduction and maternal to foetal nutrient transfer mechanism [44, 45]. Hence, the beneficial effects of vitamin D on foetal transfer mechanism can be affected by the decrease in *VDR* expression. Furthermore, it is possible that *VDR* might be a key factor in maternal to foetal nutrient transfer mechanism and adverse pregnancy outcomes and therefore serves as a strong candidate gene for our study.

The current study has some limitations. Firstly, the sample size was relatively modest; however, we were still able to identify significant associations and interactions in 183 mother and infant pairs after correction for multiple testing. Secondly, sunlight exposure variable was a self-reported outdoor activity and hence the bias involved in assessing sun exposure status cannot be ruled out. Thirdly, we have controlled for known major confounders, but we cannot completely exclude the possibility of other confounders such as the impact of vitamin D-fortified foods as this information was not collected in the present study. Compared to previous studies [1–3, 28], our study has several strengths. Firstly, the prospective cohort study analysis may reveal stable results and allows the examination of gestation-specific associations of maternal vitamin D status and newborn anthropometry. Secondly, measurements of 25(OH)D levels in different trimesters provides more information about the association between SNPs and vitamin D status during pregnancy. Fourthly, data were collected in the same season (dry season) and hence our study findings are unlikely to be affected by seasonal

variation Thirdly, study participants were enrolled from single ethnicity (Indonesian Minangkabau women), which avoids genetic heterogeneity. Lastly, this is the first study of its kind in Indonesian pregnant mothers exploring the association of maternal vitamin D status and newborn anthropometry using a genetic approach which is less prone to confounding. Future research should focus on conducting large prospective studies, Mendelian Randomization studies and clinical trials to establish the causal effect of vitamin D deficiency on adverse pregnancy outcomes.

Conclusion

In conclusion, we provide an evidence for an impact of vitamin D-related genetic variations on newborn anthropometry measurements through the influence of serum 25(OH)D levels among Indonesian pregnant Minangkabau women. Before initiating strategies for the implementation of vitamin D supplementation programs in Indonesia to prevent adverse pregnancy outcomes, further large studies are required to confirm our findings.

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Availability of data and material Data from this project will not be shared because additional results from the study are yet to be published.

Author contributions ASA carried out data collection and statistical analysis; RR carried out power and sample size calculation; ASA and KSV interpreted the data and drafted the manuscript; KSV, NIL, YY and SGM conceived, designed and supervised the study; JAL, BEA, NIL, YY and SGM helped revise the manuscript; EE assisted with data collection, monitoring and evaluation of participants, and project administration. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval and consent participate This study was conducted in accordance with the declaration of Helsinki and approved by the Ethics Committees of Medical Faculty, Andalas University (No. 262/KEP/FK/2016). All women provided written informed consent prior to the start of the data collection.

Consent for publication Not applicable.

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Pre-Pregnancy Maternal Nutritional Status and Physical Activity Levels During Pregnancy Associated with Birth Size Outcomes in Minangkabau Women, Indonesia

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Objectives: To analyse the association between maternal physical activity status and birth size outcomes and whether other determinants of confounding variable such as pre-pregnancy BMI (PP BMI) and gestational weight gain (GWG) during pregnancy affect birth size outcomes.

Methods: A prospective birth cohort study. Subject's PAL was measured at the first trimester (T1) and third trimester (T3) during pregnancy. Birth size outcomes were measured immediately after birth.

Results: The analyses included 183 mother and infant pairs with a mean newborn birth weight of 3211.75 ± 434.70 g. Pregnant women at T3 had two times lower physical activity than T1 of pregnancy (OR, 2.18; CI, 1.044–4.57; $P = 0.045$). Maternal PAL at T1 and T3 were in sedentary level (74.30% and 77%, respectively). There was no association between PP BMI and physical activity level during pregnancy. We found no significant association between PAL during pregnancy and birth size outcomes ($P > 0.05$ for all comparisons). However, we had a significant association with birth weight after our confounder adjustment ($P = 0.032$). There was a significant interaction between maternal PAL and PP BMI on birth weight and head circumference (Pinteraction < 0.05).

Conclusions: Our study provides evidence that neither maternal physical activity status nor pre-pregnancy BMI in the prenatal period are associated with birth size outcomes (birthweight, birth length, and head circumference).

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ATTACHMENT 3

Project-related Meeting Minutes

- Minute of Meeting: Sugar-Sweetened Beverages Scientific Review (19 January 2020)
- Minute of Meeting: The 4th Meeting on Sugar-Sweetened Beverages Scientific Review (12 September 2020)
- Minute of Meeting: The 68th Scientific Members Meeting on Nutritional Anemia Scientific Review (11-12 March 2020)
- Minute of Meeting: The 69th Scientific Members Meeting on Nutritional Anemia Scientific Review (28 August 2020)
- Minute of Meeting: The 70th Scientific Members Meeting on Nutritional Anemia Scientific Review (10 October 2020)

Sugar-Sweetened Beverages Meeting
19 January 2020

NO	ISSUES / ITEMS	DISCUSSIONS	NEXT STEP	PIC	DUE DATE	Status
1	ASRIM	GAPMMI cannot provide the data needed	Sent letter to ASRIM (Asosiasi Industri Minuman Rinagan)	Dhea/INA/Hilda	21-Jan-20	INA has sent a letter to ASRIM as of date 30 Jan 2020 and no feedback yet
2	Tax sugar	Need additional data on tax sugar, rafined sugar and imports	Sent Letter to AGRI (Asosiasi Gula Rafinasi Indonesia)	INA/Hilda	21-Jan-20	INA has sent a letter to AGRI as of date 30 Jan 2020 and has not yet received approval from the chairman of AGRI
3	Focus age	All population by age group		Expert team		Done
4	Target	the paper will enter Q2 because the scope of research is still national in accordance with the focus index of DIKTI		Expert team	2020	not yet
5	Sugar import trade data	data from ibu Atmarita (ILSI) about sweetness, how to import sugar year by year	Ibu Atmarita will share the data	Ibu Atmarita	22-Jan-20	not yet
6	Data SDT	Discussed SDT data that had been obtained by Prof. Ayu	compile with BPOM data that will be obtained next week by Prof. Ayu	Prof. Ayu	27-Jan-20	Not yet
7	Policy	sugar increases because there are government regulations sugar is not		Expert team		
8	Question from dr Widjaja to Ibu Atmarita	If all sugar consumption data is collected, how many percentage of simple sugar		Ibu Atmarita	21-Jan-20	Not Yet

NO	ISSUES / ITEMS	DISCUSSIONS	NEXT STEP	PIC	DUE DATE	Status
9	Recommendation from WHO	simple sugar intake recommendation does not exceed 10 of the total intake		Expert team		
10	Data Susenas	research from student's Prof. A	ask for data report from prof. ayu	Prof. Ayu	27-Jan-20	Done
11	What the result from this paper	imports and locally 2. who will consumption >> age 5 - 65 in Indonesia 3. sugar consumption from SSB, 4. health risk: country comparison with same brand (coca cola in Indonesia and abroad) 5. Characteristic SSB consumption >> socail economic, city, village, 6. Definition WHO about added sugar and sugar intake 7. Ministry of Health Regulation 2013 8. Regulation sugar tax reference to : Singapore, London, Australia 9. Cost trend (BPJS) 10. health promotion 11. PERMEN (Number 116 Year 2017) tax free 12. Increase SSB (types of beverages packaging) 13. desease	No. 12 Prof. Ayu will ask data to BPOM	Prof. Ayu and Expert team		

NO	ISSUES / ITEMS	DISCUSSIONS	NEXT STEP	PIC	DUE DATE	Status
12	Invite Prof. Bustanul Arifin From Lampung	to discuss about sugar and SSB tax	The tax is put on sugar or sweet sugar beverages because it has implications for consumers	Dr. Widjaja	next worksho	Not yet
13	Mission	proposes tax sugar based on lessons learned from developed countries and disease trends decrease Look reference from London		Expert team		
14	Title	Cannot determine because the object is incomplete	Option / while running title : 1. Trend sugar consumption in Indonesia : potential health risk : and economics burden : National health economic burden 2. The impact on SSB and health care cost 3. Tax on SSB and health care cost the tittle open discussion and take the right tittle Sometimes editors suggest titles	dr. Widjaja and expert team	21-Jan-20	Not Yet
15	Research from STAN	the impact of sugar tax free >> sugar farmers	ask journal to Prof. Ayu	Prof. Ayu	21-Jan-20	Not Yet
16	Data BPOM	Increase SSB (types of beverages packaging)	Prof. Ayu will ask data to BPOM	Prof. Ayu	27-Jan-20	Not yet

NO	ISSUES / ITEMS	DISCUSSIONS	NEXT STEP	PIC	DUE DATE	Status
17	Recommendation	Tax to Government, Public, BPOM		Expert team		

The Fourth Meeting of Special Committee: Scientific Review on Consumption of Sugar-Sweetened Beverages (SSBs) and Its Implications on Health Outcomes in Indonesia

Attendance List :

1. Dr. Widjaja Lukito
2. Prof. Ratu Ayu Dewi Sartika
3. Lindawati Wibowo
4. Prof. Saptawati Baardosono
5. Atmarita
6. M.I. Zulkarnain Duki
7. Dr. Tria Rosemiarti
8. Rizki Yusrini Pohan
9. Anindita Saraswati
10. Dewi Maryani
11. Hilda Banser

No	Issues / Item	Description	Next Step	PIC	Due Date	Status
A	Draft paper	Add reference from Prof. Ayu Can't determine the low of evidence because it has not been able to process the data	Ask Prof. Ayu to complete Must be captured that it has been learned	Linda Dr. Widjaja / Linda	14-Sep-20 14-Sep-20	Not yet
B	Sugar tax		Enter in the last paragraph	Linda	14-Sep-20 14-Sep-20	
C	Prof Tati : Socio culture	Sweet tooth first in paragraph are determinology for people who like to eat sweet Sugarcane Juice should be used by which tribe Revise Sub : The Market and patterns SSB Consumption	Linda will complete As a note in this writing change to be as note in this article	Linda Linda Linda	14-Sep-20	Done
D	Dr. Widjaja	BPOM has a supervisory role Information from Ibu Atmarita BPOM has not conduction an inspection to industry	Prof. Ayu will complete PERMEN & PERKA This paper needs to be completed with comments from Ibu Atmarita as a trigger to be informed to the government	Prof. Ayu / Linda Ibu Atmarita / Dr. Widjaja	14-Sep-20 14-Sep-20	

No	Issues / Item	Description	Next Step	PIC	Due Date	Status
E	Ibu Atmarita	This paper as a trigger for the government There is a difference with the final riskedas report	Revise figures that consume sweet - > take from riskesdas final report	Linda	14-Sep-20	Done
F	Prof. Ayu	Prof. Ayu has additional information on GGL literature and government regulations PERMEN & PERKA		Prof. Ayu / Linda	14-Sep-20	
G	Pak Zul Recommendation no. 3	Don't mention the comparison of other countries By encouraging the food and beverages industries to produce helatier product on the customer . . . because what is given is a map of Java and the center of sugar development is added to the sentence : this corresponds to a population of 70% in Java	Ex: is Cuba facing the same thing as Indonesia regarding sugar? change to produce healtier product or consuming less sugar Pak Zul will sent the Data		14-Sep-20 14-Sep-20 14-Sep-20	Done Done
H	Dr. Tria Danone's goal of this research	This paper has accommodated for Danone This paper serves as education for consumers as healtier product	Our commitment: communicate to consumers with credible scientific studies and education about sugar			Not yet

No	Issues / Item	Description	Next Step	PIC	Due Date	Status
		Danone continues to produce sugar drinks as a healthier drink alternative				
I	Dr. Widjaja Author guidline	Create this article using the APJCN journal format	Submission online at scholar one authorship includes address, zip code, phone no, email	Expert team	14-Sep-20	Done
J	Tittle	Add: It potential on health outcome	consumption of sugar sweetened beverages and its potential implication on health outcomes in indonesia	Request by Dr. Widjaja	12-Sep-20	Done

Indonesian Danone Institute Foundation

The 68th Scientific Members Meeting
11th – 12nd March, 2020

Yayasan INSTITUT DANONE INDONESIA
GIZI untuk Anak Bangsa

Discussions (1): Opening by Dr. Widjaja + Agenda

1. Review on the writing process (per year):
   - Year 2020: Review on young females and pregnant mothers, including publication + collecting data for the next review on under-five children + brainstorming research to fill the gaps on young females and pregnant mothers
   - Year 2021: Dissemination of the first manuscript + Review on under-five children, including publication + development of research to fill the gaps for young females and pregnant mothers (expected to be cohort) with available multi-years closed grants, including institutional assignment (microbiome assessments, invite MoH's involvement in the discussion, involve PhD candidates
   - Year 2022: Commencement of the research with PhD and MoH involvement
2. Discussion on whether it is possible to merge the topics of young female, pregnant mothers, and underfive children.
3. New development that needs to be discussed: To create a multi-chapter with subheadings (book), published in one supplement (e.g: TCS). --> Commission Paper. Student and staff of respective SMs are expected to help in the process. However, this will make the budget greater. Internal review will also be done. A concrete timeline may need to be created.
4. The importance of choosing what kind of journal that will publish the paper
5. Do-ability/practicability of the paper?

Discussion (2): Concern on the practicability of the Commission Paper (substance-wise)

1. Prof. Juffrie: A research team (consisted of university staff and/or students) for each topic can be formed in respective universities in order to produce the draft. A follow-up meeting shall be held afterward, in which each team is required to bring its respective research results on the assigned topics.
2. Dr. Agus: genetical aspect on anemia should be added.
3. WL: Scope of review is not limited to conventional nutritional-deficiency anemia. Disease-related anemia will also be taken into account. (refer to the outline). E.g: the relation between anemia and stunting.
4. Under recognition of causes and relations (refer to outline) to be added.
5. Research title will be reformulated after the review.

Discussion (3): Paper format (strategy)

1. Dhea: regular review paper / supplement/ special issue? -> either supplement / special issue, depending on the journal's policy.
2. Prof. Idrus: supplement usually consist of original paper. This raises a concern on whether it is possible to include review paper as a supplement. Meanwhile, special issue is not yet recognized as original paper by DIKTI. Supplement is still acceptable.
3. Prof. Juffrie: systematic review can be done to assess the relevance of the topic and to determine whether it is worth writing. The paper should be answering existing research gap. Multi-chapter is practicable so that each author is responsible for their own chapter.
4. Prof. Hardinsyah: special issue is more preferred as the journal will be easily spreaded, while book format is rather heavy and there is no guarantee on its online accessibility.
5. Each SM may work in pair with other SM and produce 2 papers.
6. It is decided the format will be in the form of special issue.

Discussion (4): Budget

1. Frontiers in Nutrition: USD 1,900 for A-type per paper. Estimated IDR 27 (exclude tax). Tax is estimated up to 20%.
2. Nutrient: 30 jt for 6 journals (special issue).
3. BMC journal: ?
4. Dhea: Based on the discussion with Dr. Tonny and Dr. Ray, there are 2 possible mechanism which will determine the budget: 1) regular 2) supplement/special issue. Pros and cons of each options should be considered. Credibility should also be taken into account.
5. Prof. Hardinsyah: Whether the budget is determined by the topics assigned to each SM? WL: Danone specialised nutrition has specify nutrition anemia. However, Indonesia is currently focusing on stunting. Nevertheless, nutritional anemia has a correlation with anemia. This can be a good basis to integrate data on stunting and nutritional anemia -> e.g. how many people with nutritional anemia are stunted.
6. The budget has been determined: IDR 800 mio for 6 papers (+ introductory)

Discussion (5): Timeline

1. Timeline: to be discussed. It depends on the deadline. Estimated time for the next meeting will be on end of June or early July (after Ied)
2. Expected starting date: April (awaiting approval from Danone)

Discussion (6): Journal Preferences

1. Regular vs Special issue
   - Downside of regular issue: journals cannot be published simultaneously as each paper submitted will be reviewed separately and it takes a much longer time.
   - Special issue can be reviewed simultaneously within 6 months - 1 year. Moreover, special issue has a better impact than regular issue.

2. Regarding Options on Journal:
   - Choosing Frontiers in Nutrition journal is quite a gamble: probability of its rating to rise in the next few years, in spite of its current status quo (have no impact factor; have yet to be included in scopus; however, expected to get its impact factor reviewed by 2020).
   - Based on scimago, Nutrients is considered as a Q1-rate journal.
   - Asia Pacific Journal of Clinical Nutrition (APJCN) journal

Discussion (7): TOPICS DISTRIBUTION and PICs:

Theme: Paradigm shift in nutritional anemia: reviewing its complexities for the future policy and strategic actions in Indonesia

1. **Background (Dr. Widjaja Lukito)**
- The magnitude of the problem in Indonesia (time, place, target/at-risk groups)
- Ongoing situation: simplification of its cause as iron-deficiency anemia
- Existing policies and implementation: iron pills, food fortification, primary health care
- Under-recognition of emerging and re-emerging causes and risk factors
- Clinical trials vs real life situations
- Objectives of the paper

2. **New insight on nutritional anemia in children and adolescent in Indonesia (Prof. Mohammad Juffrie)**
- How many under-five children with anemia are stunted, and vice versa
- Underlying mechanisms
- Evidence on nutritional intervention to overcome coexistence of anemia and stunting
- Anemia is an important indicator of poor nutrition

3. **Nutritional anemia in reproductive women and pregnant mothers in Indonesia (Prof. Indrawati)**
- Life-cycle problems
- Social determinants of anemia: roles of family and local health officers support; educational improvement
- The contribution of Indonesian women's eating habit to iron deficiency anemia

4. **Non-nutritional causes of anemia and disease-related anemia in Indonesia (Dr. Safarina dan Dr. Agussalim)**
- Genetics and epigenetics of anemia
- Anemia of inflammation
- Helminthiasis
- Infectious diseases : TB, Malaria
- Anemia and NCDs
- Social determinants of anemia: roles of family and local health officers support; educational improvement

5. **Existing policies for intervention and its implementation (Dr. Idrus J.)**

6. **Food-based approach to prevent nutritional anemia: Existing and Future (Prof. Hardinsyah)**
- Diet approach (animal food, fruit, etc.)
- Snack approach (biscuit, noodle, milk, etc.)
- Micronutrient powder (sprinkle)
- Fortification (wheat flour, noodle, sauce, soysauce, rice)
- Roles of microbiome

7. **Implications for the near future policy improvement and program implementation (tentative: Prof. Hardinsyah)**

Scientific Review on Anemia & Stunting in Indonesia: Timeline 2020

Q1 2020

Finalizing contract for each PIC (Deadline: 31 March 2020)

Q2 2020

- Finalization of first draft **(deadline: 30 June 2020)**

Independent writing process

Q3 2020

Discussion for draft improvement

- SM meeting **(2-3 July 2020)**
- Writing revision
- Finalization of second draft
- Reviving research on lactose intolerance by formulating proposal: (1) survey on lactose intolerance and (2) clinical study on lactose intolerance

Q4 2020

Discussion for final draft

- SM meeting **(8-9 October 2020)**
- Defining guest editor
- Academic editing process (proofreading)
- Submission **(target: November 2020)**

- Defining innovative research on nutritional anemia
- Designing offer for closed research grant

Scientific Review on Anemia & Stunting in Indonesia: Timeline 2021

Q1 2021

Monitoring and revising manuscript for publication process

Expectation for online publication

Q2 2021

- Defining institution to make proposal and run the closed research grant on nutritional anemia
- Defining institution to make proposal and run the closed research grant on lactose intolerance
- Drafting infographic

Q3 2021

Advocacy and socialization of nutritional anemia

- Disseminating infographic
- Advocacy and socialization to potential stakeholders

Q4 2021

- Monitoring and evaluation of research on nutritional anemia and lactose intolerance

Wrap up

1. Agreed journal form: Special issue
2. WL to send a letter to Frontiers in Nutrition and Nutrients.
3. Expected starting date of the project: early April 2020, awaiting budget approval from Danone.
4. Expected next SM meeting: end of June or early July
5. Prof. Juffrie will personally approach Dr. Ray to discuss regarding the project's budget
6. Prof. Safarina to follow up the data concerning anemia from Prof. Dr. Din Syafruddin and Dr. Alida Harahap (Thalassemia) ?

The 69th SM Meeting of Indonesian Danone Institute Foundation

28 August 2020 (19.00 – 22.00)

Attendees: Dr. Widjaja Lukito, Prof. Mohammad Juffrie, Prof. Nur Indrawaty Lipoeto, Dr. Agussalim Bukhari, Dr. Safarina G. Malik, Dr. Idrus Jus'at, Prof. Hardinsyah, Ms. Dewi Kusumastuti, Ms. Hilda Banser, Ms. Nadhila Renaldi.

Discussion on Journal Preferences

1. Dr. Widjaja has been in contact with Frontiers in Nutrition to discuss the possibility of publishing a series of nutritional anemia review articles by the Scientific Members of the Indonesian Danone Institute Foundation (SM of IDIF). Frontiers of Nutrition responded positively to the idea, stating that regional approach in a journal is also one of its interests although further discussion with its higher rank is required. This option can be an alternative to the initial plan of publishing the review articles under the Asia Pacific Journal of Clinical Nutrition (APJCN).
2. As one of the APJCN co-editors, Dr. Safarina expressed her concern over the declining quality of journal publications in APJCN and how the journal seems to be accommodating Chinese authors more lately. She considered the good and the bad for seeking other journal options. On one hand, publishing the review under Frontiers in Nutrition is deemed to be a more favorable option as it has a wider reach compared to APJCN which only covers Asia Pacific region. On the other hand, publishing under APJCN will contribute to the betterment of journal publication quality in Asia Pacific context. The latter view was also supported by Dr. Idrus. Citing journals from APJCN was highly encouraged if the SM intended to publish the review articles under APJCN.

Discussion on the Content of Review Articles

3. Dr. Widjaja's presentation - "Paradigm Shift in Nutritional Anemia: Reviewing Its Complexities for the Future Policy and Strategic Actions in Indonesia."
    - The purpose of this section is to look at nutritional anemia comprehensively so as to deliver set of policy recommendations. Based on the available literatures, fixing nutritional anemia could potentially be an acceptable strategic entry point to reduce the incident and prevalence of stunted or short stature.
    - Paper structure is as follow: a.) Introduction; b.) Anemia and nutritional anemia, where food factors would be included; c.) Nutritional anemia across the life span of Indonesians; d.) Under recognition of other causes and risk factors of anemia; e.) Nutritional anemia and covid pandemic: a time to act. This part is related to the recent publication by the Lancet concerning the relations between malnutrition and covid-19. Dr. Widjaja predicted the number of iron deficiency will increase if covid-19 case continues to rise.; and f.) how policy should be framed in the future?

4. Dr. Safarina's presentation – "Review on Non-nutritional Anemia: Malaria, Thalassemia, and G6PD Deficiency in Indonesia"
    - Dr. Safarina has been discussing with her colleagues at Eijkman Institute regarding the data intended to be used on her article review, both published and unpublished data. There are around 8,000 data on malaria in pregnant women. Therefore, it takes time to ask for permission. Unorganized data at Eijkman was also one of the obstacles in data mining process. Contributor of malaria infection and thalassemia to anemia is quate significant. She remarked the relations of G6PD deficiency to anemia is even more unique, thus important to write. Moreover, nobody in Eijkman has ever written about this topic. She planned to also include some original data in the form of table.
    - Table on risk factors of anemia among women in Sumba and Papua was shared during the meeting. These two table are important as the research was conducted specifically on pregnant women experiencing malaria (malaria pregnancy).
    - Dr. Idrus suggested to add the interaction between BMI and malaria as well as MUAC and malaria on the review.

5. Prof. Juffrie's presentation – "New Insight on Nutritional Anemia in Indonesia Children and Adolescent: A Systematic Review"
    - Dr. Widjaja reminded Prof. Juffrie to add his title to his name so as to conform with APJCN format.
    - Anemia distrupts the life cycle of children and adults in Indonesia, and is still considered as a serious public health issue. The purpose of the article review is to revisit existing research on anemia in Indonesia. This is important as many existing publications on anemia are not documented properly. In conducting the study, initial screening of 187 journals was done. Only 12 journals fit the criteria and included to the systematic review.
    - A table describing intervention approaches from each of the 12 studies is made by identifying the kind of intervention, data, findings, etc. There are 2 kinds of intervention identified from the studies: preventive intervention and therapeutic intervention. Prof. Juffrie remarked that it is difficult to conduct meta-analysis as it required raw data from each of original authors. Unfortunately, original authors are hard to contact. Prof. Hardinsyah also echoed a similar problem over meta-analysis issue, stating that unorganized data has become a problem among Indonesian scientists thus making meta-analysis hard to conduct.
    - Three discussion will be included in the review: 1.) what the Indonesian government has done so far; 2.) research on anemia prevention among children and adolescents; 3.) how the current intervention compromise with anemia prevention framework. The conclusion will answer the question on what needs to be done in the future with regards to nutritional anemia in children and adolescent in Indonesia.

6. Dr. Idrus' presentation – "Anaemia: Existing Policies for Intervention and Its Implementation"

- The objective of the review is to review policy measures and program implementation to subside iron deficiency anemia problem in Indonesia. Several related regulations are reviewed: 1.) Permenkes RI No. 88 of 2014 concerning iron folic acid (IFA) tablets standard for productive age women and pregnant mothers; 2.) Permenkes RI No. 88 of 2014 released the new technical specification for IFA tablets that was valid from 2016; 3.) Permenkes RI No. 97 of 2014 concerning health services prior to and during pregnancy; 4.) Permenkes RI No. 5 of 2016 concerning standard nutritional supplementation product.
- Based on the IFA tablets supplementation program evaluation in various areas in Indonesia, several conclusions were made: 1.) Antenatal cares were low in quality; 2.) the capacity of health personnels were low; 3.) IFA tablets program implementation did not correspond to the SOP; 4.) There are lacks of analysis, follow ups, and feedbacks from IFA tablets program reports; 5.) Insufficient facilities and infrastructures; 6.) Absence of counselling guidance, counselling material, and information media; and 7.) Inadequate IFA tablets supplies.
- The history and regulations of food fortification was also briefly explained. Dr. Idrus identified problems and potential solution to fortification program in Indonesia. national wheat flour fortification program appears to use fortification levels that are too low in relation to the wheat flour consumption patterns. Therefore, it is unlikely that a meaningful reduction in the national prevalence of iron deficiency will be achieved through this program unless current practices are changed. Furthermore, a lack of monitoring in wheat flour fortification also contributes to the failure of the program. Falsified fortification labels are reported and low-quality, unfortified wheat flour circulating in the market.
- The 2014 rice fortification for poor family pilot project (raskin) was also mentioned in the review. It is a collaboration project between the Indonesian government and Asian Development Bank (ADB) using Japan Fund for Poverty Reduction (JFPR) grant. The result of acceptance trial of fortified rice done by the SEAFAST Center of Bogor Institute of Agriculture showed that fortification did not make the color, taste, and smell of the rice different from the regular rice.
- Dr. Idrus was aware that his food fortification part might be overlapped with Prof. Hardinsyah's thus he invited everybody to give insight on whether to remove or cut a certain part.
- In respond to Dr. Widjaja's question regarding whether there is any regression data with various kinds of food fortification and evaluation data explaining the contribution of each food fortification in meeting the iron needs of Indonesian, Dr. Idrus confirmed such data is not available.
- Prof. Hardinsyah highlighted the issue of fortified wheat flour-based food in Indonesia. Aside of noodles, *gorengan* and bread are one of the most consumed wheat flour-based foods in Indonesia, with school age children as the main consumer. The existing efficacy study is focused on children. However, further evaluation on the matter has never been covered in Riskesdas anymore. Meanwhile, adults tend to lower their intake of wheat flour-based foods as they grow older. This means a

mismatch would likely occur between the existing efficacy study and the intended subject—pregnant women. Dr. Widjaja suggested to address the issue in a qualitative manner. The question on to what extend this food fortification is associated with iron supplementation in pregnant women can be left unanswered to stimulate future study.

7. Prof. Indrawati's presentation – "The Risk Factors of Iron-deficiency Anemia in Pregnant Women in Indonesia: A Meta-analysis"
    - This review is almost similar to Prof. Juffrie's. However, this review is solely focused on Indonesian publication regarding risk factors of anemia in pregnant women. Initial screening was done on 2,474 journals and only 10 journals that fit the requirement and included to the systematic review and meta-analysis. Data were obtained, among others, from Kupang, Madura, Padang, North Sumatra, Bali, Padang, and 2 hospitals located in Jakarta and Pekanbaru.
    - The analysis will examine the association between chronic energy deficiency, parity, level of education, Fe tablets consumption, and knowledge with iron deficiency anemia in pregnant women in Indonesia. Based on the analysis, chronic energy deficiency has the highest odd ration for iron deficiency risk factors, followed by parity, level of education, Fe tablets consumption, and knowledge. While age is not associated with iron deficiency anemia. Therefore, the study confirmed the role of knowledge and chronic energy deficiency with iron deficiency anemia in pregnant women in Indonesia.

8. Prof. Hardinsyah's presentation – "Food-based Approach to Prevent Nutritional Anemia in Indonesia: Existing and Future Programs"
    - The paper will discuss 4 topics: food-based/diet approach, food fortification, food supplement/iron supplementation, and microbiome/good bacteria. The review will cover what the government has done, strengths and weaknesses, and suggestion to improve the current policy.
    - Diet Approach: dietary guideline in Indonesia has changed overtime. Ten years after Indonesia's first dietary guideline in 1996, Puslitbang Gizi of Kemenkes realized that the message on the guideline was hard to be understood by commoners as it was not communicative enough. The current guideline on balanced diet recommends people to consume, among others, enough fruits and vegetables as well as source of proteins. While the current guideline is considered better, apparently there are no study to understand how well Indonesian people can understand the message and whether the guidelines affects the behaviour in society.
    - Prof. Hardinsyah highlighted the limitation of Riskesdas evaluation on nutritional anemia. There is no anemia evaluation in female adolescent and children as all the data is merged into one account—Productive Age Women. This makes the evaluation of nutritional anemia in both children and pregnant women in Indonesia hard to conduct.

- Food Fortification: assistance from CIDA and UNICEF to procide fortificant premix marked the beginning of the history of food fortification. The basic clinical evidence for this program was a clinical study among school girls in Tangerang. The result showed improvement over three years, with anemia prevalence dropping from 37% to 12%. With regards to the concern over an overlapping discussion between this section and Dr. Idrus', Dr. Widjaja suggested to keep both sections as the overlapping issue does not necessarily significant—Prof. Hardinsyah's focus is on evidence based, while Dr. Idrus' on policy analysis.
- Iron Supplementation: many subjects refuse to take iron supplementation due to its taste and side effect—nauseous, discolored stool, dizziness, etc. Despite of the iron supplementation project has been running for almost half a century, the Indonesian government has not done anything in order to increase the reception of the program. Meanwhile, the purchase of iron supplementation procurement is always done every year.

9. Dr. Agussalim's presentation – "Non-Nutritional Causes of Anemia and Disease-related Anemia in Indonesia: The Role of Non-communicable Diseases and Helminthiasis in Anemia"
    - The review structure is as follow:
        - Anemia of inflammation: 1.) definition; 2.) pathomechanism; 3.) clinical manifestation; 4.) prevalence of anemia of inflammation in the world; 5.) prevalence of anemia of inflammation in Indonesia; 6.) prevalence of diseases associated with anemia inflammation in Indonesia (type 2 DM, CKD, CVD, obesity, rheumatoid arthritis, SLE, asthma, COPD, cancer).
        - Anemia in helminthiasis: 1.) patomechanism; 2.) clinical manifestation; 3.) prevalence of anemia in helminthiasis in the world; 4.) prevalence of anemia in helminthiasis in Indonesia; 5.) Prevalence of helminthiasis in Indonesia. Dr. Widjaja offered to share data on the prevalence of helminthiasis and its association with anemia as he had previously conducted similar study.
    - A dataset table explaining the role of polymorphism in nutrigenomic patients' genes was shown during the presentation. Of the 38 samples, 60% are at risk for low iron status. There are genetic factors that influence anemia. B12 levels, B6, and folic acid are also influenced by genetic factors. Dr. Safarina reminded to omit patients' name to avoid code of ethics violation. She further suggested to use genetics modelling to examine the risk factors.
    - A systematic review table explaining data on prevalence of anemia in non-communicable disease/anemia was shown. The majority of journals used for this table were published locally. Only cross-sectional data would be included as Dr. Agussalim intended to examine the prevalence of anemia in several chronic diseases such as UTI in children, TB, DM, and obesity. Despite difficulty in accessing data, further additional data in Indonesia would be added to the systematic review soon.
    - Anemia in helminthiasis would be soon added to the text, along with a brief explanation of genetics and epigenetics of anemia.

The 70th SM Meeting of Indonesian Danone Institute Foundation

10 October 2020 (08.00 – 12.00 WIB)

Attendees: Dr. Widjaja Lukito, Prof. Mohammad Juffrie, Prof. Nur Indrawaty Lipoeto, Dr. Agussalim Bukhari, Dr. Safarina G. Malik, Dr. Idrus Jus'at, Dr. Tonny Sundjaya, Ms. Dewi Kusumastuti, Ms. Anindita Saraswati, Ms. Hilda Banser, Ms. Keisha Marsha Tuffahati.

Excused: Prof. Hardinsyah

Summary

- A new timeline for nutritional anemia review articles has been jointly agreed upon by scientific members. Manuscripts submission is targeted on the 3rd or 4th week of October 2020, while publication is expected in late December 2020. If everything is according to the plan, online publication is expected to be available in early January 2021. Following this meeting, Dr. Widjaja would be soon in contact with Prof. Mark Wahlqvist and Prof. Duo Li of APJCN. Submitting manuscripts as a bulk was more encouraged than individual submission for practicality reasons.

- Ms. Keisha was introduced as an internal editorial for nutritional anemia review articles. She has been assigned to help with academic editing and communication with regards to journal submission and follow up.
- Scientific members were encouraged to fill in necessary administrative information, including the description of each authors' contribution.
- It was agreed that several common phrases/terms in the manuscripts e.g anaemia, thalassaemia, haemoglobin would be changed into American English since APJCN has now been influenced by American English writing. Wallace academic editing will later help with editing to ensure every manuscript has the same writing style.

Update on Prof. Juffrie's manuscript – "New Insight on Nutritional Anemia in Indonesia Children and Adolescent: A Systematic Review"

- Grammatical correction, completion of administrative information including copyright form, and adjustment to references according to Vancouver style have been done. There are no significant substantial changes to the manuscript. The manuscript is mainly ready to be submitted to Wallace academic editing.
- Some minor corrections/verifications with regards to formatting were required:
  - Journal acronyms on the reference to be checked on the international list of journal publications.
  - Check the English translation of Riskesdas: Basic or Baseline Health Research?
  - Table title to be repeated in each of the new pages and should be adjusted to APJCN requirement (no line in the center).
  - Check whether subsection in the abstract is allowed. Based on a previous publication (Tanjungsari Cohort Study), this is allowed.
- Ms. Anindita conveyed an input from Danone: what refers to as in-depth analysis (line 365) should be made clear. E.g. study in the last 10 years, new insight, etc. Prof. Juffrie explained that in-depth analysis on the qualitative study is needed, especially in the last 5 years as it would be different. In-depth analysis is needed to examine imbalance between research results (data) and anemia cases found in society (facts). Later, Prof. Juffrie remarked that the answer can be found in Prof. Idrus' manuscript.

Update on Dr. Idrus' manuscript – "Anaemia: Existing Policies for Intervention and Its Implementation"

- The manuscript was deemed important as it highlighted historical elements in food fortification in Indonesia.
- Dr. Idrus and the team will make a glossary for all Indonesian terms and abbreviations.
- Initially, Ms. Nadiyah, one of the authors, was assigned as the corresponding author to enrich her experience and credibility in journal publication. Considering legal obligation as a corresponding author, making Ms. Nadiyah as the corresponding author was not encouraged as the contract for nutritional anemia is only between IDIF and Dr. Idrus. It was then agreed that Dr. Idrus would be the corresponding author.
- Some corrections/verifications with regards to formatting were required:
  - Check the English translation of Riskesdas: Basic or Baseline Health Research?
  - All footnotes should be placed after punctuation marks.
  - Clarification of the sentence concerning iron tablets received by teenage girls in a program is needed (line 237). Dr. Idrus remarked that teenage girls were supposed to receive iron tablets for 7 days during their period for one year (52 weeks). Therefore, it should be 7 x 12 tablets.
  - English translation of Kementerian Negara Urusan Pangan (=State Ministry of Food Affairs) to be checked (line 318).

- Clarification on the historical context of food fortification explaining re-implementation of wheat flour fortification (line 339) is needed. The sentence was temporarily changed into "after going through several inter-ministerial consultations, SNI wheat flour fortification was re-implemented in 2009."
- Clarification on line 336 is needed. Prof. Widjaja suggested mentioning monopolization by *Komisi Persaingan Usaha* that led to a higher price. The background story, as explained by Dr. Idrus, was started when an importer from India intended to enter the Indonesian market but hindered due to the requirement to fulfill SNI standard.
- Clarification on wheat-flour food labels examination conducted by authors (Line 398) should be done. This has been paraphrased. However, the final sentence would be the authors' decision to make.

- As vegetable oil is widely consumed by children and adults in Indonesia, authors recommended vegetable oil as a prospective fortification vehicle in the future. However, a feasibility study is still needed.

Update on Prof. Indrawaty's manuscript – "Paradigm Shift in Maternal Nutritional Anemia: Reviewing Its Complexities for the Future Policy and Strategic Actions in Indonesia"

- The review confirms two main contributing factors to anemia in pregnant women in Indonesia: knowledge and chronic energy deficiency.
- The discussion section has not been completed. However, two main topics would be discussed: Current situation of nutritional anemia in Indonesia; Future policies and strategic actions. Prof. Indrawaty would finish this within the following 1-2 weeks.
- Some corrections/verifications with regards to formatting were required:
  - Check the English translation of Riskesdas: Basic or Baseline Health Research?
  - The paragraph setting should be double space.
  - All paragraphs explaining figures and tables should be paraphrased and given more explanation. Paragraphs should not start with "Figure…" or "Tables…" as it will can confuse the reader. Suggestion: "As illustrated in Table…"
  - Table to be formatted based on the APJCN requirement.

Update on Dr. Safarina's manuscript – "Review on Non-nutritional Anemia: Malaria, Thalassaemia, and G6PD Deficiency in Indonesia"

- Paragraph 2 is still awaiting revision from Dr. Din and Dr. Alida. This is because explanations of hemoglobin concentration as a common parameter and anemia classification have not been discussed in a detailed manner.
- Dr. Alida will add on the following:
  - In the anemia and thalassemia section, an explanation of hb variant and the high prevalence of carrier in equatorial archipelago due to the many kinds of mutations will be added.

    - Interaction between α and β thalassemia until the emergence of anemia will be added.
- Description of malaria condition in Asia and Africa will be updated by Dr. Din as it was deemed not up to date. Overall, the section has comprehensively explained many kinds of malaria. The cause of severe malaria has not been included as data regarding massive RBT destruction needs to be included.
- The quality of the figure used in the manuscript is low. A higher resolution version will be updated later.
- Prof. Idrus commented on weight variable in Table 3 (Predictors of anemia in G6DP deficient vs non-deficient), highlighting the notable difference of non-adjusted (insignificant) and adjusted (significant) p value of weight. Dr. Ina will check on the matter.
- Some corrections/verifications with regards to formatting were required:
    - Spelling for "Figure", check whether to be abbreviated or not.
    - Indentation in paragraphs.
    - Change UK English to American English, e.g. anaemia to anemia, thalassaemia to thalassemia

Update on Dr. Agus' manuscript – "Non-nutritional Causes of Anaemia and Disease-related Anaemia in Indonesia: The Role of Non-communicable Diseases and Helminthiasis in Anaemia"

- Dr. Agus remarked that he had been asked to email the study program regarding a permit to use data on the genetic risk of non-nutritional anemia.
- Reference in Table 2 is required.
- Data table 8 was obtained from the hospital. Dr. Idrus commented on whether the data was allowed to be used and whether Dr. Agus has the consent of the patients involved. According to Dr. Agus, usually, if the data is secondary then it can be exempted and quoted as anonymous.
- Dr. Widjaja to give the full text of Pegelow K et al. on helminthiasis in children in Sukabumi to Dr. Agussalim.
- Some corrections/verifications with regards to formatting were required:
    - Information regarding authors' contributions, emails, and addresses.
    - The paragraph should be double space.
    - Indentation settings.
    - Table adjusted to APJCN format.
    - All footnotes should be placed after punctuation marks.

Conclusion and Next Steps

- Ms. Keisha will run through all changes made in each manuscript, edit all files in accordance with APJCN author instruction, and send the updated manuscript to each author.

- All authors will finalize their manuscripts based on the discussion during the meeting and submit the final version and copyright form to IDIF by the end of next week (2nd week of October) to ensure on-time submission to Wallace academic editing and APJCN.
- Prof. Hardinsyah to be followed up.

ATTACHMENT 4

Scientific Review Publications on Anemia & Nutritional Anemia

- Final Publication of the Nutritional Anemia Scientific Review Published in the Asia Pacific Journal of Clinical Nutrition:
  1. Lukito W, Wahlqvist ML. Intersectoral and eco-nutritional approaches to resolve persistent anemia in Indonesia. Asia Pac J Clin Nutr. 2020;29(Suppl 1):S1-S8. doi: 10.6133/apjcn.202012_29(S1).01.
  2. Lipoeto NI, Masrul, Nindrea RD. Nutritional contributors to maternal anemia in Indonesia: chronic energy deficiency and micronutrients. Asia Pac J Clin Nutr. 2020;29(Suppl 1):S9-S17. doi: 10.6133/apjcn.202012_29(S1).02.
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  5. Bukhari A, Hamid F, Minhajat R, Sheryl N, Marsella CP. Non-nutritional and disease-related anemia in Indonesia: inflammation and helminthiasis. Asia Pac J Clin Nutr. 2020;29(Suppl 1):S41-S54. doi: 10.6133/apjcn.202012_29(S1).05.
  6. Nadiyah, Dewanti LP, Mulyani EY, Jus'at I. Nutritional anemia: limitations and consequences of Indonesian intervention policy restricted to iron and folic acid. Asia Pac J Clin Nutr. 2020;29(Suppl 1):S55-S73. doi: 10.6133/apjcn. 202012_29(S1).06.

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Article Submission

Submission of articles and peer review are undertaken online using Scholar One.

Original Article

Intersectoral and eco-nutritional approaches to resolve persistent anemia in Indonesia

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Anemia in Indonesia has been of concerning persistence in all age groups for some 75 years since independence. The relationships between anemia and nutrition are complex being evident with compromised general health and nutrition. Increased micronutrient intakes, especially iron and folic acid, has alleviated the problem, but encouraged nutrient-specific micronutrient interventions as attractive policy directions as if anemia were a stand-alone disease irrespective of associated disorder. Concerted action to deal with the fundamental causality has been missing. Much of the pathogenetic pathway may be nutritional, but its multifactoriality is ultimately socioecological. Given the intransigence and progression of societal and ecosystem dysfunction, it can be expected that failure to recognize their causal importance will further entrench endemic anemia. This review deliberates the practical measures taken to recognize anemia by symptomatology, food and nutrition surveys, screening (fingerpick blood), nutrition assessment, and blood loss (menstrual and faecal). It identifies vulnerable groups including premenopausal and pregnant women, children and adolescents, unwell adults, and the dependent aged. Risk settings include food insecurity, infectious disease, non-communicable disease, inheritance and epigenetics, and socioeconomic disadvantage. Underlying socio-ecological problems are livelihood, food systems, cultural habits, belief systems, and social networks and activities. With this framework, policy directions could deal more comprehensively and effectively with the socioecological complexity which underpins and limits progress towards anemia eradication at a time of intense global food and health insecurity. It will require co-operative intersectoral and eco-nutritional approaches which take into account the need for universal, sustainable livelihoods. Recommendations have been made accordingly.

Key Words: econutrition, infectious diseases, non-communicable diseases, genetics, policy development

INTRODUCTION

Anemia is still prevalent worldwide, including in Indonesia.[1-5] It accounts for widespread morbidity which may be as non-descript and under-diagnosed as fatigue or as grave as intergenerational ill-health on account of compromised pregnancy.[6-8] Consecutive 5-year Indonesian Basic Health Research reports in 2008, 2013 and 2018 showed the persistent prevalence of anemia in various at-risk people. In 2008, the prevalence of anemia was 19.7%, 13.1%, and 9.8% in adult women, men, and children, consecutively.[9] In 2008, anemia data on pregnant women could not be considered due to the small sample size. In 2013, the prevalence of anemia were 29.7% and 26.5% in under-five boys and girls; and 22.7% and 37.1% in adult women and pregnant women.[10] In 2018, the prevalence of anemia were 27.2%, 20.3%, 38.5%, and 48.9% in adult women and men, under-five children, and pregnant women consecutively.[11] Anemia affects any at-risk population, under-five children, adolescents, reproductive-age women, pregnant women, and the aged. Although national data on anemia of the aged are not available, in a selected group of urban Indonesian elderly, Juguan et al reported that anemia was common, and the prevalence was ~25% and 32% in elderly men and women, respectively.[12] Clearly, anemia with its determinants and various health and non-health consequences, contribute to significant public health problems in Indonesia.

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The understanding of erythropoietic and iron physiology and the development of improved screening and diagnostic tools now enable more accurate typing for causality.[13] Pathogenetic biomarkers now include ferritin, transferrin saturation, hepcidin and erythropoietin,[14-16] along with inflammatory markers, enabling more distinction to be made between nutrient deficiency inflammatory anemias and other underlying disease such as chronic kidney disease and, in older people, the myelodysplastic syndrome.[13] The ready availability of a medical and nutritional history, a physical examination, finger prick blood for haematocrit, haemoglobin and microscopy for red cell morphology (and smears for malaria) still go a long way towards establishing the presumptive anemia type (refer to Table 2). However, in many developing countries, including Indonesia, it continues to be regarded principally as nutritional anemia, and is further presumed to be iron-deficiency anemia.[8,13,17-23] It is understandable given that WHO indicates that iron deficiency is the most common cause of anemia globally[24] and the Global Burden of Disease (GBD) reports now refer to inappropriate food intakes as risk factors or 'iron deficiency', rather than anemia, not being a disease, but a manifestation of various diseases.[25,26] Consequently, iron supplementation has been the policy priority to alleviate anemia. Decades of this type of program with increasing budget and different levels of compliance throughout the autonomous provinces and districts across archipelago of Indonesia has not demonstrated uniformly positive outcomes.[27] Fortification and the emerging biofortification of staple foods provide promising food-based approach, but await appropriate evaluation.[27]

With the escalating prevalence of non-communicable disease (NCD) and its underlying inflammatory mechanisms, the anemia of inflammation is of increasing relevance.[28-30] Individuals with long-term pharmacotherapy for NCDs, may also suffer from chronic occult blood loss contributing to the development of anemia.[3] Likewise, the major endemic public health problems of pulmonary tuberculosis (TB) and helminthiasis, contribute extensively to the incidence and prevalence of anemia.[3,30] In a tropical country like Indonesia, the benefits and risks of iron and folate tablet supplementation programs in areas endemic for malaria and TB cannot be overlooked.[30]

The genetics and epigenetics of anemia in Indonesia and the extent to which they contribute to anemia prevalence and its inadequate rectification by intervention programs are being clarified.[31] Anemia as found in Indonesia is complex in its underlying risk factors and ultimate causality, and in its related health and non-health consequences.

Indonesia is the largest economy in Southeast Asia region and the world's 10th largest economy in term of purchasing power. In term of population, Indonesia has a huge number of populations, which is about 250 million people in 2016. This makes Indonesia as the world's fourth most populous nation. Prior to the COVID-19 pandemic, it is predicted that by 2030, Indonesia will emerge as 7 largest economy in the world with $1.8 trillion market opportunity.[32] Therefore, alleviation of anemia is the cornerstone in materializing this prediction. It is timely to call for another review of anemia and recommend a better strategic approach in formulating the near future policies.

DEFINITIONS OF ANEMIA AND NUTRITIONAL ANEMIA

Anemia is arguably not a disease, but a manifestation of net erythropoiesis based on various underlying disorders or diseases. It is not generally defined but described by hematologic biomarkers, like low hemoglobin, low hematocrit concentrations, and low red blood cell counts, unable to meet the body's physiologic needs. In Indonesian communities, anemia is often regarded as a health complaint *'kurang darah'* (lack of blood) and *'pucat'* (pale). The World Health Organization uses hemoglobin concentration to define anemia and its severity (Table 1).[33]

Several approaches have been applied to classify anemia. In the hematologic literature, morphologic evaluation of red blood cells is used to classify anemia as presented in Table 2.[34,35] By using cytometric methods, it is nowadays possible to quantify the volume and size of red blood cells, and as a substitute for microscopic blood smear analyses, although the latter has its own value in diagnosing various blood disorders. Morphologic types of red blood cells indicate the potential causes of anemia.[5,34-36]

Nutritional anemia is that seen in association with nutritional deprivation or requiring conjoint nutritional management.[37] This may be evident with chronic energy deficiency (CED),[7] sub-optimal intakes and reduced bioavailabilities of haematinic nutrients (limited dietary di-

Table 1. Haemoglobin levels to diagnose anaemia at sea level (g/L)

Population	Non-anaemia†	Anaemia‡		
		Mild[a]	Moderate	Severe
Children 6-59 months of age	100 or higher	100-109	70-99	lower than 70
Children 5-11 years of age	115 or higher	110-114	80-109	lower than 80
Children 12-14 years of age	120 or higher	110-119	80-109	lower than 80
Non-pregnant women (15 years of age and above)	120 or higher	110-119	80-109	lower than 80
Pregnant women	110 or higher	100-109	70-99	lower than 70
Men (15 years of age and above)	130 or higher	110-129	80-109	lower than 80

References[33,36]
†Hemoglobin in grams per litre.
‡"Mild" is a misnomer: iron deficiency is already advanced by the time anemia is detected. The deficiency has consequences even when no anemia is clinically apparent.

Table 2. Morphologic assessment of anemia, and its potential risk factors and causes.

Morphology of anemia	MCV	Risk factors and causes
Microcytic	MCV <82fL	Iron deficiency Anemia of inflammation (chronic disease) Thalassemias Vitamin A deficiency
Normocytic	MCV=82–98fL	Anemia of inflammation (chronic disease) Renal disease Bone marrow failure (aplastic anemia, leukemia)
Macrocytic	MCV >98fL	Folate deficiency Vitamin B12 deficiency

MCV: mean corpuscular volme.
References[5,34,35].

versity and food intake quality, vitamins, elements, essential fatty acids, and other bioactive food components),[37] excessive nutrient loss by way of the gut (malabsorption, intestinal parasitosis, atrophic gastritis), reproductive tract (menstrual loss, lactation), integument or intravascular haemolysis (inherited or acquired including malaria),[31] with inflammatory diseases (including overfatness) and in association with a wide range of chronic diseases.[30] It is responsive, at least in part, to nutrition support if an oral, enteral or parenteral portal is available and losses can be met by intake or the underlying cause addressed. Non-nutritional anemia is where none of these situations apply.

UNDER RECOGNITION OF OTHER CAUSES AND RISK FACTORS OF ANEMIA AND MISCONCEPTION OF NUTRITIONAL ANEMIA

Many stakeholders have perceived nutritional anemia to be iron-deficiency anemia. Iron-deficiency anemia has been diagnosed without the assessment of iron status. This perception obtains because iron-deficiency anemia represents about half of nutritional anemia in developing countries including Indonesia, and because iron supplementation with acceptable recipient compliance has partly improved hemoglobin concentrations,[4,7,38] and, therefore, reduced morbidity and mortality related to IDA.[39-41] However, some reports indicate that anemia associated with iron deficiency is much less than 50% in reproductive age women, especially in developing countries, where the prevalence of anemia may be >40%, with a high burden of infection and inflammation.[2,29] Meta-analysis of anemia in pregnant Indonesian women, Lipoeto et al[7] have demonstrated that chronic energy deficiency, not iron deficiency, is the key determinant of anemia. Therefore, to reduce the burden of anemia in reproductive age Indonesian women by 50% in 2030 (as stipulated by the World Health Assembly and the Food and Agriculture Organization SDGs - Sustainable Developments Goals as Target 2.2),[42] it is timely to consider other underlying causes of anemia in Indonesia like infection burden, and implement targeted intervention strategies.

Indonesia has the second highest incidence of tuberculosis (TB) after India.[43] WHO acknowledges that TB is a communicable disease that is a major cause of ill health, one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent (ranking above HIV/AIDS).Nutritional factors are involved in susceptibility to it in Indonesia.[44] Without adequate treatment, chronic TB infection leads to malnutrition with further health consequences like anemia.[45-48] In a case-control study, Karyadi et al[49] reported that ~60% of active TB patients *vs* 20% of healthy controls were anemic.[50] Anemia in TB individuals is related to inflammation as evidenced by high ferritin concentrations in TB-associated anemia,[48,51] and adequate treatment of TB, not iron supplementation, to some extent, improve the hemoglobin status. Excess of iron due to iron supplementation to active TB sufferers potentially leads to exacerbation of TB and worsen the outcome of TB since M tuberculosis scavenges iron from the host-cell transferrin-iron acquisition pathway, which enhances its growth in the alveolar macrophages.[52,53]

Malaria is highly endemic in the eastern part of Indonesia, namely East Nusa Tenggara and Papua.[31,54] It is evident in many studies that in malaria-endemic malaria, anemia, so called malaria-associated anemia, is prevalent. The pathophysiology of anemia is described by Malik et al.[31] In the eastern part of Indonesia, malaria-associated anemia may worsen anemia related to malnutrition,[1,8,9] helminthiasis,[55] and inherited disorders related to red blood cells like hemoglobinopathies.[31]

In malaria endemic areas, anemia and iron/folate deficiency seem to protect individuals against malaria infection.[31,56-59] Despite the unknown definitive mechanisms for this phenomena, available data revealed that iron supplementation to young children living in an endemic area may increase the risk of malaria-related hospitalization and mortality.[60-63] Morbidity among breast-fed infants given iron supplementats is dependent on hemoglobin concentration being greater when Hb was ≥110 g/L.[64] Reticulocytosis stimulated by iron supplementation,[64] with a younger and larger RBC population increases their susceptibility to the malarial parasite and may lead to overwhelming parasitosis, especially in infants.[63,65]

In pregnant women, malaria-associated anemia is complex. It leads to adverse pregnancy outcomes like low-birth weight due to preterm delivery and intra-uterine growth retardation, most likely caused by placental malaria.[66-68] Iron deficiency may confer protection against malaria and all-cause mortality during early childhood, while needed for optimal neurodevelopment.[57] The management of anemia in malaria-endemic areas needs

consideration of whether at-risk people have access to effective primary health care; and whether effective malaria case management is in place.[31,56,66] Malaria management and prevention arrangements must be in place prior to iron and folate supplementation. Interventions with biofortified grains and legumes, and bioavailability generated by food biodiversity, are safer and more preferable than iron and or folate supplementation. Since helminthiasis may co-exist with malaria and contribute to anaemia as well, its conjoint management is also required.[31,56,66,69]

THE NEED TO ADDRESS INTERSECTORAL AND ECO-NUTRITIONAL DESCRIPTION IN ANEMIA AND NUTRITIONAL ANEMIA

Perhaps one of the major weaknesses in many literatures on anemia and nutritional anemia of any forms, is the lack of eco-nutritional description. It has become apparent that human biology is strongly associated with its ecosystem, and, any disturbances, potentially lead to ecosystem health disorders.[71,72] As a megadiverse country, Indonesia is rich in plant foods and animal species, which support hematinic nutriture for its population. Therefore, it is fair to assume that iron- and vitamin B-rich foods are available in the daily life of Indonesian communities. In available publications of nutritional anemia, data on how background dietary patterns and consumption of iron- and vitamin B-rich foods are very limited. Consumption of varied food does not only mean consumption of iron-rich foods, but also means consumption of vitamin C-rich foods, given vitamin C enhances iron absorption. This may mean a reduction in phytate-rich foods consumption, as phytate inhibits iron absorption, but this is better managed by the inclusion of foods with phytase which retain inositol since phytate is a hexaphosphate. There is evidence that inositol is protective against metabolic disease, as in diabetic neuropathy.[72,73] This illustrates the advantage of consumption of biodiverse foods for better health outcomes.[74] (Table 3) Practical guidelines to obtain food variety scores should be developed, and the food variety check list as developed for Australians, could be developed for Indonesians.[71]

Socio-cultural factors affect food habits and dietary patterns. In many cultural contexts with patrilineal and matrilineal systems, marginal income generation, intra-household food distribution is discriminatory, with women and children getting less nutritious foods at mealtime.[75-79] In many Indonesian ethnic groups, food avoidance is traditionally practised, sometimes based on valid observation over generations; for example, pregnant mothers may not be allowed to consume fish as it is believed to cause helminth infestation. The increasingly wide use of smart phones may affect these traditions for better or worse, but provide opportunity for anemia mitigation.[80,81]

Table 3. Required food variety score to achieve dietary adequacy.

Total food variety score	Dietary adequacy
30 or more per week	Very good
25–29 per week	Good
20–24 per week	Fair
Less than 20 per week	Poor
Less than 10 per week	Very poor

The concept of dietary adequacy embraces that of essential nutrient adequacy, but also takes into account other food components and food properties.[71]

The inter-sectoral and eco-nutritional approaches enable us to deliberate practical measures taken to recognise anaemia by symptomatology, food and nutrition surveys, screening (fingerpick blood), nutrition assessment, blood loss recognition (menstrual and faecal). It identifies vulnerable groups including premenopausal and pregnant women, children and adolescents, unwell adults and the dependent aged. Risk settings include food insecurity, infectious disease, non-communicable disease, inheritance and epigenetics and socioeconomic disadvantage. Underlying socio-ecological problems are livelihood, food systems, cultural habits, belief systems, and social networks and activities (Figure 1).

ANEMIA AND THE COVID-19 PANDEMIC

Since the first two confirmed covid cases in early March 2020 in Indonesia, no decline in incidence has been in evidence before the calendar end of 2020. By mid-December 2020, there were more than 600,000 positive COVID-19 cases with the deaths approaching 20.000. The clinical syndromes of SARS-CoV-2 infection are many. The most common symptoms are fever (77%), dry cough (81%), expectoration (56%), headache (34%), myalgia or fatigue (52%), diarrhea (8%), and haemoptysis (3%). Three percent have shortness of breath on hospital admission. The median time from exposure to onset of illness is 4 days (ranges 3-5 days), and from onset of symptoms to first hospital admission is 2 (ranges 1-4) days. On hospital admission, ground-glass opacity (GGO) is the most common radiologic finding on chest computed tomography (CT) (56.4%). No radiographic or CT abnormality is found in 17.9% patients with nonsevere disease and in 2.9% of patients with severe disease. Lymphocytopenia is present in 83.2% of admissions, and of prognostic consequence for disease severity and mortality.

Anemia is an independent risk factor for adverse outcomes of community-acquired pneumonia, and this appears to apply with COVID-19 infection. Tao et al have reported that, among 222 COVID-19, patients, ~ 35% were anemic.[81] Of those who were anemic, 58% and 42% were classified as mild and moderate to severe anemia, respectively. In severe COVID-19 patients, hemoglobin concentrations is lower than those with mild COVID-19. With respect to anemia, serum iron deficiency is detected in COVID-19 patients and associated with severity and mortality. However, the relationships between iron deficiency and susceptibility to infection is moot . There is no evidence that iron supplementation in COVID-19 patients mitigates clinical progression of the disease.

The most evidence-based nutritional approach to COVID-19 and its complications, even where vaccination is available is to enhance innate immunity and to ensure the most optimal health and nutritional status compatible with physical (not social) isolation and compromised food systems.[83-85]

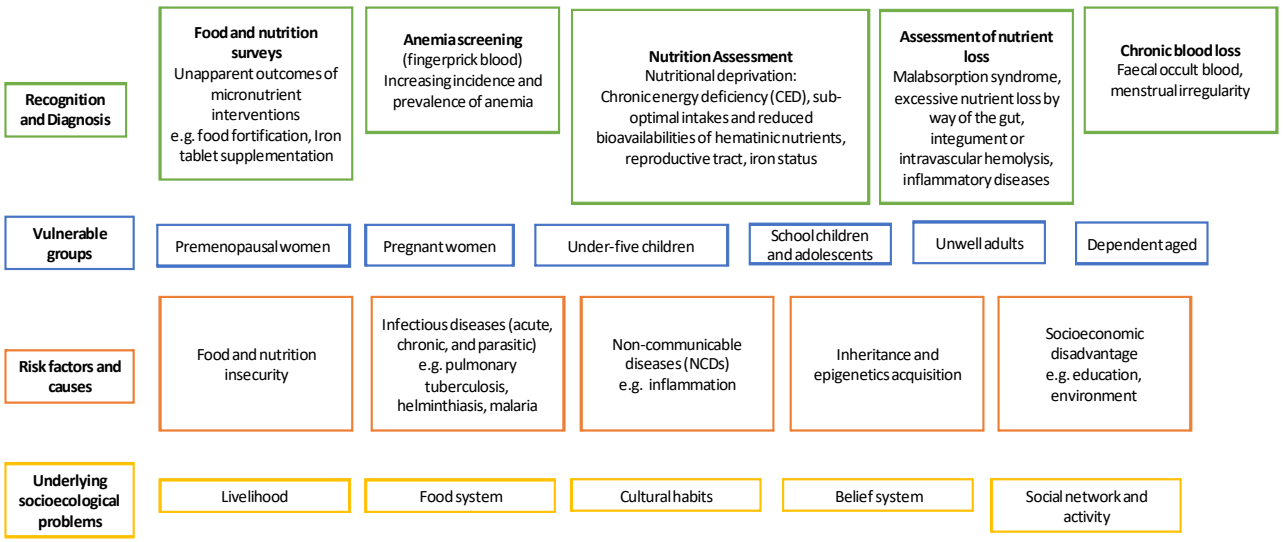

Figure 1. Conceptual framework for anemia in Indonesia.

RECOMMENDATIONS

1) Recognise that, currently, ***anemia in Indonesia remains endemic with an underlying societal and epigenetic persistence, and a co-existently high burden of TB, malaria, NCDs and other neglected diseases*** as barriers to its mitigation, which constitute an imprimatur for action.
2) Recognise that ***the endemicity of malaria and linkage with anemia is greatest in the eastern part of Indonesia***, where it is combined notably with inherited anaemias, a situation which might be more effectively addressed by socioculturally enhanced interventions and governance.
3) ***Empower local government*** which, since 2000, has had a consequential role in elevating the livelihoods of Indonesian people, to extend more effectively into the health and nutrition sectors. Intersectoral communication should be encouraged within and beyond the health and nutrition sectors.
4) Recognise that most health problems, including anemia, require a 'one package solution', albeit ecological and socio-cultural.
5) Mitigate underlying the ***root and multifactorial socio-ecological causes*** and risk factors for anemia in Indonesia.
6) Establish ***an independent national authority*** to integrate evidence-based strategies to reduce the burden of anemia in Indonesia.
7) Be ***action-orientated***, with vigilant monitoring and evaluation, and to support research in progress for better solutions. Action plans would take into account age and gender; women who are adolescent, of reproductive-age, pregnant and lactating would be specifically identified; the endemicity of infectious diseases like TB, malaria, and helminthiasis would be factored in. Biomarkers to allow the differential diagnosis of anemia would include serum ferritin to define not only iron-deficiency anemia, but also to provide an inflammatory marker together with C-reactive protein, and hepcidin, possibly in sub-samples of the target population.

The conceptual framework proposed in this review is intended to provide relevant stakeholder policy direction to deal more comprehensively and effectively with the socioecological complexity which underpins and limits progress towards anemia eradication at a time of intense global food and health insecurity. It will require co-operative intersectoral and eco-nutritional approaches which consider the need for sustainable livelihoods for all and require innovative financial arrangements, for which a consensus is evolving.[86]

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AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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Review Article

Nutritional contributors to maternal anemia in Indonesia: Chronic energy deficiency and micronutrients

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Background and Objectives: Despite enduring efforts in Indonesia to eliminate anemia in pregnancy, it remains a major nutritional problem. Its nutritional contributors were reevaluated. **Methods:** A meta-analysis of reports on anemia during pregnancy in Indonesia from January 2001 to December 2019 in the PubMed and ProQuest databases was conducted. Pooled ORs were obtained in fixed- and random-effects models. Funnel plots and Egger's and Begg's tests were used to evaluate publication bias. Review Manager 5.3 and Stata version 14.2 were used for analysis. **Results:** A total of 2,474 articles were appraised. Systematic review and meta-analysis were performed on 10 studies including 4,077 participants. Chronic energy deficiency had the highest OR for the risk of anemia (3.81 [95% CI: 2.36–6.14]) followed by greater parity (OR=2.66 [95% CI: 1.20–5.89]), low education level (OR=2.56 [95% CI: 1.04–6.28]), and limited health knowledge (OR=1.70 [95% CI: 1.17–2.49]), whereas older age and inadequate iron supplementation were not apparently associated with maternal anemia ($p > 0.05$). **Conclusion:** Future policies and strategic action to reduce nutritional anemia during pregnancy in Indonesia should increase emphasis on local nutritional epidemiology to establish the pathogenesis of anemia and the validity of stand-alone single-nutrient interventions. Attention to chronic energy deficiency as a barrier to preventing anemia in pregnancy may be necessary to enable health workers and women at risk to be better informed in their efforts.

Key Words: anemia, pregnancy, risk factors, chronic energy deficiency, policies

INTRODUCTION

Anemia is a main cause of morbidity and mortality in pregnant women worldwide. Globally, 40% of pregnant women have anemia.[1] Studies have indicated that anemia is a serious health problem among pregnant women, with a prevalence of 66.2% in Sudan, 25.2% in Northwest Ethiopia, 90.5% in Pakistan, 84.5% in India, 40.4% in Southeastern Nigeria, and 22.0% in Uganda.[2–7] The Indonesia Basic Health Research 2018 survey reported that anemia occurred in 48.9% of pregnant women and was the most common among those aged 15–24 years.[8]

The mitigation of anemia during pregnancy in Indonesia and elsewhere may be limited by the widespread assumption that anemia is primarily caused by iron deficiency despite its likely multifactorial etiology; therefore, it is managed using a single-micronutrient approach with iron supplements, excluding other contributors. Risk factors might include age, a background dietary pattern with compromised nutrient bioavailability, chronic energy deficiency, parity, education level, iron supplementation, health knowledge, prenatal care, preconception and intercurrent health status and comorbidities such as menorrhagia, inflammatory and infectious diseases, and inherited hemolytic disorders such as glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and hemoglobinopathies.[9-11] Anemia in pregnant women in Indonesia has unique risk factors that might differ from that in pregnant women in other countries.

Despite efforts to prevent maternal anemia through maternal and child health programs and iron tablet supplementation, its incidence remains high. Other unaddressed factors may play a role. A meta-analysis of available reports in Indonesia might increase understanding on the putative multifactoriality of anemia in pregnancy and inform policies and strategic actions for its mitigation.

MATERIALS AND METHODS

Study design and research sample

This meta-analysis complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement.[12] The samples in this study were

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research articles published from January 2001 to December 2019 in the PubMed and ProQuest online databases. In each study, we identified risk factors for maternal anemia in Indonesia.

Operational definitions

Independent variables in this study were risk factors for maternal anemia, and the dependent variable was maternal anemia. Chronic energy deficiency was defined as a measured mid upper arm circumference of <23.5 cm.

Research procedure

First, data were collected from published research articles that identified the risk factors for maternal anemia in Indonesia in the PubMed and ProQuest online databases (Figure 1).

The following keywords were used to search titles and abstracts in the literature: ("risk factors" OR "determinant factors") AND ("anemia") AND ("Indonesia"). A total of 2,474 articles were identified by searching the titles, abstracts, and full text of articles.

Articles were excluded if (a) maternal anemia was not an outcome, (b) they were not cross-sectional studies, or (c) they included insufficient data for extraction.

Data collection technique

Data were collected in an online search. The collected data were limited to articles published in English and In-

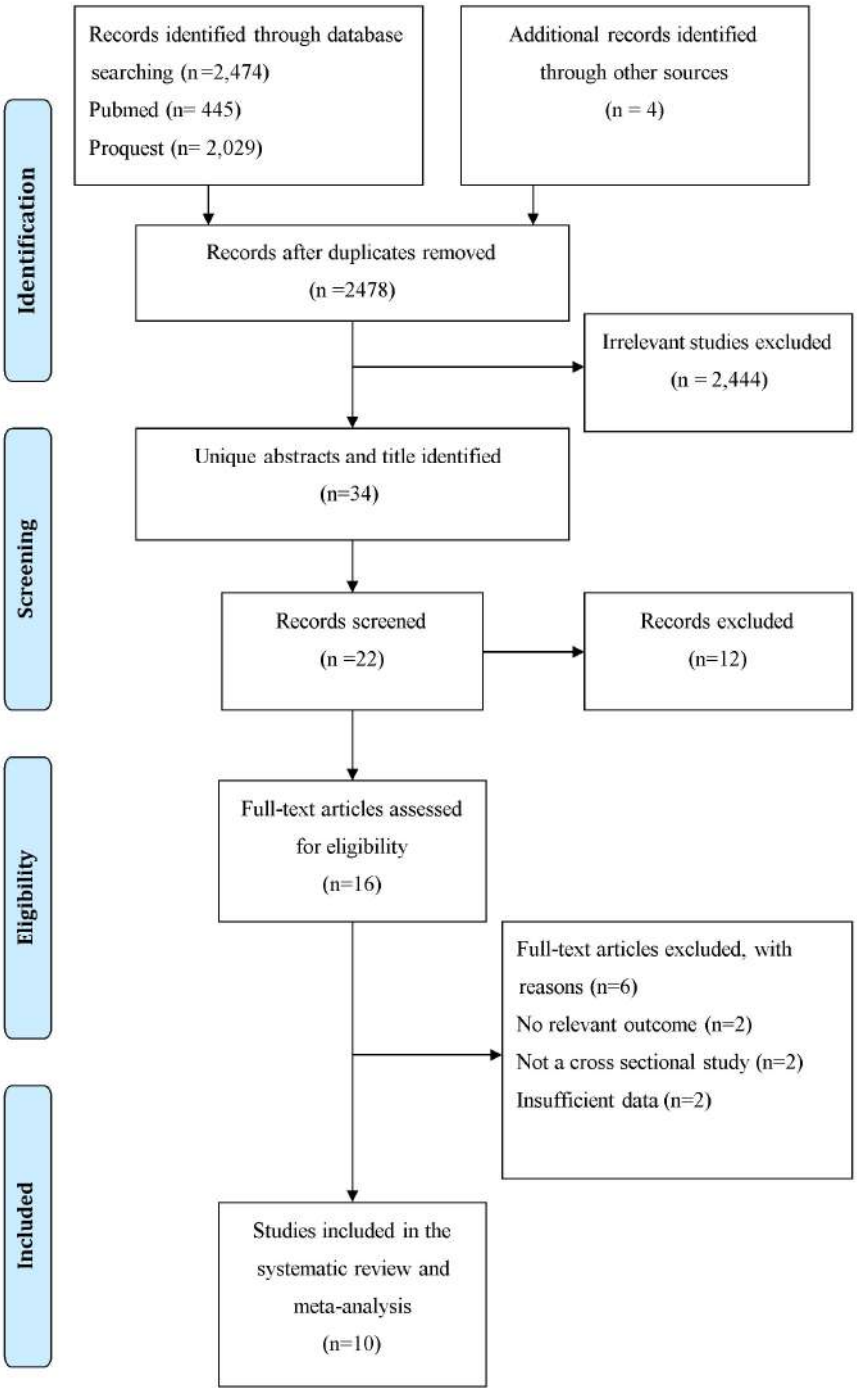

Figure 1. Publication selection protocol.

donesian that presented original research. The publication dates of articles were limited to January 2001–December 2019. Research participants were limited to humans only. Unique articles with conceivably significant titles were inspected, whereas insignificant articles were excluded. The full text of possibly significant unique articles was evaluated, after which nonessential articles were excluded. Inclusion criteria were research articles on risk factors for maternal anemia in Indonesia with a cross-sectional and observational analytical study design. Articles were excluded if (a) the inclusion criteria were non fulfilled, (b) their full text was unavailable, or (c) data provided in text were insufficient for extraction. The original author name, study location, study type, number of samples, and risk factors were also collected from the articles.

Information from all articles that fulfilled the inclusion criteria per a standardized protocol was carefully extracted by two investigators, and contradictions were settled by three different investigators. The Newcastle–Ottawa Quality Assessment Scale (NOS) was used to evaluate the quality of research articles. Articles were categorized as having poor (scores of 0–3), moderate (scores of 4–6), or high quality (scores of 7–9).[13]

Data analysis

Data analysis was conducted to obtain the pooled and combined ORs of collected articles. ORs with 95% CIs were utilized to pool results. These tests revealed articles with the minimum statistical power and small sample sizes that had significant heterogeneity (I^2 >50%). Articles with significant heterogeneity were assessed using a random-effects model, and those with homogeneity were assessed using a fixed-effects model. Review Manager 5.3 was used for data analysis. Publication bias was assessed using Egger's and Begg's tests and graphed on funnel plots. A two-tailed p value of <0.05 indicated significant publication bias. Stata version 14.2 was used to analyze publication bias.

RESULTS

Table 1 lists the results of the analysis of 10 studies including 4,077 pregnant Indonesian women evaluated for presumed maternal anemia and its potential risk factors. Covariates included older age, limited education, limited knowledge, inadequate iron supplementation, greater parity, and chronic energy deficiency.

As illustrated in Figure 2, chronic energy deficiency had the highest OR (OR=3.81 [95% CI 2.36–6.14]), followed by greater parity (OR=2.66 [95% CI 1.20–5.89]), limited education (OR=2.56 [95% CI 1.04–6.28]), and limited knowledge (OR=1.70 [95% CI 1.17–2.49]). Older age and inadequate iron supplementation were not associated with maternal anemia (p>0.05). Older age, limited education, inadequate iron supplementation, and greater parity exhibited heterogeneity in terms of the risk of maternal anemia ($p_{\text{heterogeneity}}$ <0.05; I^2 >50%), indicating variation in research on maternal anemia. Limited knowledge and chronic energy deficiency exhibited homogeneity in research on anemia ($p_{\text{heterogeneity}}$ >0.05; I^2 <50%); therefore, in population-level analyses, the results regarding these risk factors were consistent despite differences in time, place, and conditions.

Figure 3 indicates the heterogeneity of older age, limited education, inadequate iron supplementation, and greater parity in research on maternal anemia because the plot is asymmetrical about the vertical line. However, the funnel plots confirmed that limited knowledge and chronic energy deficiency were homogeneous in research on maternal anemia because the plot was symmetrical about the vertical line.

Figure 4 presents publication bias among studies on risk factors for iron-deficiency maternal anemia in Indonesia. These funnel plots were then tested using Egger's and Begg's tests (Table 2).

Table 2 indicates that Egger's and Begg's tests revealed no significant publication bias in included studies (p>0.05).

DISCUSSION

Among the prospective determinants of anemia during pregnancy in Indonesia, chronic energy deficiency had the highest OR, followed by greater parity, limited education, and limited knowledge. The Indonesian Ministry of Health has supported iron tablet distribution to pregnant mothers for generations. Baseline Health Research[24,25] reports have considered these efforts to be successful when more than 80% of mothers receive 90 iron tablets in the final trimester, but some studies have indicated that compliance with tablet consumption is low.[26,27]

Current situation of maternal nutritional anemia in Indonesia

The results of this study demonstrated the situation of iron-deficiency anemia in pregnant women in Indonesia. Systematic reviews and meta-analyses have revealed problems of low knowledge among pregnant women on maternal anemia in terms of its impact and prevention as well as chronic energy deficiency.

Limited knowledge among pregnant women on anemia prevention is evident in Indonesian Basic Health Research reports, which have demonstrated that approximately 40% of pregnant women receive information on pregnancy complications and 60% receive iron tablets usage services. Nevertheless, not all pregnant women who receive iron tablets consume them correctly, and more than 90% of pregnant women are not reached.[24,25] Moreover, iron deficiency may or may not be a cause of their anemia. Women are held accountable for managing and preventing maternal anemia even though its epidemiology and pathogenesis are inadequately understood and presumptive. The extent to which a woman's diet is sufficient, whether her iron bioavailability is questionable, and whether nutrient loss or comorbidities are present remain largely unknown, if not ignored. In reality, women in the reproductive age group and preconceptionally are ill prepared in nutritional health. They also have compromised intrapartum support services because of the narrow assessment of nutritional and nonnutritional risks.

Chronic energy deficiency in pregnant women may result from low awareness of the importance of dietary quantity and quality during pregnancy.[27] In the first trimester, pregnant women often experience nausea or vomiting with decreased food consumption, meaning that the needs of the mother and fetus are not met.[29,30] A study

Table 1. Systematic review of risk factors for maternal anemia in Indonesia

First author	Region	Study type	Patients characteristic	Sample size	Risk factors	Anemia parameter	Iron deficiency	NOS
Aji et al[13]	Padang	Cross sectional study	Women in early pregnancy	176	Socioeconomic, knowledge, Pre-pregnancy BMI status, Fe tablets consumption	Hb <11 g/dL	N/A	7
Seu et al[14]	Kupang, West Timor	Cross sectional study	Pregnant women who visited antenatal care in PHC Facilities	102	Underweight/ chronic energy deficiency	Hb <10.5 g/dL	Shine and Lal index (SLI) ≥1,530	7
Diana et al[15]	Madura	Cross sectional study	Anemic pregnant women	252	Dietary diversity	Hb <10 g/dL	N/A	7
Lestari et al[16]	North Sumatera	Cross sectional study	Not available	140	Knowledge, parity and chronic energy deficiency	Hb <11 g/dL	N/A	7
Ani et al[17]	Bali	Cross sectional study	Women with a year postpartum period	163	Parity, chronic energy deficiency	Hb <11 g/dL	N/A	7
Lisfi et al[18]	Padang	Cross sectional study	Mother's third trimester of pregnancy	44	Fe tablets consumption	Hb <11 g/dL	N/A	6
Mariza[19]	Lampung	Cross sectional study	Pregnant women who visited independent Midwifery	102	Level of education, social and economic	Hb <11 g/dL	N/A	7
Opitasari et al[20]	Two hospitals in Jakarta	Cross sectional study	Mother's third trimester of pregnancy	1,202	Parity, age	Hb <11 g/dL	N/A	7
Ristica et al[21]	Pekanbaru	Cross sectional study	Pregnant women	212	Level of education, knowledge, Fe tablets consumption, chronic energy deficiency, age	Hb <11 g/dL	N/A	7
Suega et al[22]	Bali	Cross sectional study	Not available	1,684	Educational background, Fe tablets consumption	Hb <11 g/dL	Ferritin serum <20 µg/L	7
Total				4,077				

NOS: Newcastle–Ottawa Quality Assessment Scale; articles were classified as having poor (scores of 0–3); moderate (scores of 4–6); and high quality (scores of 7–9).[12]

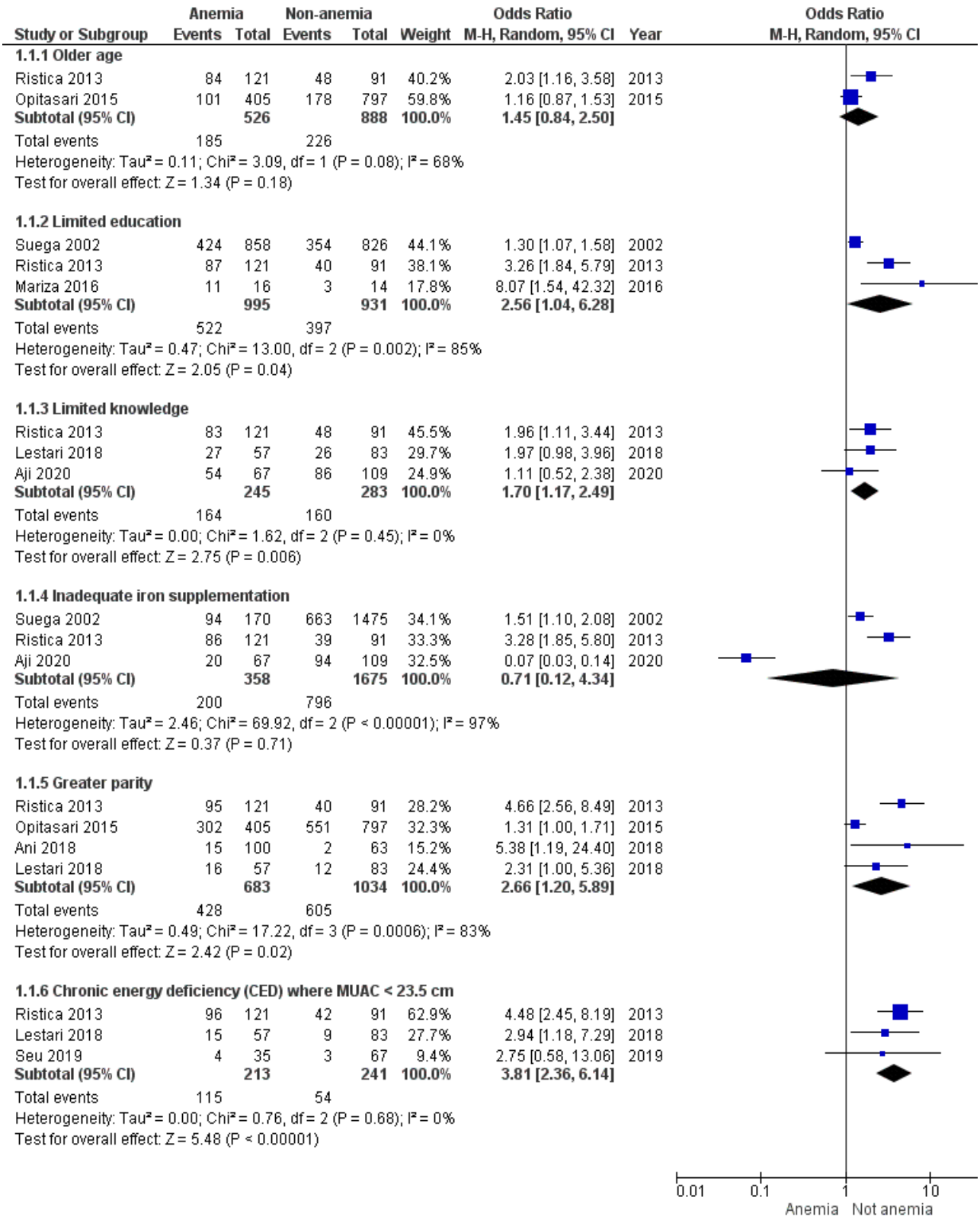

Figure 2. Meta-analysis of the likelihood of anemia in pregnancy by maternal and child clinical metrics.

conducted in West Sumatra, Indonesia,[30] reported the nutrient intake of 360 pregnant mothers, indicating that their energy intake reached only two-thirds of the RDA; their iron intake was approximately half of the RDA for Indonesian people. Although their protein intake exceeded the RDA, their intake of folic acid and fiber was more than a third of the RDA. The study also reported that the median food intake of pregnant women with chronic energy deficiency was lower than normal nutritional status for local dietary patterns. Pregnant women with normal nutritional status consumed more plant-based foods, meat, fish coconut milk, and dairy products.[31]

Chronic energy deficiency and anemia appear to be concurrent in pregnancy. A reduction in chronic energy deficiency may also reduce anemia. However, a study conducted in India[32] revealed no significant association of iron deficiency and energy intake with the risk of anemia and chronic energy deficiency. The study suggested that

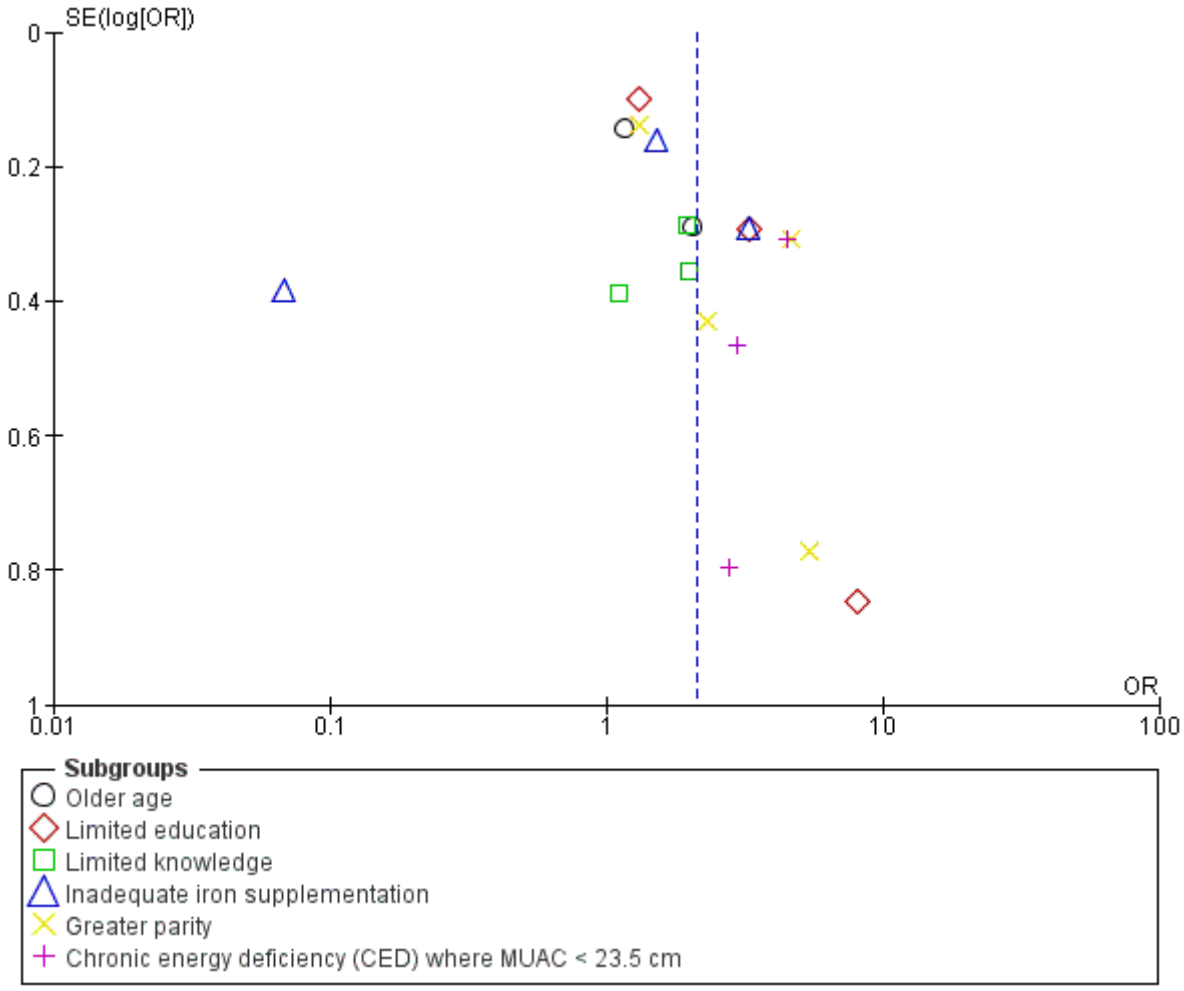

Figure 3. Funnel plots of risk factors for iron-deficiency anemia in pregnant women in Indonesia.

although diet optimization is obviously crucial for overall health, interventions that focus solely on diet may have limited efficacy in reducing the prevalence of anemia.

Prenatal care should be personalized to account for ethnicity, culture, education level, knowledge level on pregnancy, and diet. Educational efforts through increasing communication, information, and education can be used as a health promotion strategy in primary, secondary and tertiary education.[32] Information media widely used by health facilities in Indonesia tend to be conventional, namely involving counseling, brochures, and leaflets. The current rapid growth of the Internet and social media use presents an opportunity to disseminate information, increase literacy, and provide education.[33] As a result, educational content can become more engaging by utilizing interactive media; information can also be more widely shared and accessible than information shared using conventional methods.

Future policies and strategic actions

Many factors can affect the occurrence of maternal anemia, including chronic energy deficiency, iron deficiency in the diet, iron malabsorption, and the level of compliance with iron tablet consumption.[9,10] These factors are related to the knowledge of pregnant women regarding anemia and its effects and prevention methods. Knowledge is a factor that stimulates health behavior. If pregnant women understand the consequences of anemia and how to prevent it, they will exhibit favorable health behavior.[18,23] For example, the problem of nutritional anemia among pregnant women in Indonesia is related to chronic energy deficiency during pregnancy, which is caused by imbalanced nutrition of both macronutrients and micronutrients. Consequently, pregnant women are at risk of nutritional disorders. This condition occurs because pregnant women have insufficient knowledge on anemia.[14,17]

Lack of knowledge regarding anemia affects health behavior, especially during pregnancy. Consequently, pregnant women may have suboptimal health behavior to prevent anemia in pregnancy. Pregnant women who have little knowledge on anemia may not have a balanced diet of macronutrients, micronutrients, and foods containing iron because of their ignorance both before and during pregnancy.[16,21]

Knowledge regarding anemia can be increased through counseling based on the characteristics of target groups to ensure that informational materials can be accepted by all pregnant women even though their characteristics are different. For example, providing education to pregnant women with a low education level requires a different method from that used to counsel highly educated pregnant women.[34,35]

Policies that can be enacted by the government include campaigns, advocacy, education, and behavioral change communications for the prevention of anemia in pregnant

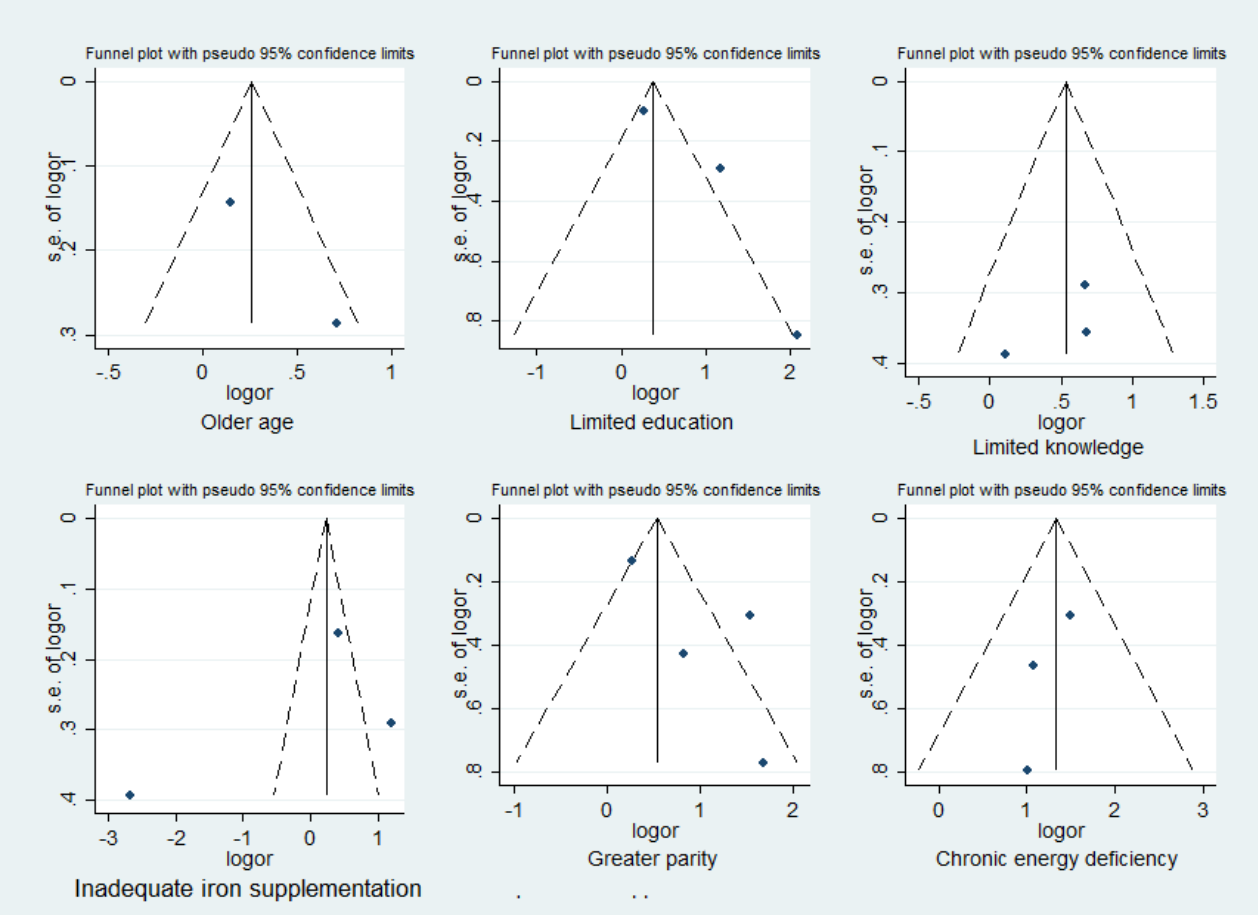

Figure 4. Publication bias for studies on the risk factors for iron-deficiency anemia in pregnant women in Indonesia

Table 2. Publication bias among studies based on Egger's and Begg's tests

Risk factors	Publication bias	
	Begg's test	Egger's test
Older age	0.317	0.310
Limited education	0.602	0.216
Limited knowledge	0.316	0.290
Inadequate iron supplementation	0.317	0.312
Greater parity	0.497	0.217
Chronic energy deficiency	0.602	0.358

p>0.05, no publication bias.

women by using innovative methods and various communication channels. These policies should be aimed at the systematic and innovative dissemination of iron anemia prevention information to pregnant women to increase awareness and community commitment. This policy strategy includes (a) involving the community, mothers, and first-level health service facilities in increasing awareness of iron-deficiency anemia prevention in pregnant women and the health benefits for both pregnant women and babies as well as pregnancy outcomes and (b) developing nutritional advocacy, communication, and mass mobilization by using clear and attractive messages tailored to specific age groups and enacting strategies that can be used by all stakeholders from the central level, namely that of the Ministry of Health of the Republic of Indonesia, to the community health level, namely first-level health facilities and independent midwives; support from organizations and all related parties can be disseminated through innovative communication channels, such as nonelectronic media and electronic social media.

Action programs to increase knowledge among pregnant women, namely in the form of campaigns, advertisements in various media, and collaboration with influential figures to promote prevention to the target audience and the wider community, can facilitate the prevention of maternal anemia. Radio and bus advertisements as well as leaflets, posters, and idol artists promoting anemia prevention in pregnant women improved anemia prevention in Ethiopia.[35] The use of posters, leaflets, and idol advertisements was effective in reducing the prevalence of maternal anemia in the Philippines.[37,38]

Apart from advertising, activities that empower communities are necessary to enable health cadres to recognize, prevent, and manage anemia in pregnant women,

thereby increasing community-based social support. Through community involvement and empowerment efforts with health cadres, support for the prevention and management of maternal anemia can increase. Community empowerment activities to prevent maternal anemia include increasing the capacity of health cadres and pregnant women in first-level health facilities through efforts to increase knowledge.

Conclusion

In Indonesia, as expected, education level, health knowledge, parity, and iron supplementation (typically with folic acid) are associated with maternal anemia. The strong association of chronic energy deficiency with maternal anemia compared with any of the other factors indicate the need for more widespread of health and food system considerations. Future strategies should engage women in the reproductive age group by using programs that optimize general health and nutrition to ensure health at conception and uncompromised fetal development throughout pregnancy.

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AUTHOR DISCLOSURES

The authors declare no conflicts of interest.

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Review Article

Nutritional anemia in Indonesia children and adolescents: Diagnostic reliability for appropriate management

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Background: Nutritional anemia in Indonesian children and adolescents is generally regarded and treated as iron-deficient anemia, as it is in individuals in other age groups. **Objectives:** Yet, it remains a public health threat without comprehensive management or a sustained solution. **Methods:** This review seeks to improve understanding of impediments to its resolution. Relevant studies reported in the past 5 years were identified in PubMed, Science Direct, Crossreff, Google Scholar, and Directory of Open Access Journals databases. **Results:** In all, 12 studies in several Indonesian cities provided the basis for the review. Most were conducted in schools, indicating the potential of these institutions as targets for intervention but pointing to serious deficiencies in identification of the problem across the archipelago and in remote and rural areas. No study has evaluated coexistent anemia and malnutrition, which likely would have revealed the multi-factoriality of nutritional anemia. Data regarding nutrition education, food-based innovation, and supplementation, which may alleviate anemia in children and adolescents, are available, although study lengths and sample sizes have limited interpretation and comparison. **Conclusions:** Broadly, three intervention approaches to nutritional anemia have been undertaken, namely food-based interventions, nutrient supplementation, and nutrition education. Some progress has been made with these approaches, presumably through increases in iron intake. More information is needed regarding the underlying causality and pathogenesis, suboptimal food patterns, and comorbidities, any of which might limit the effectiveness of programs designed to resolve childhood and adolescent anemia in Indonesia.

Key Words: multifactorial anemia, adolescent, children, Indonesia, nutritional interventions

INTRODUCTION

Nutrition-related anemia places a burden on the global public health sector, including the health care system in Indonesia.[1,2] It affects 1.62 billion people worldwide, mostly children, adolescents, and women.[3,4] In Indonesia, the Ministry of Health reported increasing prevalence of nutrition-related anemia among pregnant women, from 37% in 2013 to 48.9% in 2018. More than 80% of women aged 15–24 years are affected.[5] Children and adolescents face the same problem. In 2013, according to the Basic Health Research survey, more than 50% of Indonesian children and adolescents were anemic, consisting of 28% of children under 5 years and 26% of children aged 5–14 years.[6] A smaller study of 645 Indonesian elementary students revealed similar findings, with 27% of them being anemic. Aside from anemia, 20% had stunted growth, 14% had low weight for height, and 14% were overweight or obese.[7] Anemia often coexists with malnutrition.[8] Children with stunted growth have a 2.3-times higher risk of anemia than those without stunted growth.[9] Alzain[10] also mentioned that anemia and body height have a significant association.

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Overcoming this problem is essential because anemia can have physical, cognitive, and emotional impacts. Pollitt[11] proposed that anemia can change cerebral function during infancy, affecting the ability to learn. Other studies have mentioned that anemia during childhood has long-lasting effects on neurodevelopment, including on the auditory and visual systems.[12,13] The condition is associated with other nutritional statuses. A study conducted in Vietnam determined that malnourished children, whether underweight or wasted or with stunted growth, were more likely to be anemic.[14] A study conducted in rural China indicated that improvement in anemia status increased the cognitive function of children.[15]

The WHO proposed iron and folic acid supplementation as a strategy to prevent anemia in adolescence.[16] In Indonesia, anemia management in pregnant and adolescent women is focused on iron supplementation, often independent of other approaches. These approaches might include understanding sociodemographic and lifestyle characteristics and managing community food systems, food pattern optimization, food fortification, nutrition education, probiotic administration, menstrual irregularities, comorbidities, and inter-current infections.[17-19]

This review gathers recent reports on the occurrence, prevention, and management of anemia among young Indonesians. The focus on children and adolescents reflects the greater prevalence of poor dietary practices in this age group, the risk of post-pubertal anemia in girls, and the propensity to infection.[16] Timely preventive strategies for anemia in early life have implications for future health. Pollitt[11] advocated conducting community-based trials to find effective ways of overcoming anemia. The present review seeks to identify current weaknesses and opportunities for governments, food and health systems, and community health workers attempting to reduce the burden of nutritional anemia among young Indonesians.

METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[20]

Inclusion and exclusion criteria

The authors determined the focus of the study by using the participant, intervention, comparison, outcome (PICO) approach summarized in Table 1

The eligibility criteria consisted of experimental studies carried out in Indonesia and related to the effects of nutritional interventions on anemia and malnutrition. Children and adolescents were regarded as the study population. The studies reviewed were limited to research conducted in Indonesia and published in English or Indonesian during 2015–2020. Articles that were not primary studies (such as reviews) or not published in a journal were excluded.

Table 1. PICO approach to study selection

Participants	Indonesian children or adolescent
Interventions	Nutrition intervention (nutrition education, food-based intervention, supplementation)
Comparisons	Indonesian children or adolescent who did not receive interventions
Outcomes	Hemoglobin level, knowledge, attitude

PICO: participants, interventions, comparisons, outcomes.

Search strategy

The articles were identified through a search on the following major electronic databases: PubMed, ScienceDirect, Crossref, Directory of Open Access Journals, and Google Scholar. Search terms used included "anemia AND (children OR adolescent OR infants) AND nutrition AND Indonesia AND intervention." The search strategy was adapted according to the database. Studies reported up until July 2020 were retrieved to be assessed for eligibility.

Study selection

The authors selected articles initially by reading titles and abstracts. Rayyan, a web application for systematic reviews (https://rayyan.qcri.org/), was used to review the articles. Subsequently, the authors independently read the full texts of the selected articles. Articles were included that met the eligibility criteria of this systematic review. Any disagreements that arose among the reviewers were resolved through discussion.

Data extraction and quality assessment

The following data were extracted for analysis: author name, year of publication, study location, sample size, type of nutrition intervention, data analysis method, and findings. The quality of the selected articles was assessed using the Cochrane risk of bias assessment tool.[21]

RESULTS

The study was conducted in two stages, initial research and article review. From the initial research, a total of 198 articles were obtained from various databases. During the initial review, 161 articles were excluded because they did not meet the inclusion criteria. Another was excluded during the full-text review due to a high score of potential bias. In the end, 12 studies were included; 6 were published in English and 6 were published in Indonesian (Figure 1).

All the research was conducted in Indonesia, namely in cities on Sumatra Island (3),[22-24] in Java (6),[25-30] in Madura (1),[31] in Kalimantan (1),[32] and on Sulawesi Island (1).[33] Six studies focused on anemia prevention in adolescents, and the others focused on anemia prevention in children. Specifically, three targeted children under 5 years of age. Of these studies, 75% were conducted at a school (either a primary or a junior or senior high school). This review offers perspectives on three anemia prevention approaches, namely food-based interventions, nutrition education, and supplementation. One food-based innovation made use of local foods such as *nagara* nut (*Vigna unguiculata* subsp. cylindrica) and *haruan* fish (*Channa striata*), which are rich in nutrition and easy to obtain.[32] Five studies tested the effects of a food-based intervention or supplementation combined with nutrition education.

No study reported the effect of the intervention on the coexistence of anemia and undernutrition among the individuals involved. The study by Budiana et al[28] tested the

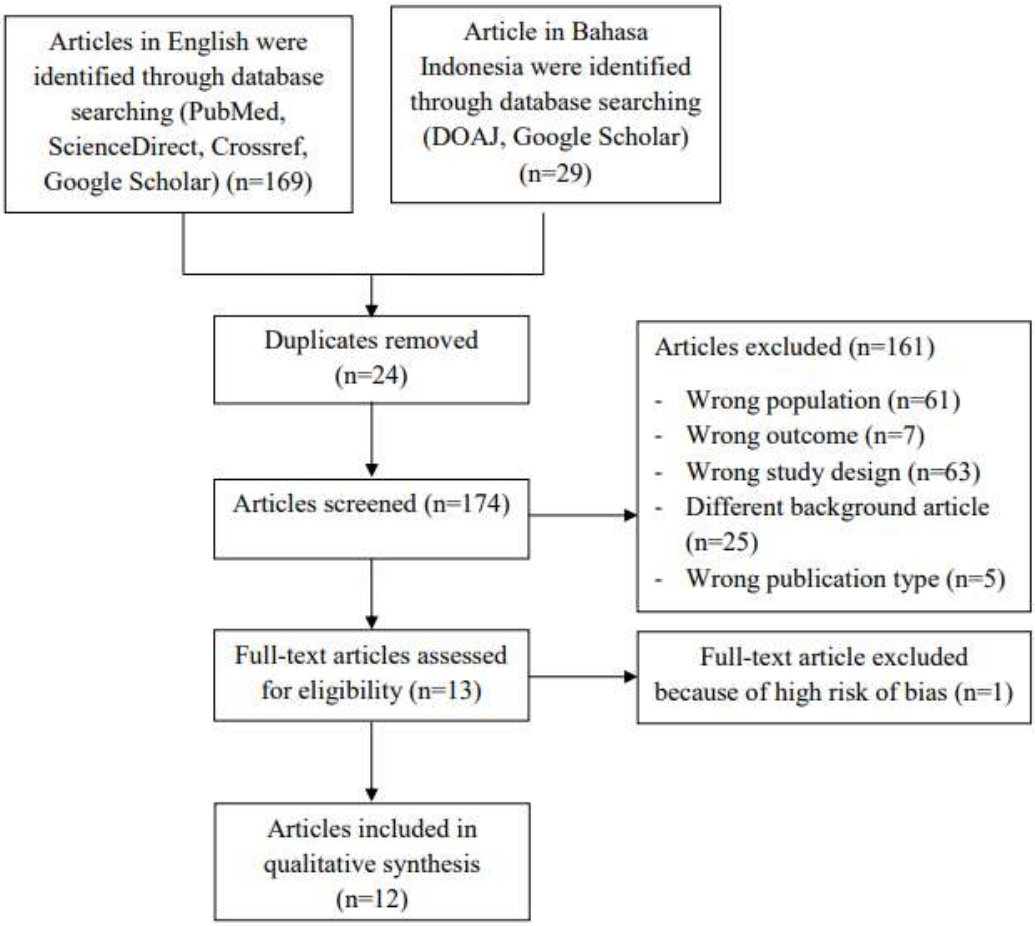

Figure 1. Information retrieval protocol.

effects of *Taburia* (a multimicronutrient powder) on hemoglobin (Hb) levels in anemic and wasted children aged under 5 years. However, the study did not report its effect on their nutritional status, only anemia. Another noteworthy study carried out by Sekiyama et al[26] investigated how a sustainable school lunch program can affect the nutritional status of children. Of the 68 participants, 32% had stunted growth, 3% were underweight, and 17% were overweight. During the program, the children received food with significant increases in protein, fat, calcium, and vitamin C, which improved the nutritional status of undernourished children. The complete results are provided in Table 2

DISCUSSION

Anemia is a major public health problem in Indonesia. The Basic Health Research report did not specify the type of anemia. Many researchers assume that the most common type is iron deficiency anemia (IDA), following the WHO, which mentioned that IDA is the most prevalent type of anemia worldwide.[22,23,34,35] This is in accordance with the research of Yip (1994) in Khusun et al,[36] who argued that the incidence of iron deficiency increases with the prevalence of anemia in a country. However, anemia has more than a single cause.

Anemia may be multifactorial, on account of diet, blood loss, chronic infection, micronutrient, or inherited red cell or Hb abnormalities. This is not to suggest that it necessarily has a complex causality and pathogenesis. Notably, the primary cause may well be related not to diet but instead to blood loss resulting from menstrual irregularities such as menorrhagia in women during the reproductive years, intestinal helminthiasis such as ascariasis or hookworm, or, in later life, large bowel tumours;[37,38] alternatively, it may result from malabsorption (as in cases of celiac disease). Nutritional measures are generally required, regardless of whether dietary characteristics are the primary factors.[39] The notion that most Indonesian cases of anemia are due to iron deficiency should be reevaluated; this may not be true for many cases of anemia. Understanding the distribution and prevalence of types of anemia is critical to designing targeted interventions.

Few published reports on anemia in Indonesia have provided direct evidence of iron deficiency or other causes. Few studies of anemia have reported iron deficiency, inflammation, or other biomarkers such as serum transferrin receptor (sTfR), serum ferritin, High-sensitivity C-reactive Protein (HS-CRP), IL-6, alpha 1-acid glycoprotein, or hepcidin. In chronic disease or infection, inflammation can occur, which results in increased use of iron as an essential component in the transport system.[40] Of the publications considered in this review, only three used ferritin as a biomarker of anemia. The remaining nine only reported on Hb levels and not red cell morphology or iron status. Thus, the type of anemia cannot be specified. Ferritin may be an indicator of iron deficiency and iron stores without any change in hematocrit or serum iron due to its role in inflammatory response.[30] Some 20% of Indonesian children aged 48–59 months have anemia

Table 2. Interventions for anemia prevention among young Indonesians by study design, locale, age, gender, diet, use of supplements, and outcomes

First author, year	City	Number of individuals		Intervention	Anemia biomarkers	Dietary information	Supplement
		Intervention	Control				
Zuraida et al, 2020a	Bandar Lampung	55 female adolescents (mean age 15 y)	47 female adolescents (mean age 15 y)	Nutrition education in the form of an "anemia free club" for 12 weeks	· Hemoglobin (Hb) levels were measured only preintervention. · 41 individuals from the intervention group and 43 the from control group had low Hb levels (10.1–11.9 g/dL).	· Dietary intake was measured twice (pre-post) using a food-frequency questionnaire. · Postintervention, the intakes of energy, iron, protein, and fat by subjects were significantly higher (p<0.05) than in the control.	This study did not include subjects who consumed any supplements.
Zuraida et al, 2020b	Bandar Lampung	55 female adolescents	47 female adolescents	Nutrition education in the form of an "anemia free club" for 12 weeks	· Hb levels were measured. · The control group had a higher percentage of individuals with low Hb levels (10.1–11.9 g/dL) than the intervention group (91.49% and 74.55%, respectively).	No information.	No information.
Muslihah et al, 2017	Madura	Two intervention groups, each with 56 infants (aged 6-59 months)	56 infants	· The lipid nutrient supplement paste—small quantity (SQ-LNS) group received 20 g of SQ-LNS per sachet per day for 6 months · The biscuit *Makanan Pendamping-Air Susu Ibu* (MP-ASI or complementary foods) group received three 30-g biscuits per day for 6 months	· Hb levels were measured three times (preintervention, mid-intervention, and postintervention). · The Hb levels in the SQ-LNS group were significantly higher than those in the control and biscuit groups (10.47±1.09 vs 9.98±0.97 vs 10.07±0.60 g/dL).	No information.	· The effects of supplement in the form of SQ-LNS were compared with fortified biscuit and control. · SQ-LNS contained energy (118 kcal), protein, essential fatty acids, 22 vitamins and minerals.
Sari et al, 2018	Banyumas	31 female students from SMA (senior high school) Negeri 2 Banyumas	39 female students from SMA Negeri 4 Banyumas	Six nutrition education meetings about anemia prevention (presentations, games, and lectures)	· Hb levels were measured. · Hb levels were significantly increased (from 12.17±1.29 to 12.68±1.22 g/dL) in the intervention group after treatment but not in the control group.	No information.	No information.

Table 2. Interventions for anemia prevention among young Indonesians by study design, locale, age, gender, diet, use of supplements, and outcomes (cont.)

First author, year	City	Number of individuals		Intervention	Anemia biomarkers	Dietary information	Supplement
		Intervention	Control				
Sekiyama et al, 2017	Bogor	68 elementary school students (boys and girls, mean age of 9 years)	–	· School lunch feeding intervention for 1 month (lunchbox contained rice, a vegetable dish, heme and nonheme protein dishes, and fruits) · The results were not categorized by gender	· Hb and hematocrit (Hct) levels were measured twice (preintervention and postintervention). · Hb (11.9±0.9 vs 11.2±0.9 g/dL) and Hct (34.0%±2.7% vs 31.7%±3.0%) levels were significantly increased after the intervention (p<0.05).	· Intakes of protein (41.7 vs 36.7 g), calcium (240 vs 205 mg), and vitamin C (64 vs 12.5 mg) were higher during the intervention compared with before the intervention (p<0.05). · The intake of fat (36.6 vs 47.3 g) was lower during the intervention (p<0.05).	No information about supplement consumption.
Syahwal and Dewi, 2018	Banjarbaru	Two intervention groups (P1 and P2), each consisting of 15 anemic female adolescents	15 anemic female adolescents	· P1 was given a snack bar made of *nagara* nut flour and *haruan* fish and 12 iron supplements · P2 was given a snack bar made of *nagara* nut flour and *haruan* fish · The control group was given 12 iron supplements · Foods and/or supplements were administered thrice a week for 1 month	· Hb levels were measured. · All individuals were cured of anemia after the intervention (Hb >12 g/dL). · The Hb levels of P1 were significantly higher than those of P2 and the control after the intervention (p<0.05). · Hb levels of P2 and the control were not significantly different postintervention.	No information.	No information.
Rusdi et al, 2018	Padang Panjang	17 anemic female adolescents (no information about age)	17 anemic female adolescents (no information about age)	The treatment group was given 100 g of guava processed into juice, once per day for a week	· Hb and ferritin levels were measured twice (preintervention and postintervention). · Significant increases in Hb and ferritin levels were observed postintervention in each group (p<0.001). · After the intervention, Hb levels in the intervention group were higher than those preintervention (12.48±0.67 vs 10.50±1.04 g/dL). · After intervention, the ferritin levels of the intervention (36.63±8.09 vs 57.40±14.09 µg/L) and control groups (33.63±6.15 vs 40.35±6.80 µg/L) were higher than those preintervention. ·	No information.	No information.

Table 2. Interventions for anemia prevention among young Indonesians by study design, locale, age, gender, diet, use of supplements, and outcomes (cont.)

First author, year	City	Number of individuals		Intervention	Anemia biomarkers	Dietary information	Supplement
		Intervention	Control				
Susanti et al, 2016	Tasikmalaya	P1: 59 and P2: 58 anemic female adolescents	58 anemic female adolescents	· P1: an iron supplement was given once a week and every day during menstruation · P2: an iron supplement was given once a week, accompanied by nutrition education · Control: an iron supplement was given once a week · The iron supplement consisted of 60 mg of elemental iron and 0.25 mg of folic acid · Nutrition education about anemia was provided through lectures, discussions, and pamphlets	· Hb levels were measured. · No significant differences in Hb levels after the intervention were observed between the three groups (ΔHb P1: 0.60; P2: 0.43; C: 0.52).	No information.	· Iron tablets (60 mg of elemental iron and 0.25 mg of folic acid). · The highest rate of compliance in taking supplements was observed for the P2 group (81.9%), and the lowest was observed for the P1 group (48.8%). · Iron supplementation in adolescents is better provided intermittently.
Budiana et al, 2016	Majalengka	33 anemic-wasting children aged 3–5 years	33 anemic-wasting children aged 3–5 years	· The treatment group was given *Taburia* (a sprinkle supplement) and nutrition counseling over a 2-month period · The control group received only nutrition counseling · The results did not differ by gender	· Hb levels were measured twice (postintervention and preintervention). · Hb levels were significantly increased postintervention in both the intervention (12.31 vs 11.14 g/dL) and control groups (11.8±0.53 vs 10.9±0.71 g/dL) (p<0.001). · The increase in Hb levels in the intervention group was significantly higher than that in the control group (1.55±0.98 vs 0.86±0.54 g/dL) (p<0.001).	· Dietary information was based on the percentage of adequacy of nutritional recommendations (no absolute number was reported). · Adequacy percentages of energy (94% vs 89%), protein (113% vs 106%), vitamin C (46% vs 40%), and Fe (74% vs 62%) were increased postintervention.	Supplementation in the form of *Taburia* (a sprinkle supplement) containing vitamin A, vitamin B complexes, vitamin D_3, vitamin E, vitamin K, vitamin C, folic acid, pantothenic acid, iron, iodine, zinc, and selenium.
Mulyantoro et al, 2015	Wonosobo	Three intervention groups (P1, P2, and P3), each consisting of 37 children aged 9–12 years	37 children aged 9–12 years	· P1 was given a supplement (840 µg iodine and 60 mg elemental iron) · P2 was given an iodine supplement (840 µg) · P3 was given an iron supplement (60 mg FeSO4) · The control was given a placebo · All supplements were given once a week for 13 weeks	· Ferritin levels in P1 (34.17 vs 51.19 µg/L) and P3 (36.85 vs 44.42 µg/L) were increased, whereas those in P2 were decreased (35.79 vs 33.52 µg/L). · The increase in ferritin levels in P1 and P2 (18.52 vs −2.63 µg/L) was significantly different (p<0.05).	No information.	Supplementation of iodine, iodine + iron, and iron was given to P1, P2, and P3.

Table 2. Interventions for anemia prevention among young Indonesians by study design, locale, age, gender, diet, use of supplements, and outcomes (cont.)

First author, year	City	Number of individuals		Intervention	Anemia biomarkers	Dietary information	Supplement
		Intervention	Control				
Kahayana et al, 2016	Semarang	P1: 30 children aged 10 months with normal nutritional status	30 children aged 10 months with normal nutritional status	· P1 was given 75 mg of vitamin C syrup during feeding time for 2 months · The control group was given a placebo	· Hb, serum iron, ferritin, total iron-binding capacity, and hepcidin levels were measured preintervention and postintervention. · Serum iron (45.70±17.4 vs 44.06±18.16 µg/dL) and ferritin (39.87±31.27 vs 36.43±25.33 µg/L) levels of the intervention group were significantly increased after the intervention (p<0.05). · No significant difference was noted for any biomarkers between the intervention and control groups either preintervention or postintervention.	Dietary information only compared the behavior of drinking formula milk, instant complementary food, and fruit consumption. No significant difference was observed between the two groups.	Supplementation in the form of vitamin C (75 mg) was compared with a placebo.
Manoppo et al, 2019	North Sulawesi	P1: 34 children aged 5–12 years with iron-deficient anemia	32 children aged 5–12 years with iron-deficient anemia	· P1 was given iron supplements with the addition of *L. reuteri* DSM 17938 · The control was given an iron supplement · The iron supplement was given in the form of 2 × 60 mg of elemental iron · *L. reuteri* DSM 17938 therapy was given as 3 × 108 CFU/day · The length of the intervention was 14 days	· Hb, hematocrit, and reticulocyte hemoglobin equivalent (Ret-He) levels were measured preintervention and postintervention. · Only Ret-He levels postintervention differed significantly between P1 (28.50 pg/L) and the control group (27.50 pg/L) (p<0.05).	No information.	Supplements in the form of 300 mg of sulfate ferrous (equivalent to 60 mg of elemental iron) were given.

Table 3. Classification of iron deficiency anemia

Stages	Hemoglobin	Ferritin (ng/mL)	sTfR (ng/L)	Transferrin (mg/dL)
Iron deficiency	Normal	<20	<5	360
Iron-deficient erythropoiesis	Normal	<12	>5	>380
Iron deficiency anemia	Lower	<12	>5	>380

sTfR: soluble transferrin receptor.
Adapted from Lianos and Jose with minor modification.[41]

according to their Hb levels, but only 12% have low ferritin.[41] Although Hb alone does not provide an indication of anemia causality, many Indonesian studies of anemia provide no further information.

Chronic iron deficiency is well-known as a common cause of anemia.[42-44] Naigamwalla et al[45] described three stages in IDA; iron deficiency, iron-deficient erythropoiesis, and finally IDA. Iron deficiency can occur for various reasons, one of which is the iron from dietary intake being too low for daily needs. Adolescent girls and women also lose iron due to blood loss during menstruation.[46] If an iron deficiency occurs latently, the body is not able to produce red blood cells properly. This causes the next stage, iron-deficient erythropoiesis, which is characterized by reduced heme synthesis and the formation of microcytic or hypochromic erythrocytes.[45] If this continues, it causes IDA. Lianos and Jose[42] described the characteristics of blood biomarkers according to the stages of anemia (Table 3).

As Table 3 indicates, further tests are required to confirm that cases are truly anemia due to iron deficiency. This is crucial because iron supplementation is currently central to anemia prevention and management programs. Clearly, where the prevalence of infection and inflammation is high, iron deficiency is not the only reason for anemia.[47] Often, it depends on contextual factors such as geographical location, the burden of infectious disease, and coexistence with other types of nutritional anemia; thus, further research is required.[44]

Infection is closely related to causality in anemia. Malaria, an example of an acute infection, causes anemia as a result of red blood cell damage due to parasites.[48] Another study conducted in Bandung, Indonesia, revealed that 63% of adult patients with pulmonary tuberculosis had anemia.[49] Research on 400 school-aged children in Vietnam reported a prevalence of hookworm infection of 92%; 25% of the infected were anemic (Hb <11.5 g/dL), and 2% had iron deficiency (TfR >8.5 mg/L). More than 30% exhibited elevated levels of C-reactive protein (≥8 mg/L) and 80% exhibited elevated levels of immunoglobulin E (>90 IU/mL).[50] This reinforces the notion that anemia occurring in areas with high infection rates might not be due to iron deficiency.

Iron status assessment among Indonesian people is commonly based on food intake and the types of food consumed.[51] This has several weaknesses resulting in inaccurate data because the assessment of food intake is based on estimation. The Indonesian Food Consumption Survey of 2018 revealed that the consumption of heme iron was lower than that of nonheme iron (32.2% vs 67.8%, respectively).[52] Fitri et al determined that the consumption of meats, fruits, and lentils in Indonesia has remained low.[53]

Policy directions addressing anemia among young populations

Indonesia has focused on anemia prevention through a program of iron-folate supplementation in the form of iron (60 mg $FeSO_4$) and folic acid (0.25 mg), otherwise known as iron tablets or *Tablet Tambah Darah* (TTD).[54] This program, intended for women of childbearing age, began in 1997.[55,56] In 2016, the Indonesian government adopted the iron supplement program launched by the WHO in 2011, where iron tablets are administered once a week at school.[55] The Indonesian Basic Health Research initiative in 2018 determined that 76.2% of adolescent girls received TTD, 80.9% of them at school and 19.1% elsewhere.[5] By region, Bali had the highest rate of iron supplementation (92.6%), and West Kalimantan had the lowest (9.6%).[57] In the *Taburia* program, the micronutrient sprinkle contains vitamin A, vitamin B_1, vitamin B_2, vitamin B_3, vitamin B_6, vitamin B_{12}, vitamin D_3, vitamin E, vitamin K, vitamin C, folic acid, pantothenic acid, iron, iodine, zinc, and selenium.[54] This program is aimed at improving the overall nutritional status of children under 5 years of age and has improved Hb counts in children.[28,58,59]

Iron supplementation is at the core of anemia prevention programs. An iron supplementation program targeting female adolescents and women of childbearing age should be evaluated briefly. The Indonesian Basic Health Research 2018 report noted that 76.2% of young women had received iron tablets in the previous 12 months. However, only 3.7% received iron tablets of ≥52 grains, and only 1.4% consumed them.[5] Many studies have been conducted in Indonesia to determine the effect of iron supplements in increasing Hb levels, but few have actually tested their effect on serum iron status. In this review, six studies tested the effects of iron or multimicronutrient supplements.[27-31,33]

As a country with large geographic and cultural variations, the nationally established youth iron supplementation program is likely inappropriate. Certain areas in Indonesia are particularly prone to infectious diseases. An example is malaria, which has a high prevalence in some areas of Papua.[60] A study by Schumann and Solomons[61] on a population of pregnant women with malaria discovered that iron supplementation actually increased the risk of infants being born with malaria. These results are consistent with research by Indrawanti[62] in Papua, Indonesia, which identified that infants had a nine-times greater risk of developing malaria if the mother was infected with malaria. Furthermore, at 3 months of age, infants had a three-times greater risk of experiencing nutritional problems, including underweight, wasting, or stunted growth. Other infectious diseases are also present in Indonesia, such as tuberculosis, worms, and HIV. Indonesia has a

helminth infection prevalence rate of 45%–65%,[63] and data suggest that in 2017, Indonesia became one of the top three countries for number of cases of tuberculosis, with 8% of total cases in the world.[64] Furthermore, approximately 0.3% of the population aged 15 years or over are HIV-positive.[65]

Anemia prevention among children and adolescents

The results of the present review indicate that the prevention of anemia in children and adolescents in Indonesia has been based principally on three approaches: food-based interventions, nutrition education, and micronutrient supplementation, independently or in combination. Three of the articles examined nutrition education as a strategy for preventing anemia in adolescents,[22,23,25] and two others combined nutrition education with micronutrient supplementation.[28,66] No changes in the anemia indices of hemoglobin (Hb) or hematocrit (Hct) were evident when nutrition education interventions alone were applied. Micronutrient supplementation accompanied by nutrition education had a greater impact on Hb levels than did supplementation or education alone.[28] Previous studies have shown, however, that education changes knowledge and attitudes as well as consumption patterns.[22,23,67,68] Several countries have adopted multiple dietary approaches that combine nutrition education and sufficiently improve dietary quality to prevent anemia.[69,70] These have inevitably identified advantageous non-iron food and food pattern factors. Likewise, comprehensive educational interventions combined with food supplementation that benefits the child's general health and nutritional status is of hematological benefit.[71,72]

Evidently, anemia prevention strategies in Indonesia mostly target school-aged children,[21-27,29,30,32,66] with only three of the twelve reports being on children under 5 years old.[28,30,31] The target population predicates the type of intervention, and nutrition education, school feeding programs, and iron supplementation (TTD) are seen as more suitable and feasible for school-aged children who can be managed independently at school without reliance on their caregiver. Needless to say, opportunity costs and ethical considerations arise in not involving caregivers. With children aged under 5 years, parents and caregivers have an obligatory, vital role, and their goals are made more achievable by an aid such as *Taburia*, a micronutrient sprinkle that is mixed into food.[28,58,59] Locally sustainable school lunch interventions with traditional Sundanese meals for students improve the quality of children's food intake, their Hb and Hct levels, and their nutritional status.[26] Experiences in other countries confirm that school program–based approaches to anemia prevention in children have merit.[73-76]

Current approaches compromise anemia prevention

The efficacy of interventions to reduce anemia has both educational and therapeutic dimensions.[77] The possible pathways of the role of nutrition education in anemia prevention are preceded by improvements in nutrition knowledge.[23,25,70,78] Understanding the concept of anemia prevention leads to positive changes in behavior as well as iron status,[79] and providing education to caregivers may improve their feeding practices.[69,71] Caregivers with improved knowledge, skills, and self-efficacy are more likely to practice better hygiene in food preparation as well as ensure the proper composition of complementary diets.[80] However, whether an educational intervention can affect behavior depends on how knowledge is transferred by field technicians and their skills in conducting community activities.[81] Anemia prevention using an education approach has been implemented in some developing countries as an alternative strategy in cases of limited access to iron-rich food/heme iron sources.[82,83]

The consensus of the UNICEF, United Nations University (UNU), WHO, and Micronutrient Initiative (MI) is that if the prevalence of anemia among pregnant women is higher than 40%, then the administration of iron–folic acid supplements should also be provided to female adolescents.[16] The provision of iron supplements from adolescence is cost effective and enables an iron store to be accumulated before pregnancy.[84-86] However, although it is theoretically effective, a refusal to consume iron supplements persists in some countries.[16,87] Tolkien et al[88] proved that it this is due to the side effects of iron supplementation, such as black stool, constipation, nausea, and iron aftertaste.

Rusdi et al[24] and Kahayana et al[30] reported that the serum ferritin levels of individuals after an intervention were increased compared with individuals who received a placebo. In an intervention with guava juice,[24] serum ferritin increased from 36.63±8.09 μg/L to 57.40±14.09 μg/L; vitamin C supplementation[30] increased it from 36.43±25.33 μg/L to 39.87±31.27 μg/L (p<0.05). This is probably a reflection of the form of the vitamin C, either as a supplement or in guava juice, with the juice increasing iron absorption. An increase in serum ferritin means an increase in iron reserves. Iron derived from plant foods is classified as nonheme iron, which is more difficult to absorb (only 1%–10% uptake).[89] Nonheme iron is also generally associated with phytate, dietary fiber, and calcium, which inhibit absorption. If it is consumed together with a source of vitamin C, however, much more iron will be absorbed.[90-93] Vitamin C has many roles, including acting as an antioxidant, promoting immune function, and increasing the absorption of nonheme iron. Vitamin C plays a role in iron kinetics and red blood cell formation. The WHO[16] recommends giving weekly iron supplements if high compliance is observed. This preventive program has been proven to be cost effective, with fewer side effects, easier management, and greater efficacy than daily iron supplementation. In Indonesia, national monitoring of compliance with iron supplementation among adolescent girls is rarely reported. A small study by Susanti et al[27] involving 117 Indonesian female students determined that providing nutrition education is more effective than iron supplementation only. Titaley et al reported similar findings[94]; better knowledge can increase the compliance of pregnant women in consuming iron–folic acid supplements.

Iron supplements are rarely given to Indonesian children under 12 years old. In 1999, the UNICEF/WHO proposed that iron supplementation is necessary in children aged 6–18 months if the prevalence of anemia in children exceeds 40%.[95] However, the WHO also warned against iron supplementation in children who have an

infectious disease because of the potential adverse effects.[96] Iannotti et al[97] explained that the administration of large amounts of iron can increase the number of pathogens and thus increase the risk of infection. A study of 478 Indonesian 4-month-old infants proved that iron supplementation effectively reduces the incidence of anemia but is inadequate for supporting their growth.[98] In the present review, the only study targeting Indonesian infants made use of food fortification to address anemia.[31]

In the past 5 years, 9 of the 12 studies on anemia prevention were carried out in schools. Schools are a potential environment for health promotion.[99] Moreover, a 12-year compulsory education program is in place; thus, children and adolescents spend most of their time in school.[100] In Indonesia, approximately 147,500 elementary schools, 37,000 junior secondary schools, and 25,300 senior secondary schools exist.[101] Despite their potential, collaboration between the education and health sectors is lacking. Research on school health promotion policies in the United States revealed that program implementation has been suboptimal due to the weakness of existing policies.[102]

Many health promotion programs for anemia prevention can be implemented in schools. In this review, three studies recommended nutrition education in schools for the prevention of anemia in adolescents.[22,23,25] One study recommended implementing a school lunch program,[26] two recommended a food-based approach,[24,32] and one recommended a supplementary intervention.[27]

The School Lunch Program proposed by Sekiyama et al[26] has not become a national program yet because of the wide variability of school characteristics in Indonesia. This is in contrast to several other countries, including Japan, which has had a national policy in place since 1954, governed by the School Lunch Act, to improve student health.[103] A study among 627 vulnerable households in Uganda reported substantial improvements in anemia status; the prevalence of anemia was significantly reduced in 25.7% of adolescent girls after they participated in a school feeding program.[104] Similar results were reported by Krämer et al[105] regarding the provision of iron-fortified salt in a school feeding program in India.

Anemia prevention studies in school settings had small sample sizes compared to Indonesia's total population of school-aged children. This makes generalizing the results difficult. The School Lunch Program carried out by Sekiyama et al,[26] although yielding good results, only involved 68 students. Not much research on anemia prevention in Indonesia has been conducted with large samples.

Anemia and sex

Both men and women can experience anemia. Various studies have shown that women, especially adolescent girls, have a higher risk of developing anemia due to menstruation.[16,27,37,42] Research by Susanti et al[27] on iron supplementation in adolescent girls revealed that taking a supplement once a week and every day during menstruation led to low adherence (48.8%) compared with the combination of once-weekly supplement consumption with nutrition education (81.9%).

In the reviewed studies, six included boys, either children or infants.[26,28-31,33] However, none stratified anemia based on gender. In research by Faiqah and Irmayani[106] on data for children under 5 years, reported by the 2013 Indonesian Basic Health Research, gender was significantly (p<0.001) associated with anemia. Of the 39,706 anemic children aged under 5 years, 57.9% were girls and 42% were boys. Another study of 712 Indonesian adolescents also discovered a significant relationship (p<0.001) between gender and incidence of anemia. Women and teenage boy account for up to 30% and 20% of anemia cases, reespectively.[107] No information regarding the types or causes of anemia has been provided. However, the results indicate that boys also experience anemia. Unfortunately, they have not been targeted for anemia prevention programs. Childhood and adolescence is a key phase for growth and development for both male and female individuals in which health status, including anemia, plays an essential role.[11,12,13,42] A need exists for programs such as anemia-related nutrition education and screening for boys as well as for girls.

Future directions

Anemia, like other public health problems, is multifactorial. The United States Agency for International Development[108] recommended an anemia prevention framework for children. This framework was based on the need to strengthen leadership, capacity, and policy in implementing various concordant programs in agriculture and health sectors. The authors suggested a need to identify the specific causes of anemia in smaller areas (such as cities/regions or provinces) and recommend preventive measures accordingly. Anemia in Indonesian children and adolescents may not be due to iron deficiency alone. Iron supplementation without understanding the exact underlying causes can lead to ineffective and inefficient programs.[109-111]

This review had several limitations. First, research only from the last 5 years was reviewed. Second, a meta-analysis was not feasible because of the low number of anemia intervention studies in Indonesia. Third, a major limitation is that the reports reflected the prevailing view among nutritionists and health policymakers that the causes of anemia are solely related to nutrition. This view does not take into account the likely multifactoriality of anemia and socioeconomic development. This entrenched approach has been fostered by an often commercial product–prescriptive approach with supplements rather than one in which food and health systems are informed and community-engaged. To say that anemia is strictly caused by iron deficiency, even if this is partly the case, blinds the intervener to the more complex causality and pathogenesis that may be involved and to the solutions actually required.

Conclusions

Despite the limitations identified in this review of studies on anemia among children and adolescents in Indonesian cities, progress has been made in these locations in terms of prevention and mitigation through food-based approaches, nutrition education, and nutrient supplementation (often unduly restricted to iron). These three types of intervention have ameliorated anemia among young people. Interventions across the Indonesian archipelago with

attention to underlying causality and pathogenesis, socioculturally sensitive education, more optimal food patterns, and integrated embedment in local food and health systems would further alleviate the burdens of disorder and disease among young Indonesians.

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AUTHOR DISCLOSURES

The authors have no conflicts of interest to declare.

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Original Article

Non-nutritional anemia: Malaria, thalassemia, G6PD deficiency and tuberculosis in Indonesia

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Anemia affects people worldwide and results in increased morbidity and mortality, particularly in children and reproductive-age women. Anemia is caused by an imbalance between red blood cell (RBC) loss and production (erythropoiesis), which can be caused by not only nutritional factors but also non-nutritional factors, such as inflammation and genetics. Understanding the complex and varied etiology of anemia is crucial for developing effective interventions and monitoring anemia control programs. This review focusses on two interrelated non-nutritional causes of anemia: malaria infection and RBC disorders (thalassemia and G6PD deficiency), as well as tuberculosis. According to the Haldane hypothesis, thalassemia occurs as a protective trait toward malaria infection, whereas G6PDd arises in malaria-endemic regions because of positive selection. Indonesia is a malaria-endemic region; thus, the frequency of thalassemia and G6PD deficiency is high, which contributes to a greater risk for non-nutritional anemia. As Indonesia is the second global contributor to the newly diagnosed tuberculosis, and active pulmonary tuberculosis patients are more anemic, tuberculosis is also contributes to the increasing risk of anemia. Therefore, to reduce anemia rates in Indonesia, authorities must consider non-nutritional causes that might influence the local incidence of anemia, and apply co-management of endemic infectious disease such as malaria and tuberculosis, and of genetic disease i.e. thalassemia and G6PDd.

Key Words: hemoglobin, malaria, thalassemia, G6PD, tuberculosis

INTRODUCTION

Anemia affects more than 1.93 billion people worldwide,[1,2] mostly children aged <5 years and women.[1,3] Anemia increases morbidity and mortality rate, particularly in children and reproductive-age women.[4,5] Anemia also contributes to poor birth outcomes,[4,6] impaired neurological development in children, and decreased work productivity in adults.[7]

Anemia is defined by a hemoglobin (Hb) concentration and/or red blood cell (RBC) count below the normal values and insufficient to fulfill an individual's physiological needs.[8] Typically, Hb concentration is the most common hematological assessment method and indicator for the diagnosis of anemia at the population level and in clinical practice. Anemia is caused by an imbalance between RBC loss and production (erythropoiesis). RBC loss may occur because of premature destruction (hemolysis) and/or acute blood loss. Reduced erythropoiesis can be caused by nutritional, inflammatory, and genetic factors. Anemia classification is commonly based on the biological mechanism, such as hemolytic anemia (inflammation), or RBC morphology (e.g., hereditary spherocytosis).[9] Understanding the complex and varied etiology of anemia, including the non-nutritional cause, is crucial for developing effective interventions and monitoring anemia control programs. In this review, two interrelated non-nutritional causes of anemia, namely malaria infection and RBC disorders (thalassemia and G6PD deficiency), are discussed. Malaria-endemic regions, such as Indonesia, have a high frequency of thalassemia and G6PD deficiency, which increases the risk for non-nutritional anemia. Discussion also include tuberculosis, which is associated with anemia, since Indonesia is the second global contributor to the increased cases of newly diagnosed tuberculosis. In Indonesia, patients with active pulmonary tuberculosis are more anemic with poor nutritional status. Thus, tuberculosis is also a contributing factor for the increasing risk of anemia.

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ANEMIA AND MALARIA

Malaria, a mosquito-borne disease caused by the parasite belonging to the genus *Plasmodium*, has become a major cause of anemia in tropical regions.[10] In 2018, an estimated 228 million cases of malaria were reported worldwide, compared with 231 million cases in 2017 and 251 million cases in 2010. In 2018, an estimated 405,000 people died of malaria globally, compared with 416,000 estimated deaths in 2017 and 585,000 in 2010.[11] Five *Plasmodium* species can infect humans: *Plasmodium falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi*.[12] Of these, *P. falciparum* is the more virulent and is responsible for approximately 1–3 million deaths per year, mainly in children and pregnant women.[13] *P. falciparum* infection may cause severe malaria syndrome, including severe anemia (defined as Hb concentration <5 g/dL).[10] By contrast, *P. vivax*, the commonest and most widespread species, is a largely nonlethal malarial species; however, it can also cause severe malaria syndrome because of relapse cases due to the flaring up of hypnozoites in the liver.[14]

The pathophysiology of anemia caused by malaria infection is complex and influenced by multiple factors.[15] During malaria infection, merozoite-stage parasites invade RBCs to undergo the asexual intraerythrocytic developmental cycle.[16] This results in a noticeable loss in RBCs due to parasite maturation and macrophage-mediated disruption of infected RBCs in the bone marrow.[17] However, the principal contributor to anemia severity is the accelerated disruption of uninfected RBCs, as observed in severe malaria cases caused by *P. falciparum*[18] and *P. vivax*.[19] Studies have revealed that, similar to infected RBCs, uninfected RBCs also exhibit reduced deformability,[18,20] which may impair microcirculatory flow[21] and trigger splenic retention and phagocytosis,[22] thereby contributing to malarial anemia. Moreover, studies have reported that increased apoptosis[23] and accelerated senescence[24] of uninfected RBCs, as well as the destruction of non-parasitized RBCs through opsonization and complement dysregulation,[25–27] greatly contribute to anemia caused by falciparum and vivax malaria. Furthermore, malarial anemia is compounded by defective development of RBCs in the bone marrow (dyserythropoiesis), which is mainly caused by the release of various immune mediators by both the host and parasite cells.[28]

In many developing countries burdened by malaria, the destruction of RBCs induced by the parasite at the end of the infection exacerbates pre-existing anemia; this typically due to malnutrition, helminthiasis, or inherited disorders related to RBCs, such as hemoglobinopathies.[29,30] The level of transmission also influences anemia severity.[31] In areas with high malaria transmission (e.g., sub-Saharan Africa), where most of the patients have developed immunity because of frequent exposure to malaria infection, anemia is predominantly observed in young children (aged <5 years).[14,32] As the children grow into adulthood, they develop immunity against the malaria infection, such that in adolescence nearly all malaria infections are asymptomatic.[31] By contrast, in regions with unstable and low transmission of malaria, in which protective immunity from malaria is not achieved, the age group that is most affected by malarial anemia tends to shift toward adolescents and young adults.[33]

Malaria is highly endemic in Eastern Indonesia, and most infections occur on the islands of Papua and East Nusa Tenggara,[34] as illustrated in Figure 1.[35] Annual

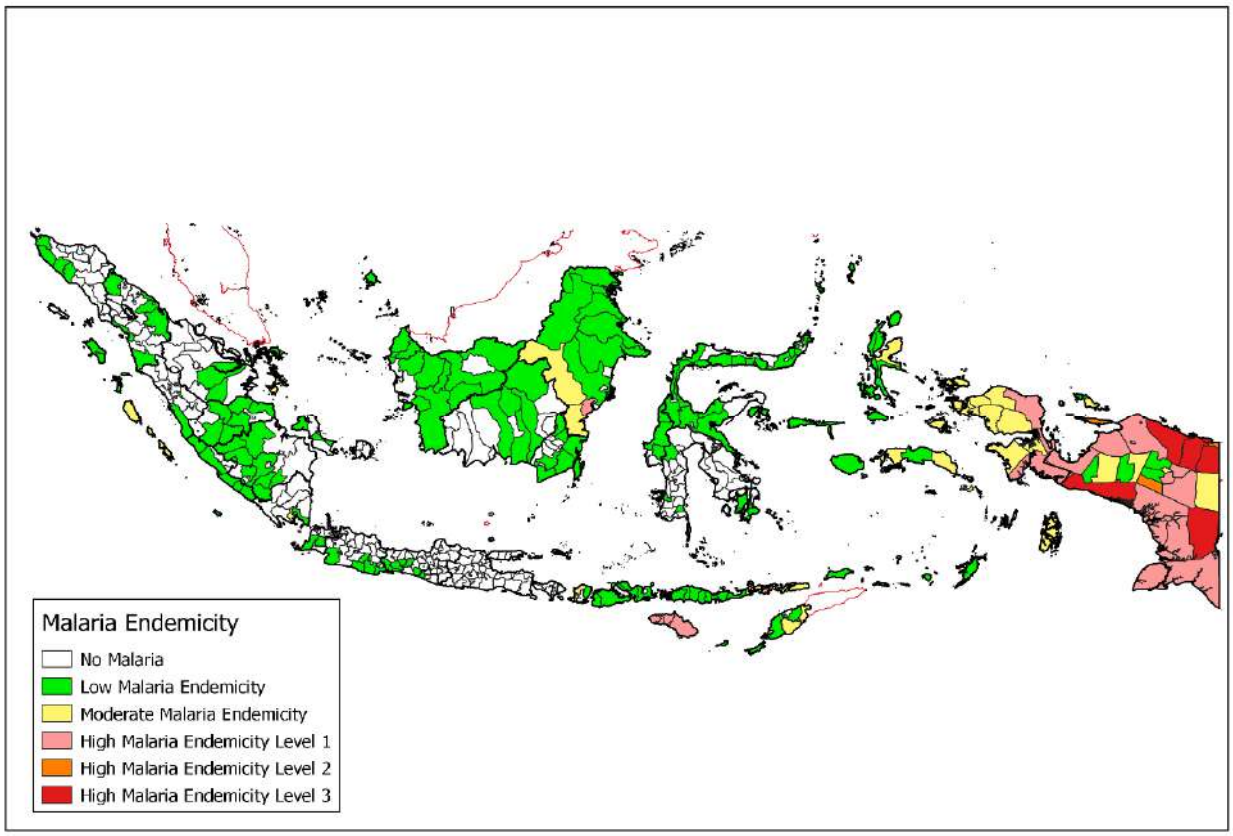

Figure 1. Malaria distribution in Indonesia. Source: World Malaria Report 2019.[11]

Table 1. Risk factors for anemia in women living in Sumba and Papua

Variable	Non-anemic (N=1481)	Anemic (N=2993)	Crude OR (95% CI)†	Adjusted OR (95% CI)‡
Malnourished, n (%)				
No	1094 (73.9)	2105 (70.3)	Reference	Reference
Yes	387 (26.1)	888 (29.7)	1.19 (1.04-1.37)***	1.36 (1.17-1.59)***
Malaria, n (%)				
No	1387 (93.7)	2731 (91.2)	Reference	Reference
Yes	94 (6.3)	262 (8.8)	1.42 (1.11-1.81)**	1.44 (1.13-1.84)**

MUAC: mid-upper arm circumference; OR: odds ratio; 95% CI: 95% confident interval.
Anemia criteria: hemoglobin <11 mg/dL for pregnant women or hemoglobin <12 mg/dL for nonpregnant women.[8] Malnourished: mid-upper-arm circumference <23 cm.[87]

†Unadjusted logistic regression. ‡Adjusted logistic regression after controlling for underweight, malnourished, and malaria status.

**p<0.010, ***p<0.001

parasite incidence in Indonesia was 0.84 in 2018 and 0.93 in 2019.[35] According to a related study conducted in Southern Papua, malaria infection due to *P. falciparum*, *P. vivax*, and *P. malariae* contributes to severe anemia risk, particularly in patients infected by mixed *Plasmodium* species, thus contributing to increased mortality risk.[15] Moreover, the burden of malaria-related anemia during pregnancy is overwhelming: almost 50% of pregnant mothers in Indonesia are anemic.[36] Malaria infection is a risk in approximately 6.3 million annual pregnancies in Indonesia.[37] Anemia is closely correlated with malaria infection, and in endemic regions, malaria is a major cause of anemia[31] as well as a large contributor to maternal anemia during pregnancy, resulting in poor birth outcomes.[38,39]

Asymptomatic microscopic parasitemia is associated with increased risk of anemia[40] and adverse birth outcomes, including premature delivery and low birth weight newborns.[41] In the Asia–Pacific region, 70% of pregnancies occur in malaria-endemic regions, of which 7% occur in Indonesia.[37] Malaria contributes to increased risk of anemia among women living in Sumba and Papua, independent of nutritional status (determined by body mass index and mid-upper arm circumference; Table 1).[42] Studies on the burden of malaria in West Sumba Regency, where malaria transmission is seasonal, revealed that anemia prevalence increased in younger children (aged <10 years) during the wet season.[43] Subsequent studies monitoring the efficacy of an antimalarial drug reported that the common clinical manifestation in the patients screened and involved in the studies was mild to severe anemia (Asih et al[44] and unpublished data, Eijkman Institute). Common concomitant genetic disorders that are also prevalent in Sumba include thalassemia, G6PD, and Southeast Asian ovalosytosis.[45,46]

The management of anemia in malaria endemic areas requires an intersectoral approach between nutritionists, hematologists, and infectious disease practitioners. This is because iron supplementation, rather than the provision of nutritious food as with biofortified grains and legumes, and bioavailability generated by food biodiversity, can exacerbate malaria, even to the point of overwhelming parasitosis.[47–51] This consideration applies to placental malaria in particular where even periconceptional iron is a risk factor.[52,53]

ANEMIA AND THALASSEMIA

Haldane (1949)[54] proposed that the high frequency of thalassemia in Mediterranean populations might be due to natural selection that resulted in increased prevalence of protective traits toward malaria infection; this is known as the Haldane hypothesis or malaria hypothesis. As a result of this survival advantage against malaria, inherited RBC disorders such as thalassemias are the most common diseases attributable to single defective genes. Considering its selective pressure in the human genome, malaria is regarded as an evolutionary force of some genetic diseases that mainly present as abnormal Hbs and RBC enzyme deficiencies.[55]

The thalassemias—characterized by decreased Hb production—are the most common inherited hemoglobin disorders and also the most common human monogenic diseases.[56] The two main types of thalassemia are α and β thalassemia, referring to the affected globin chains.[57,58] On the basis of globin chain expression, thalassemia can be classified as α^+ and α^0 or β^+ and β^0.[59] Although these disorders are most common in tropical and subtropical regions, they are now encountered in most countries because of global population migration and marriage between ethnic groups. Of all globin disorders, α thalassemia is the most widely distributed and occurs at high frequencies throughout tropical and subtropical regions; in these areas, carrier frequency can reach up to 80%–90% in the population.[60,61] For β thalassemia, the carrier frequency is approximately 1.5% of the global population (80–90 million people), with approximately 60,000 individuals with clinical manifestations born annually.[62]

Thalassemias are a heterogeneous group of anemias that result from defective synthesis of the globin chains of adult hemoglobin. In Southeast Asia, α-thalassemia, β-thalassemia, hemoglobin E (HbE), and hemoglobin Constant Spring (HbCS) are prevalent. HbE and HbCS are hemoglobin variants that cause a decrease in hemoglobin production. HbE mutation alternates the mRNA splicing, whereas HbCS mutation produces unstable mRNA due to a stop codon shift that causes longer but unstable mRNA, resulting in the reduction of the α-globin chain. The gene frequencies of α^0-thalassemia in Indonesia range from 1.5% to 11.8% and that of α^+-thalassemia from 3.2% to 38.6% (unpublished data, Eijkman Institute).[63] The gene frequencies of β-thalassemia in Indonesia vary from 0.5% to 17.45% for the HbE mutation and 0.5% to 5.4% for the

other β-thalassemia mutations (unpublished data, Eijkman Institute).

α-Thalassemia

α-Thalassemia is an autosomal recessive hereditary RBC disorder due to mutations in the α-globin genes, causing a decrease in or absence of α-globin chain production; it is characterized by microcytic hypochromic anemia. The clinical phenotype of α-thalassemia varies from almost asymptomatic to lethal hemolytic anemia. α-thalassemia is a condition related to a deficit in the production of α-globin chains, which form a tetrameric molecule together with β- or γ- globin chains of the hemoglobin molecule. Healthy individuals have four α-globin genes: two sets of two tandemly encoded (in *cis)* genes, located on chromosome 16 in band 16p13.3.[60]

The α-globin chains are subunits for both fetal (α2γ2) and adult (α2β2) hemoglobin; therefore, homozygous α-thalassemia can cause anemia in fetuses and adults.[58] The most frequent mutation of α-thalassemia is deletion of one (α^+-thalassemia) or both (α^0-thalassemia) of the α-globin genes. The severity of clinical and hematological phenotypes (degree of microcytic hypochromic anemia) is closely correlated with the reduction of α-globin chain synthesis in each mutated α gene.[64]

β-Thalassemia

The other autosomal recessive hereditary RBC disorder is β-thalassemia, which is caused by mutations in the β-globin gene. β-thalassemia is characterized by the reduction in or absence of β-globin chain synthesis, resulting in reduced Hb, decreased RBC production, and anemia. On the basis of the clinical manifestations, β-thalassemia is classified as thalassemia major, thalassemia intermedia, and thalassemia minor.[59,62]

The beta globin gene maps in the short arm of chromosome 11 at position 15.4. Approximately 200 β-globin gene mutations have been reported.[65] β-globin gene mutations result in a reduction or absence of β-globin chains production, with variable phenotypes ranging from severe anemia to clinically asymptomatic. The clinical severity of β-thalassemia is associated with the imbalance between the α-globin and non–α-globin chains.

Even though thalassemia is closely associated with anemia, some of the hematologic features of the RBCs could appear normal in the thalassemia trait, as observed in our population studies in several ethnic groups in Indonesia (Table 2). The prevalence of anemia (according to Hb concentration) in the population of Banjarmasin and Ternate was 11.4% (67/587; cutoff is <12 g/dL for women individuals and <13 g/dL for men individuals; according to the World Health Organization criteria[8]). We applied trait thalassemia screening according to the complete blood count, Hb analysis, and blood smear of these 67 individuals with anemia; we noted that only approximately 82% exhibited an indication of thalassemia (microcytic hypochromic). If molecule detection were also included, the confirmed thalassemia cases would be even lower. However, those with nonconfirmed thalassemia with microcytic hypochromic anemia could still harbor

Table 2. Clinical characteristics of individuals with and without anemia in the Banjarmasin and Ternate population

Population	Variable	Non-anemic	Anemic	*p*
Banjarmasin		(N=179)	(N=19)	
	Age [years, median (IQR)]	20.0 (19.0-21.0)	19.0 (19.0-20.0)	0.175
	Sex [n (%)]			
	Male	74 (41.7)	1 (5.3)	0.002
	Female	105 (58.3)	18 (94.7)	
	Hb [mg/dL, median (IQR]	14.1 (13.3-15.2)	10.8 (10.6-11.7)	<0.001
	MCV [fL, median (IQR)]	84.7 (82.3-87.5)	80.0 (71.4-82.7)	<0.001
	MCH [pg, median (IQR)]	28.3 (27.4-29.2)	24.4 (21.4-26.1)	<0.001
	MCHC [g/dL, median (IQR)]	33.2 (32.5-33.8)	31.2 (30.6-32.2)	<0.001
	RDW [n (%)]	13.4 (13.0-13.9)	15.7 (14.7-17.0)	<0.001
	HbA2 [n (%)]	2.8 (2.7-2.9)	2.6 (2.5-2.9)	0.021
	HbF [n (%)]	0.3 (0-0.5)	0.0 (0.0-0.4)	0.281
	HbE [n (%)]	2 (1.0)	0 (0.0)	1.000
Ternate		(N=341)	(N=48)	
	Age [years, median (IQR)]	20.0 (17.0-21.0)	19.5 (18.8-20.0)	0.185
	Sex [n (%)]			
	Male	146 (42.8)	1 (2.1)	<0.001
	Female	195 (57.2)	47 (97.9)	
	Hb [mg/dL, median (IQR]	14.0 (13.1-15.6)	11.2 (9.6-11.6)	<0.001
	MCV [fL, median (IQR)]	82.9 (80.4-85.2)	74.6 (66.6-79.2)	<0.001
	MCH [pg, median (IQR)]	28.2 (26.9-29.3)	23.4 (19.9-25.4)	<0.001
	MCHC [g/dL, median (IQR)]	33.8 (32.9-34.9)	31.4 (29.5-32.4)	<0.001
	RDW [n (%)]	13.6 (13.1-14.3)	15.7 (14.8-19.2)	<0.001
	HbA2 [n (%)]	2.8 (2.6-2.9)	2.5 (2.3-2.7)	<0.001
	HbF [n (%)]	0.3 (0.2-1.0)	0.2 (0.0-0.9)	0.036
	HbE [n (%)]	4 (1.2)	2 (4.2)	0.162

Hb: hemoglobin; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width; HbA2: hemoglobin subunit alpha 2; HbF: fetal hemoglobin; HbE: hemoglobin E.
World Health Organization anemia criteria were employed: hemoglobin <12 mg/dL for women or hemoglobin <13 mg/dL for men.[8]
The *p* values were calculated using either the Wilcoxon–Mann Whitney U test for continuous variables or Fisher's exact test for categorical variables. Significant *p* values are in bold ($p<0.05$). Unpublished data, Eijkman Institute.

thalassemia traits because a comprehensive molecular screening has not yet been conducted; in this case, screening was only performed for the most common mutations. Microcytic hypochromic anemia could result from not only thalassemia but also iron deficiency because thalassemia can coexist with iron deficiency. However, in cases where thalassemia is not confirmed, the microcytic hypochromic anemia is most likely due to iron deficiency. Hence, nutritional anemia could coexist with RBC disorders, such as thalassemia.

We included hemoglobin analysis when screening for thalassemia, either in patients at our genetic clinic or as part of our population studies. We observed that RBC morphology (microcytic hypochromic) was similar between thalassemia and iron deficiency anemia and noted that this similarity could obscure the real cause of the underlying anemia because both abnormalities are commonly noted in the Indonesian population. Therefore, iron status must be examined to confirm the cause of the anemia, which is crucial to determining prevention, therapy, and management strategies. However, government guidelines do not include iron status examination for determining the cause of anemia. The current policy is to provide iron supplementation for every person with anemia. Thus, we propose complete blood count and iron status screening in the Indonesian population in cases where iron supplementation does not improve iron content.

ANEMIA AND GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY

Another genetic disorder associated with the selective pressure of malaria is glucose-6-phosphate dehydrogenase deficiency (G6PDd), which has been reported to confer resistance to malarial infection.[66–68] Population genetic analyses of the G6PD locus have supported the association between G6PD and malaria; these studies have revealed that the frequency of G6PD gene mutations have increased recently in certain geographic regions where malaria is endemic, as a result of positive selection.[69,70]

The G6PD gene is located on chromosome X and maps to Xq28, making the disorder X-linked; consequently, men can only be hemizygous G6PD normal or hemizygous G6PD deficient. Women can either be homozygous G6PD normal, homozygous G6PD deficient, or heterozygous because women have two *G6PD* alleles. Similar to most X-linked genes, G6PD is affected by the random X-chromosome inactivation phenomenon, and somatic cells in G6PD heterozygous women are a mosaic of G6PD-normal and G6PD-deficient RBCs.[71–73]

G6PDd is a common RBC enzyme disorder worldwide, affecting approximately 400 million people. The clinical manifestations of G6PDd are broad, ranging from asymptomatic to acute hemolytic anemia, renal failure, and death. These manifestations result from mutations in the G6PD gene that cause instability in the produced enzyme. Approximately 400 biochemical variants are known, but only 186 mutations have been genotyped.[74] These mutations are region- or ethnic-specific. In Indonesia, G6PDd is most prevalent in malaria-endemic areas, such as south Lampung, central and south Kalimantan, and most of eastern Indonesia, such as Sumba and Papua. Certain variants, such as Vanua-Lava, Viangchan, Coimbra Shunde, are found predominantly in eastern Indonesia.[75,76]

Most individuals with G6PDd do not exhibit any symptoms unless exposed to exogenous agents that trigger oxidative stress resulting in acute hemolytic anemia. In affected individuals, a defect in the G6PD enzyme causes RBCs to break down prematurely in response to oxidative medication, infections, or fava beans, leading to hemolytic anemia that may be severe and life-threatening.[77] We noted no difference in G6PD enzyme activity between those with and without anemia in normal conditions (i.e., not exposed to oxidative agents), whereas older age and being a woman increased the risk for acute hemolytic anemia (Table 3).

TUBERCULOSIS

Anemia is also found in association with tuberculosis. In Taiwan's nationwide population-based study covering 12 years of data, iron deficiency anemia was associated with a 99% increased incidence of tuberculosis compared with the matched group, which supports the hypothesis that individuals with micronutrient deficiency, including iron deficiency, are more susceptible to infections.[78] Data from study conducted in Indonesia showed that patients with active pulmonary tuberculosis are more anemic with

Table 3. Predictors of anemia in those with and without G6PD deficiency

Variable	Non-anemic	Anemic	Crude		Adjusted	
	(N=424)	(N=182)	OR (95% CI)	*p*	OR (95% CI)	*p*
Age (years)	15.0 (10.0-32.0)	30.0 (16.3-40.0)	1.03 (1.01-1.04)	<0.001	1.03 (1.02-1.05)	<0.001
Weight (kg)	39.0 (23.0-48.0)	40.0 (34.3-45.0)	1.01 (1.00-1.03)	0.045	1.00 (0.98-1.02)	0.947
Sex						
Female	210 (49.5)	139 (76.4)	Reference		Reference	
Male	214 (50.5)	43 (23.6)	0.3 (0.21-0.45)	<0.001	0.27 (0.17-0.41)	<0.001
G6PD activity						
Non-deficient	399 (94.1)	170 (93.4)	Reference		Reference	
Deficient	25 (5.9)	12 (6.6)	1.13 (0.55-2.29)	0.743	1.31 (0.59-2.90)	0.502
Malaria						
Negative	415 (97.9)	176 (96.7)	Reference		Reference	
Positive	9 (2.1)	6 (3.3)	1.57 (0.55-4.48)	0.398	2.68 (0.87-8.26)	0.085

G6PD: glucose-6-phosphate dehydrogenase; OR: odds ratio; 95% CI: 95% confident interval.
World Health Organization anemia criteria were employed: age <5 years, Hb <11 mg/dL; age 5–11 years, Hb <11.5 mg/dL; age 12–14 years, Hb <12 mg/dL; age >15 years, Hb <12 mg/dL for female individuals or Hb <13 mg/dL for male individuals.[8]
Data were extracted from Satyagraha et al.[75]

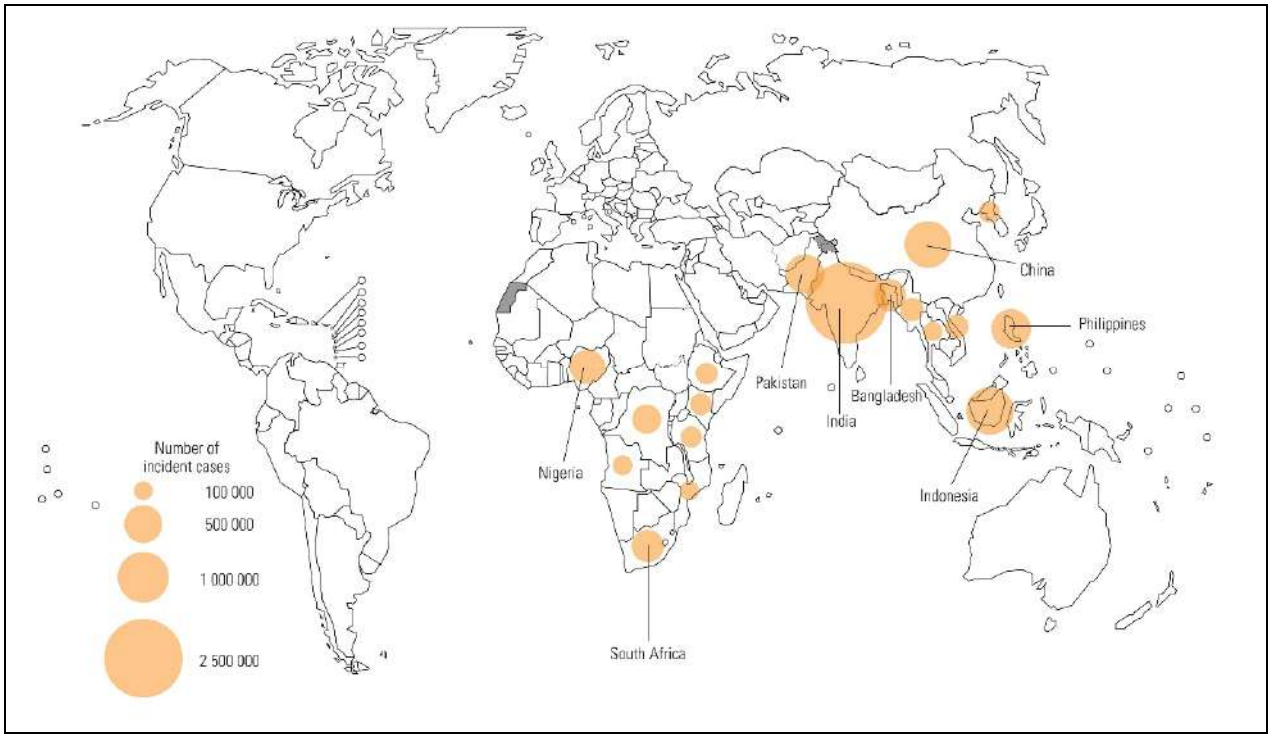

Figure 2. Countries that had at least 100 000 incident cases of TB in 2019. Source: Global Tuberculosis Report 2020.[80]

poor nutritional status as compared to healthy subjects.[79] Indonesia is ranked second (8.5%) as the biggest contributors to the global increase of newly diagnosed tuberculosis, after India (26%) (Figure 2).[80] Nevertheless, similar with malaria, iron supplementation may exacerbate tuberculosis, since the tuberculosis causative pathogen, *Mycobacterium tuberculosis*, requires iron for essential metabolic pathways. Therefore, in tuberculous areas, iron supplementation approaches to the problem should be avoided without co-management of tuberculosis and monitoring for iron biomarkers, since the management of dietary iron is most likely influential in supporting the outcome of this disease.[81–86]

CONCLUSION: THE ROLE OF MALARIA, THALASSEMIA, G6PD DEFICIENCY AND TUBERCULOSIS IN ANEMIA IN INDONESIA

The prevalence of anemia is high in Indonesia.[36] The health authorities tend to highlight iron deficiency and/or malnutrition as the cause of anemia. Indonesia is an archipelago country with numerous islands, ethnic groups, cultures, languages, as well as tropical and genetic diseases including malaria, thalassemia, and G6PD deficiency. Multiple malaria infections can cause severe anemia in children or adults living in malaria-endemic areas. Genetic factors that have arisen from malaria pressure in these areas can also cause anemia. Thus, anemia does not occur solely due to malnutrition and iron deficiency but can be due to other internal or external factors, which may play a role in modulating the incidence of anemia in Indonesia. Whenever iron supplementation does not improve anemia status, particularly microcytic hypochromic anemia, practitioners should consider other causes. In our population studies, the prevalence of both thalassemia trait and iron deficiency was high, both of which contribute to the high prevalence of anemia. Therefore, in the management of anemia in the Indonesian population, conducting complete blood count screening, Hb analysis, and iron status examination is necessary, because anemia could be due to either chronic infection (e.g., malaria, tuberculosis) or genetic disorders (e.g., thalassemia and G6PDd). Anemia, particularly in children, may cause irreversible neurological damage that may affect the quality and global competitiveness of future human resources. Anemia in adults limit the quality of people's work and their productivity. Thus, to eliminate anemia in Indonesia, the authorities should employ a comprehensive and multidisciplinary approach in collaboration with research and government institutions. Anemia elimination in Indonesia requires a knowledge of local pathogens, as well as nutritional factors, especially since iron supplementation may otherwise worsen infectious disease such outcomes as in malaria and tuberculosis.

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AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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Review Article

Non-nutritional and disease-related anemia in Indonesia: A systematic review

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Non-nutritional anemia, the second most common type of anemia worldwide after nutritional anemia, includes the anemia of inflammation (AI) and that due to helminthiasis. In this review, we examine the contribution that non-nutritional anemia makes to incidence in Indonesia. Anemia due to helminthiasis is a common problem in Indonesia and contributes to prevalence, particularly in children under 5 years. We conducted a systematic literature review based on Google Scholar and Pubmed for non-nutritional anemia. We supplemented this with hemoglobin and chronic disease data in Makassar where prevalence and type of anemia were available. To effectively reduce anemia prevalence in Indonesia, interventions should address both nutritional and non-nutritional contributing factors, including infection and genetic predisposition.

Key Words: anemia of inflammation, helminthiasis, non-nutritional anemia, chronic disease, iatrogenic anemia

BACKGROUND

Anemia is a major public health problem in Indonesia.[1-3] Despite the various efforts of the Indonesian government, such as providing iron and folic acid supplements to pregnant women and food fortification, anemia prevalence has remained high.[4] Anemia typically presents as a symptom of a disease caused by various factors, including that that are nutritional and non-nutritional.[5] The primary causes of nutritional anemia include low nutrient intake but may also be nutritionally responsive and secondary.[6] The secondary causes include impaired absorption, blood transport, metabolism, and storage of nutrients. Because genetic factors underlie the secondary causes, their pathomechanisms are increasingly being delineated through nutrigenomics. For instance, gene polymorphisms affect nutrient metabolism, causing variations in the nutritional requirements for erythrocyte formation. Therefore, to prevent anemia, individuals with such gene variants are required to consume certain nutrients at levels higher than the recommended daily allowance.

Anemia of inflammation (AI) and iron deficiency (ID) anemia (IDA), the two most common forms of anemia worldwide, often coexist in developing countries where the prevalence of malnutrition and infectious disease is typically high.[7] AI is a frequently reported anemia in hospitalized patients and those with ***chronic, metabolic, or infectious disease***. AI prevalence typically increases along with that of its associated diseases including diabetes mellitus (DM), CVD, cancer, tuberculosis (TB), malaria[8] and HIV infection in Indonesia. Obesity, the metabolic syndrome, type 2 DM (T2DM) and CVD are also associated with anemia. In addition, Anemia is also a key feature of ***chronic kidney disease (CKD)***, itself a serious complication of T2DM and hypertension.

Helminthiasis is endemic disease in Indonesia (particularly in <5-year-old children), and contributes to anemia. Therefore, for comprehensive anemia management, the health authorities, systems and workers must identify and mitigate the underlying non-nutritional factors. Intersectoral and eco-nutritional approaches are needed to resolve persistent anemia in Indonesia.[1]

This systematic review discusses AI pathomechanisms and prevalence in Indonesia and globally. Several Indonesian studies, not only of anemia in infectious, chronic, and metabolic disease, but also in helminthiasis are considered. The genetic variations contributory to nutrient absorption, transport, metabolism, and storage and to erythropoiesis are considered.

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METHODS

We searched the PubMed databases as well as Google Scholar and Google search engines for relevant literature using the following keywords: "anemia," "hemoglobin," "inflammation," "kidney," "obesity," "chronic disease," "heart failure," "helminthiasis," "tuberculosis," "HIV," and "Indonesia." Original articles published in both international and Indonesian journals, unpublished theses, and registry data were selected. In total, 39 Indonesian studies from Indonesian journals (35 studies) and university theses (4 studies) were finally included. Internationally published articles on AI in Indonesia were scant. The studies were typically cross-sectional or descriptive, with some o only reporting the proportions or mean hemoglobin levels without describing anemia type. Anemia in helminthiasis data were mostly observational, conducted in Indonesia and published variously in international and Indonesian journals. The definitions of anemia varied with different cutoff points for hemoglobin.

We also obtained data for Makassar from patients of the Clinical Nutrition Department, Universitas Hasanuddin affiliated to the Dr. Wahidin Sudirohusodo Hospital, in Makassar, Indonesia from July 2019 to September 2020.

INFLAMMATION

AI most commonly presents as a mild-to-moderate ***normocytic normochromic anemia,*** which is caused by systemic inflammation that inhibits erythrocyte formation and survival. In AI, hemoglobin rarely drops below 8 g/dL. In contrast to IDA, which is characterized by low serum iron and ferritin, AI exhibits low serum iron but normal or high serum ferritin levels. This phenomenon may be due to the iron redistribution in AI shifting from the location of utilization to that of storage, particularly in the hepatic and splenic mononuclear phagocyte system.[9]

AI is commonly found in patients with chronic systemic inflammatory conditions including both infectious and noninfectious diseases. Thus, AI is typically associated with chronic systemic inflammatory diseases including TB, malaria HIV, acquired immunodeficiency syndrome (AIDS), immune-mediated diseases (e.g., systemic lupus erythematosus), cancerous and hematological malignancies, obesity, T2DM, anemia in elderly persons, anemia in critical illness, congestive heart failure, CKD, and chronic pulmonary diseases.[10]

Tropical infectious diseases, which are typically acute (e.g., typhoid fever), are highly prevalent infectious diseases in Indonesia. The prevalence of other acute infectious diseases, such as diphtheria, pertussis, and morbilli, is extremely low due to successful vaccination by the Indonesian government. However, the prevalence of chronic infectious diseases such as TB and chronic hepatitis remains high, both in children and adults. In Indonesia, the highest prevalence of infectious diseases is seem with upper respiratory tract infection, diarrhea, and pneumonia (4.4%–9.3%, 6.8%–8%, and 2%–4%, respectively), followed by filariasis, pulmonary TB, hepatitis, and malaria (0.8%, 0.42%, 0.39%, and 0.37%, respectively (Indonesian Basic Health Research Data, 2018).[4]

Pathophysiology

Inflammation that occurs in both infectious and noninfectious diseases can lead to increased levels of cytokines, particularly tumor necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-1, and IL-6. IFN-γ elicits leucocyte proliferation, thus activating macrophages to phagocytose erythrocytes and shortening the erythrocyte life; TNF-α inhibits erythroid precursor proliferation; and IL-6 promotes liver hepcidin synthesis.[11,12] Moreover, proinflammatory cytokines suppress erythropoietin production; this natural mechanism reduces iron availability in the blood to inhibit the survival and reproduction of microorganisms that use iron. Although this adaptative mechanism is beneficial in mitigating acute infections, its chronic continuation in chronic infections can lead to AI and disrupt metabolism.[11]

In plasma, iron binds to transferrin, which carries it to the bone marrow for hemoglobin synthesis. Hepcidin is an iron-regulating hormone that binds to ferroportin to block the iron transfer from duodenal enterocyte cells, macrophages, and liver cells to blood plasma. Under normal conditions, hepcidin synthesis is regulated by the number of iron stores and serum iron levels. However, in low-grade chronic inflammatory conditions such as those in obesity and anemia, increased hepcidin levels have been reported worldwide, including in Indonesia.[13] Hepcidin also worsens impaired renal function and is associated with inflammation.[14]

AI is typically normocytic and normochromic, which means that AI exhibits normal erythrocyte size and normal hemoglobin content (Table 1). In some cases, particularly those of chronic inflammation, AI may be microcytic (small erythrocyte size) and hypochromic (low hemoglobin content).[7]

CHRONIC AND METABOLIC DISEASE

Noncommunicable diseases (NCDs) or chronic diseases result from a combination of factors including those that are genetic, behavioral, and environmental. In Indonesia, hypertension and T2DM incidence is 84 and 20 per 1000 population, respectively.[4] The prevalence of anemia in some chronic diseases among the patients from our department is illustrated in Figure 1.

The prevalence of obesity, a major risk factor for metabolic syndrome, has also increased considerably in Indonesia (Table 2A). In adults, central obesity prevalence

Table 1. Differences in IDA and AI biomarkers

Biomarker	Iron deficiency anemia (IDA)	Anemia of inflammation (AI)
Mean corpuscular volume	Low	Normal
Mean hemoglobin volume	Low	Normal
Reticulocyte hemoglobin content	Low	Normal
Serum transferrin	High	Low
Serum transferrin receptor	High	Normal
Serum ferritin	Low	High
Serum hepcidin	Low	High

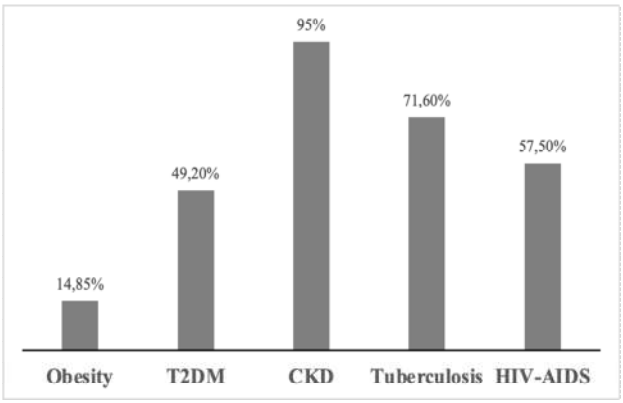

Figure 1. AI prevalance in patients at Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia.

has reached 31%—exceeding the global obesity and overweight prevalence (13% and 39%, respectively).[15] This means that 1 in 3 Indonesian adults has central obesity and thus has an increased metabolic syndrome risk compared with general population.[4]

Corresponding to the increasing national prevalence of obesity reported in Indonesian Basic Health Research (Riskesdas) 2018,[4] Herningtyas et al also found a high metabolic syndrome prevalence (21.7%) among 8573 individuals from 20 provinces and of 27 ethnicities in Indonesia—with the most common metabolic syndrome components being a low HDL concentration and hypertension.[16]

The obesity–ID association has been discussed previously.[17,18] Obesity induces inflammation, thereby increasing the cytokine and hepcidin levels and thus promoting the sequestration of iron in the mononuclear phagocytes system, particularly in the liver and spleen, and reducing iron absorption in the gut.[13]

In four extracted studies including obese individuals,[19-22] the average anemia incidence was 14.85% (range: 6.9%–30%), but not all studies mentioned the anemia type (Table 2B): Wijayanti et al[19] found 12% (4.3% men and 23.8% women) of the included 50 obese individuals to have anemia, but they neither detailed the type of anemia observed nor included nonobese controls in their study. Although obesity is associated with ID, anemia prevalence was lower in obese individuals than in their normal-weight counterparts.[20,21,23] In some conditions, micronutrient deficiency, such as vitamin B-12 or folate deficiency, inflammation, sickle cell disease, bone marrow disorders, thalassemia, and other hemolysis types, might contribute to total anemia.[23,24]

In a Taiwanese study, Huang et al[25] reported BMI to be positively associated with hemoglobin levels, meaning that the BMI the lower is, the higher is the risk of anemia. Moreover, BMI is correlated positively with serum ferritin levels but inversely with serum iron levels. Hence, the BMI–IDA association can be defined to be similar to the definition of IDA.

Moreover, in two Indonesian studies, the anemia prevalence was higher in nonobese individuals than in obese

Table 2A. Obesity by BMI for age groups in Indonesia[1]

No	Age group	Prevalence (%)	CI 95%
1	Children 5–12 years old†	9.2	9.0–9.5
2	Adolescent 13–15 years old†	4.8	4.6–5.1
3	Adolescent 16–18 years old†	4	3.8–4.3
4	Adult >18 years old	21.8	21.7–22.0
5	Adult with Central Obesity	31	30.8–31.2

†Body mass index for age obesity Z score was used.

Table 2B. Anemia in obesity in Indonesia

No	Author	Population	Study design	Anemia prevalence (%)
1	Wijayanti et al., 2018[19]	50 obesity patients. No nonobesity controls	Cross-sectional study	12%
2	Heryati et al., 2014[20]	38 elementary school students with overweight and obesity and 62 students with normal nutritional status	Cross-sectional study	10.5% of obese students 21% in normal nutritional status students
3	Sukarno, Marunduh, Pangemanan, 2016[21]	29 subjects with BMI >25 kg/m^2 31 subjects with BMI <25 kg/m^2	Cross-sectional study	6.9% in obese subjects 15.78% in BMI <18.5 8.33% in BMI 18.5–24.9
4	Nisa, Nissa, Probosari, 2019[22]	30 obesity and 30 non-obesity (based on BMI over age) patients age 15–18 years old	Cross-sectional study	30% in obese subjects and 30% in nonobese subjects

Table 3. Anemia in T2DM in Indonesia

No	Author	Population	Study design	Anemia prevalence (%)
1	Wijaya et al., 2015[26]	46 patients with T2DM with mildly to severely impaired renal GFR (Data from the medical records)	Cross-sectional study	80.4% total anemia, 26.1%, 39.1, 15.2% in mildly, moderately, and severely impaired GFR, respectively
2	Wijaya et al., 2014[27]	192 T2DM patients in RSUP Sanglah Hospital, Bali (Data from the medical record)	Cross-sectional study	Total anemia 41.67%, mild anemia 76.25%, moderate anemia 21.25%, severe anemia 2.5%
3	Balela, Arifin, Noor, 2014[28]	78 T2DM patients	Cross-sectional study	57% in patients with T2DM <5 years 86% in patients with T2DM ≥5 years

GRF: glomerular filtration rate; T2DM: type 2 diabetes mellitus.

individuals: Heryati et al[20] found that among elementary students (aged 10–12 years), anemia was present in 21% of those with normal nutritional status and in only 10.5% of those overweight and obese. Among adults, Sukarno et al. found that nonobese participants with a BMI of <18.5 and 18.5–24.9 kg/m^2 had an anemia prevalence of 15.78% and 8.33%, respectively, whereas obese participants with a BMI of >25 kg/m^2 had an anemia prevalence of only 6.9%.[21] However, none of these studies performed any serum iron assessments. Hence, future studies investigating the iron status–obesity association in Indonesia are warranted.

Type 2 diabetes mellitus

In the Indonesian Basic Health Research in 2018, T2DM prevalence in individuals aged >15 years was 2%[4] based on diagnoses made by a physician—higher than the 2019 global T2DM prevalence (estimated to be 9.3% [i.e., 463 million persons]).[29]

Moreover, the prevalence of AI in T2DM was high in Indonesia: 27.9% and 33.4% in well-controlled and poorly controlled T2DM, respectively.[30] This trend accords with that found by another study: 50 (34%) of 146 patients with T2DM had anemia.[31]

Both obesity and T2DM are associated with low-grade chronic inflammation.[32] In addition, hyperglycemia in T2DM can lead to increased free radical production and worsened inflammation.[33] Hyperglycemia is directly associated with the development of inflammation, as shown by increased levels of proinflammatory cytokines such as IL-6, TNF-α, and nuclear factor κB.[31] Increased IL-6 concentration can lead to a reduction in the sensitivity of the erythrocyte progenitor to erythropoietin and induce apoptosis in immature erythrocytes, in turn reducing the hemoglobin concentration.[34,35]

Studies on anemia in T2DM in Indonesia have generally focused on patients who have experienced complications in the kidney such that the cause of anemia is a combination of inflammation and impaired erythropoietin production.[26-28] The anemia incidence can increase up to 80% with increases in disease duration and kidney disorder severity.[26,28] Based on the Indonesian studies (Table 3), the average prevalence of anemia in T2DM is 49.2%.

In the data on anemia in T2DM obtained from our department patients (Table 4), the prevalence of anemia in T2DM was 79.6%—higher than the prevalence indicated by the national data. The reason for this phenomenon may be the following: as a referral hospital, our hospital receives patients with high-severity T2DM. According to our data, of 93 patients with T2DM, 74 (62.8%) patients had anemia. Of these, 58 (78.3%) had normocytic normochromic anemia, 8 (10.8%) had microcytic hypochromic anemia, 7 (9.5%) had microcytic normochromic anemia, and 1 (1.4%) had macrocytic hypochromic anemia. Our study were was in line with the 2019 study of Saraswati et al[30] in Indonesia: even when the HbA1c levels indicated severe T2DM, the mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were normal; moreover, the mean hemoglobin concentration was 13.5 (range: 8.3–17.7) g/dL.

Normocytic normochromic anemia is a common type of anemia in chronic diseases due to the erythrocyte lifecycle being shortened to 80 days in these diseases; moreover, the circulating erythrocyte removal process is related to inflammatory processes.[31]

Chronic kidney disease

Anemia in CKD was initially considered to be associated with impaired erythropoietin production, and thus, it was not considered to be AI. However, recently, inflammation was found to be involved in anemia in CKD. Inflammation increases hepcidin synthesis, promotes erythrophagocytosis, suppresses erythropoiesis in the bone marrow, and reduces erythropoietin production in the kidney. According to the 11th Report of the Indonesian Renal Registry, 78% of patients with CKD had hemoglobin concentrations <10 g/dL.[39] Patients with CKD have the highest rate of anemia, among other chronic metabolic diseases, particularly at the advanced CKD stage, reaching up to 95% (Table 5).[36-40] Minhajat et al[38] found that 95.38% of patients with CKD had anemia, most (88.56%) of whom were at CKD stage 5. Normocytic normochromic anemia was the predominant (66.13%) type of anemia in CKD, consistent with a characteristic of AI. However, microcytic hypochromic anemia was noted only in 13.71% of the patients.

Cardiovascular disease

According to the 2018 Indonesian Basic Health Research (Riskesdas),[4] CVD prevalence in Indonesia is 15 per 1000 population. In their 2018 Indonesian study, Dzakiyah et al[41] found the prevalence of anemia in chronic heart failure to be 37.5%, with most (78.1%) of the participants having NYHA Functional Class III heart failure. The

Table 4. Prevalence of anemia in various diseases in patients at Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia

Disease	n	Mean hemoglobin (g/dL)	Prevalence of anemia (%)	Type of anemia
Malignancy	92	8.1	88	70.4% Normocytic normochromic 12.4% Microcytic hypochromic 3.7% Normocytic hypochromic 1.2% Macrocytic hypochromic 12.3% Microcytic normochromic
Tuberculosis	28	11.1	67.8	57.9% Normocytic normochromic 10.5% Microcytic hypochromic 21% Normocytic hypochromic 5.2% Macrocytic hypochromic 5.2% Microcytic normochromic
HIV	58	10.4	89.6	80.7% Normocytic normochromic 9.6% Microcytic hypochromic 1.9% Normocytic hypochromic 3.8% Macrocytic hypochromic 3.8% Microcytic normochromic
Cardiovascular disease	105	11.7	62	67.9% Normocytic normochromic 29.3% Microcytic hypochromic 3% Normocytic hypochromic
T2DM	93	11.1	79.6	78.4% Normocytic normochromic 10.8% Microcytic hypochromic 9.4% Microcytic normochromic 1.3% Macrocytic hypochromic

T2DM: type 2 diabetes mellitus.

prevalence of anemia in heart failure regardless of the ejection fraction is up to 30% in outpatients and up to 50% in hospitalized patients. Anemia is associated with mortality in heart failure, with a crude mortality risk of up to 1.96. Moreover, in heart failure, anemia might be caused by several neurohormonal activations, which increase inflammatory cytokine levels, resulting in functional ID. Moreover, heart failure can cause renal dysfunction and thus eventually affect erythrocyte production. Loss of appetite in heart failure is also a common finding that leads to absolute ID. Finally, fluid retention can cause hemodilution, which in turn results in reduced hemoglobin concentrations.[42,43]

In our collected patient data, the prevalence of anemia in CVD (including heart failure and myocardial infarction) was 62% (Table 4). Of the 105 patients admitted to the cardiovascular ward, 65 (62%) patients had anemia, of whom 44 (67.7%) had normocytic normochromic anemia, 19 (29.2%) had microcytic hypochromic anemia, and 2 (3%) had normocytic hypochromic anemia. Therefore, in CVD, the predominant type of anemia was normocytic and normochromic—consistent with the characteristics of AI.

Because ID prevalence potentially contributes to ane-

Table 5. Anemia in CKD in Indonesia

No	Author	Population	Study design	Prevalence
1	Adiatma DC et al., 2014[36]	35 CKD patients with hemodialysis. stage 1-4 CKD 29%, stage 5 CKD 71%	Cross-sectional study	Total anemia: 86%, anemia of chronic disease 80%, IDA 10%, hemolytic anemia 3.3%, posthemorrhagic anemia 6.7%
2	Aisara S, Azmi S, Yanni M. 2018[37]	104 CKD patients with HD	Observational-descriptive study	Hb <7: 6.7% Hb 7-10: 68.3% Hb >10: 25%
3	Minhajat, 2016[38]	130 CKD patients stage 3b (2 pts), stage 4 (8 pts) stage 5 (120 pts), 43% with HD in RSUP dr. Wahidin Sudirohusodo Makassar	Cross-sectional study	Total anemia: 95.38% (88.56% in stage 5) Normocytic normochrom: 66.13% Microcytic hypochromic: 13.71%
4	PERNEFRI. 11th Report of Indonesian Renal Registry, 2018[39]	87,710 chronic kidney disease patients	Registry	Hb <10: 78% Hb >10: 22%
5	Suega K, Bakta M, Dharmayudha TG et al. 2005[40]	26 CKD-dialytic patients 26 CKD-predialysis patients	Cross-sectional study	96.2% in dialytic group 30.8% in the predialysis group

CKD: Chronic Kidney Disease; IDA: Iron Deficiency Anemia; HD: Hemodialysis; RSUP: Rumah Sakit Umum Pusat (Central General Hospital); PERNEFRI: Perhimpunan Nefrologi Indonesia (Indonesian Nephrology Association); Hb: Hemoglobin.

mia in heart failure, further relevant studies are recommended.

CANCER

In cancer, anemia can occur independently due to chemotherapy, typically as a consequence of chronic inflammation, and its features can resemble those of anemia in chronic inflammatory diseases. In most cases, anemia in cancer is normochromic and normocytic, with normal-to-low serum iron levels, low total iron-binding capacity,[44] and possibly, normal-to-high serum ferritin levels.

In an Indonesian study,[45] 50% of the four hematology and lymphoma malignancy cases had anemia; moreover, 47.8% of patients with solid cancer had anemia, and the factor that significantly influenced the hemoglobin concentration was radiotherapy dose: when the dose was <60 and >60 Gy, anemia prevalence was 29.4% and 57.6%, respectively. However, in 2002, Harrison et al[46] found that 41% of patients with cancer has anemia before radiotherapy initiation, and this number increased as radiotherapy progressed. Moreover, anemia prevalence was the highest in patients with uterine or cervical cancer both before and after radiotherapy (75% and 79%, respectively), and patients with head and neck cancer had the lowest mean hemoglobin concentrations during radiotherapy (1.8 g/dL).

According to our data on department patients with malignancies such as colon cancer, head and neck cancer, and ovarian cancer, the prevalence of anemia in cancer was 88% (Table 4). Of 92 patients with malignancy, 81 (88.1%) had anemia, of whom 57 (70.4%) had normocytic normochromic anemia, 10 (12.3%) had microcytic hypochromic anemia, 3 (3.7%) had normocytic hypochromic anemia, 10 (12.3%) had microcytic normochromic anemia, and 1 (1.2%) had macrocytic hypochromic anemia. Thus, our data indicated that the most common type of anemia in cancer was normocytic and normochromic—the typical AI.

TUBERCULOSIS

The highest TB burden in the world is in India, followed by China and Indonesia.[47] Indonesia has a pulmonary TB prevalence of 0.4%.[4] As a disease involving chronic inflammation, the incidence of anemia in TB is high. Pulmonary TB can be characterized by several inflammatory markers, such as C-reactive protein (CRP) and other cytokines (i.e. IFN-γ, IL-6 and TNF-α). Hence, in patients with pulmonary TB, anemia may be caused by AI, blood loss, hemoptysis, malnutrition, and pyridoxin deficiency (a side effect of isoniazid).[48]

Of all studies found in our literature search, most (n=13) were discussed anemia in patients with pulmonary TB (Table 6). The average prevalence of anemia in pulmonary TB was 50%–70%, including that of normocytic normochromic and microcytic hypochromic anemia being 5.8%–54.8% and 47%–81.48%, respectively (Table 6).[48-60] In Indonesia, in addition to inflammation, a combination of many factors such as low protein and micronutrient intake can contribute to anemia.

In one study,[61] the use of antimicrobial agents in patients with anemia in pulmonary TB completely alleviated the anemia in nearly one-third of the patients after 1 month of treatment and in approximately half of the patients after 2 months of treatment.

In the extracted Indonesian studies, the average prevalence of anemia in TB was 71.6%. In our department patients with pulmonary TB, anemia prevalence was 67.9%. Of 28 patients with pulmonary TB, 19 (67.9%) had anemia, of whom 11 (39.2%) had normocytic normochromic anemia, 4 (14.2%) had normocytic hypochromic anemia, 2 (7.2%) had microcytic hypochromic anemia, 1 (3.6%) had macrocytic hypochromic anemia, and 1 (3.6%) had microcytic normochromic anemia. In 2019, Mukherjee et al[63] also found normocytic normochromic anemia to be the predominant type of anemia in pulmonary TB, with a prevalence of 56.9%.

HIV/AIDS

In 2018, Indonesia had 640 000 individuals living with HIV, and it had an HIV infection prevalence of 0.17% among all age groups and of 0.4% among adults.[62] In 2017, the number of new HIV cases was 1.94 million globally. Although the number of new cases has decreased recently, the increased use of antiretroviral therapy has increased patient survival and in turn increased HIV prevalence (with 35.8 million individuals living with HIV).[63]

Being an infectious disease, HIV/AIDS also leads to AI in many patients (prevalence reaching 76%; Table 7).[64-67] In the Indonesian studies, the average prevalence of anemia in HIV/AIDS was 57.5%. In our department patients (Table 4), the prevalence of anemia in HIV/AIDS was 89.6% (the relatively high prevalence might be due to the generally high disease severity among our referral hospital's patients). Of all 58 patients with HIV/AIDS, 52 (80%) had anemia, of whom 42 (80.7%) had normocytic normochromic anemia, 5 (9.6%) had microcytic hypochromic anemia, 2 (3.8%) had macrocytic hypochromic anemia, 2 (3.8%) had microcytic normochromic anemia, and 1 (1.9%) had normocytic hypochromic anemia. Consistent with other worldwide reports, we also found normocytic normochromic anemia to be the predominant type of AI.

PREGNANCY

Anemia in pregnancy is common worldwide, particularly in developing countries.[5] In Indonesia, the prevalence of anemia in pregnancy (at age >15 years) was 45.1% in 1997; it then increased to 46.5% in 2000, decreased to 37.5% in 2008,[68] and finally, increased again to 48.9% in 2018.[4] The etiology of anemia in pregnancy is multifactorial. However, in general, ID is assumed to be the major cause[69,70] because anemia diagnosis is generally based on hemoglobin measurement alone. Other possible etiologies of anemia include erythrocyte disorders (e.g., thalassemia), malaria, inflammatory diseases, hookworm infestation, and other micronutrient deficiencies, which may be significant factors depending on the geographic setting and population type.[70]

More detailed laboratory examinations are required to distinguish the underlying etiologies. In their study on 399 women in the first trimester of pregnancy, Siridamrongvattana et al[71] found an unexpectedly low prevalence of anemia (19.3%), ID (20.1%), and IDA (6%); of the 77

Table 6. Anemia in pulmonary TB in Indonesia

No	Author	Population	Study design	Anemia prevalence
1	Kalma et al., 2019[49]	21 samples, including seven patients with treatment of 2 months, seven patients with treatment of 4 months, and seven patients with treatment of 6 months at Maccini Sawah Public Health Centre Makassar	Cross-sectional study	Normal hemoglobin level (42.86%) and anemia (57.14%).
2	Sundari et al., 2017[54]	74 pulmonary TB-infected patients: 61% men, 39% women; ages ranged from 18 to 63 (32.6 + 12.2) years; 24 (32%) with the Beijing strain, and 50 (68%) with non-Beijing strain infections.	Cross-sectional study	Hemoglobin level ranged from 8.6 to 14.8 (11.8) g/dL and 8.1 to 16.5 (12.0) g/dL for the Beijing strain and non-Beijing strain, respectively, with more anemia found in Beijing strain patients (71%) than non-Beijing strain (62%) patients.
3	Adzani, Dalimoenthe, Wijaya, 2016[48]	49 pulmonary TB patients	Cross-sectional study	Total: 63.26% of patients with anemia. In men: mild anemia 57.14%, moderate anemia 42.86%; in women: mild anemia 58.82%, moderate anemia 41.18%. In men: 42.86% normochromic normocytic, 42.86% hypochromic microcytic, 7.14% normochromic microcytic, and 7.14% hypochromic normocytic; in women: 5.88% normochromic normocytic, 47.06% hypochromic microcytic, 17.65% normochromic microcytic, 29.41% hypochromic normocytic.
4	Sadewo et al., 2014[55]	692 pulmonary TB patients in West Borneo (2010–2012)	Cross-sectional study	76.4% anemia -59.1% mild anemia -54.8% normocytic normochromic anemia
5	Lasut et al., 2014[56]	67 patients with pulmonary TB at Prof. Dr. R. D. Kandou Manado General Hospital (January 2014–December 2014)	Cross-sectional study	Among 67 patients, 45 patients had hemoglobin levels below the normal value or anemia (65.67%)
6	Fauziah et al., 2013[57]	30 patients with pulmonary TB, 15 men and 15 women (Haji Abdul Halim Hasan Public Health Centre Binjai)	Cross-sectional study	Hemoglobin level before treatment: men: 15.4±0.68, women: 12.94±0.33. After 3 months of treatment, men: 11.88±0.52, women: 10.42±0.44.
7	Fathan et al., 2013[58]	61 pulmonary TB patients in West Nusa Tenggara Barat Province Hospital	Case–control study	Total anemia: 78.7%; normocytic normochromic: 19.52%; microcytic hypochromic: 81.48%
8	Lokollo et al. 2010[59]	22 pulmonary TB patients aged 1–14 years in Kariadi Hospital Semarang	Case–control study	40.9% with anemia
9	Purnasari et al., 2011[60]	30 pulmonary TB child patients at Community Pulmonary Health Center (BKPM) Semarang in Jun–Jul 2011. Patients aged 1–11 years	Cross-sectional study	43.3% of pulmonary TB pediatric patients were anemic. Anemia of chronic disease was found at 61.5%, and iron deficiency anemia at 38.5%.
10	Pramono & Meida, 2003[50]	66 pulmonary TB patients; 43 men, 23 women, PKU Muhammadyah Hospital, Yogyakarta	Cross-sectional study, retrospective from medical records (2000)	65.15% anemia: 100% men, 0% women
11	Karyadi, 2000[51]	41 active TB patients (25 men, 16 women) in Cipto Mangunkusumo Hospital and 41 healthy participant (25 men, 16 women)	Case–control study	58.5% TB patients had anemia; 21.9% healthy controls had anemia. TB patients had mean hemoglobin concentrations 13% lower than healthy controls and 11% lower median hematocrit.
12	Karyadi, 2002[52]	110 TB patients before antituberculosis treatment	Double-blind, placebo-controlled trial	57% TT patients before antituberculosis treatment

TB: Tuberculosis; BKPM: Balai Kesehatan Paru Masyarakat (Community Pulmonary Health Center).

Table 7. Anemia in HIV/AIDS in Indonesia

No	Author	Population	Study design	Anemia prevalence
1	Wisaksana et al., 2011[66]	611 HIV/AIDS patients – ART naïve	Cross-sectional study	Total anemia: 49.6% of 611 ART-naïve patients. Mild anemia: 62%, mod–severe anemia: 38% 67.36% with a high ferritin level
2	Yolanda, 2016[67]	201 HIV/AIDS patients who underwent voluntary counseling and testing	Cross-sectional	76% anemia 5.5% pancytopenia
3	Massang, Edward, Purwanto, 2018[68]	68 HIV/AIDS patients, 34 with Antiretroviral agents and 34 without Antiretroviral agent; nutritional anemia was excluded	Cross-Sectional	Total Median Hb: 11.7 g/dL Median Hb in ARV group: 10.60 Median Hb in non-ARV group 12.63
4	Defiaroza, 2018[69]	10 HIV/AIDS patients	Descriptive	Mean: 13 gr%, SD: 2.26 gr%

ART: Antiretroviral Therapy; ARV: Antiretroviral.

women with anemia, 24 (31.2%) had ID, 20 (26.0%) had thalassemia-related genes, and 33 (42.9%) had unknown underlying factors.

Pregnant women have been reported to have systemic low-grade inflammation,[72] which is correlated with AI.[9] However, Finkelstein et al reported a relatively low prevalence of inflammation (CRP >5 mg/L: 17%; ambulatory glucose >1.0 g/L: 11%) and AI (hemoglobin <11.0 g/dL and serum ferritin >15.0 µg/L plus CRP>5 mg/L or ambulatory glucose >1.0 g/L: 2%) in pregnant women.[73] Nevertheless, AI risk in pregnant women with chronic infectious or metabolic diseases may still be high.[9]

In 2018, Judistiani et al[74] found that 7.5% (201) of pregnant women had anemia, with 24.9% of them noted to have hyperferritinemia. Moreover, proinflammatory cytokine levels increased in women with late pregnancy.

However, the authors did not report any inflammatory markers and reported a positive correlation between ferritin status and anemia only in the first trimester. In addition, they reported that pregnant women with low cholecalciferol levels tended to have anemia, particularly in the third trimester (relative risk: 2.96; 95% CI: 0.36–24.53). Nevertheless, vitamin D deficiency is associated with inflammatory status, and supplementation can alleviate the inflammatory status in some diseases.[75]

HELMINTHIASIS

Infection by soil-transmitted helminths (STH; i.e., helminthiasis), including *Necator americanus* (hookworm), *Ascaris lumbricoides*, and *Trichuris trichiura*, represents a major community health concern in regions worldwide.[76] The pathological process underlying the host response for helminthiasis may lead to inflammatory conditions.[77] In helminthiasis, altered intestinal iron uptake and iron metabolism and intestinal bleeding can lead to ID.[78,79] Moreover, the destruction of the intestinal mucosa impedes the absorption of nutrients, including micronutrients such as iron, negatively affecting the host's nutritional status and immune system.[80]

Globally, a main cause of IDA is infection by parasites such as hookworms, whipworms, and roundworms, which results in intestinal bleeding in the stool.[81] Hookworm infection leads to anemia by inducing chronic intestinal blood loss: infection by *Ancylostoma duodenale* and *N. americanus* can cause blood loss of 0.15–0.2 mL per day. These hookworms release anticlotting factors such as coagulase to prevent blood clots and ensure continuous blood flow.[82]

Disruption of iron absorption can also be due to damage to the intestinal integrity caused by the inflammatory process. Helminthic infection can increase inflammation: in a host, the existence of helminths is detected by the epithelial or immune cells in response to worm products; these cells then release cytokines (e.g., IL-25) from the enterocytes, promote Th2 cell proliferation, and upregulate effector mechanisms (e.g., evocation of eosinophils by IL-5), all to destroy the parasite. However, the helminths manipulate the host immune system by releasing molecules to facilitate the formation of a leaky epithelial barrier.[83] In general, this damage to intestinal integrity can reduce intestinal iron uptake and induce anemia: in children with such parasitic infections, malnutrition may occur due to a lack of essential nutrients, resulting in nutritional anemia.[84]

Prevalence of anemia due to helminthiasis in Indonesia

Approximately 42% of global STH infections occur in Southeast Asia. Of children with STH infections in Southeast Asia, 64% are from India, 15% from Indonesia, and 13% from Bangladesh. In Indonesia, 17 million preschool-age children and 42 million school-age children have an STH infection.[85] STH infection is thus one of Indonesia's leading public health issues, with a high prevalence in the range of 45%–65%. In Indonesia, the highest STH infection prevalence is 80%, mainly in areas with poor sanitation.[86] In a cross-sectional survey in Semarang, Central Java, STH infection prevalence was approximately 34% in 6466 individuals aged 2–93 years.[87] Pegelow et al[88] reported that soil-transmitted nematode infection was predominant in 8–10-year-old children in the rural area of Sukaraja, West Java: based on the testing of 348 stool samples, *T. trichiura* infection was the most prevalent (76%), followed by *A. lumbricoides* (44%) and hookworm (9%) infections. Among 365 blood samples, anemia prevalence was 13%. Moreover, the prevalence of low nutritional status was 51% in general. Table 8 lists the prevalence of anemia in helminthiasis in Indonesia from several studies.[88-98]

In several districts of North Sumatra, helminthiasis prevalence differed considerably between suburban and rural areas. A report from Medan, North Sumatra, reported a high STH infection prevalence in school-age chil-

Table 8. Anemia in Helminthiasis in Indonesia

No	Population/Location	Lab examination	Prevalence (%)					
			Any†	HK	AL	TT	SS	Anemia
1	60 students from five grade 3 and 4 elementary schools in North Pontianak, West Kalimantan[91]	Kato–Katz thick smear Blood tests	16.7					55
2	140 stools of school-age children, Makassar Sulsel[93]	Katokatz method	33.6		24.3	27.9		
3	A total of 331 individuals, aged 1 month to 44 years, Mimika Papua[94]	A single stool sample, using Real Time-Polymerase Chain Reaction for SS		17.2	23.9	18.4	32	
4	132 students, aged 8–12 years, Medan and Deli Serdang Sumut[89]	Direct examination and Kato–Katz method Cobas e601 in the hematology laboratory	7.6					11.4 (serum iron)
5	3 to 70 years Controls: n=244; intervention: n=283 Two villages, Central Java, Indonesia[95]	Microscopically, according to the Willis-Mollay flotation technique	STH: 21.7% in controls and 25.8% in the interventional group					
6	629 children aged 1–59 months from 800 households Mimika Papua[92]	Katokatz method Hb by electronc coulter counter (HB <10 gr/dL = anemia)	37.9 (105/269)	13	27.9	20.8		24.5 (122/497)
7	99 children (3–13 years old) in two villages (intervention and control) south of Semarang City[96]	Microscopic method	20					
8	418 boys and girls aged 0 to 12 years at recruitment[97]	Katokatz method Hb		-	30.6	23.4		22.4
9	8 to 10-year-old students from 10 schools located in the rural district of Sukaraja, West Java, Indonesia[88]	348 stools 365 blood samples		9	44	76		13
10	Two elementary schools in Makassar, the capital city of South Sulawesi[98]	340 stools from individuals of high socioeconomic status 271 stools from individuals of low socioeconomic status Katokatz method	22.4 vs 90.4		5.9 vs 76.8	19.1 vs 87.1		
11	1982 people assigned to albendazole treatment and 2022 to a placebo Ende, East Nusa Tenggara[90]	Polymerase Chain Reaction for HW and AL, microscopic for TT	Baseline Placebo vs Albendazole Any helm 87.2 (571/655) vs 87.7 (533/609) HK 74.5 (509/683) vs 77.3 (486/629) AL 34.9 (238/683) vs 33.2 (209/629) TT 27.1 (258/953) vs 27.8 (237/852)					

†Any: any helminthiasis. HK: hookworm; AL: *Ascaris lumbricoides*; TT: *Trichuris trichiura*; SS: *Strongyloides stercoralis.*

dren (40.3%).[89] Nasution et al[99] reported that STH infection prevalence was 76.8% in Singkuang (56 children) and 87.2% in Sikapas (242 children) primary schools: the prevalence of *A. lumbricoides* infection was 58.9% in Singkuang and 69.8% in Sikapas, that of *T. trichiura* infection was 57.1% in Singkuang and 78.1% in Sikapas, and that of hookworm infection was 1.8% in Singkuang and 19.4% in Sikapas. A consecutive fecal analysis of 132 8–12-year-old students during May–October 2016 in Public Primary School 060925 Amplas, Medan, and 101747 Hamparan Perak, Deli Serdang, indicated that the prevalence of helminthiasis was 7.6%, with that of low serum iron levels being 11.4%.[89]

In North Pontianak, West Kalimantan, helminthiasis was noted in 16.7% of 60 elementary school students, with an anemia prevalence of 55%.[91] In Mimika, Papua, helminthiasis was present in 105 (43%) of 269 children. Anemia (defined as hemoglobin <10 g/dL) was noted in 122 (24.5%) of 497 included children and was associated with hookworm carriage (OR: 2.6, p=0.026) and *Plasmodium*–helminth coinfection (OR: 4.0, 95% CI: 1.4–11.3, p=0.008).[92]

A cohort study[100] on 442 pregnant women in Purworejo District, Central Java, reported that the anemia prevalence was the highest in the second trimester (approximately 37.1%). Moreover, low iron stores were noted in approximately 49.5% women in the third trimester. Most of the included pregnant women (69.7%) were infected with at least one species of intestinal helminths; *T. trichiura* was the most common, followed by hookworm and *A. lumbricoides*.

OTHER CAUSES OF NON-NUTRITIONAL ANAEMIA

Genetic factors

Genetic disorders can also lead to non-nutritional anemia. Iron absorption may be impaired due to genetic abnormalities in the metal divalent transporter-1 gene (*MDT1*). Mutations in *MDT1* have been noted in patients with microcytic anemia, low serum ferritin levels, and liver iron overload.[101] After the iron is absorbed, it is carried by transferrin (TF) in the blood to the liver storage areas, spleen, red bone marrow, and tissues with demand for iron.[102,103] Genetic abnormalities in the TF gene can cause

atransferrinemia and IDA.[104] Moreover, iron carried by TF enters the tissue after being captured by the TF receptor (TFR). Thus, genetic abnormalities in the TFR gene can also cause anemia.

Hepcidin, a regulator of iron levels in the body, inhibits iron absorption by binding to MDT-1. Hepcidin can also attach to ferroportin and block the release of iron from the macrophages to be carried to the site of erythrocyte synthesis. *TMPRSS6* encodes the enzyme maptriptase-2, which controls hepcidin levels and thus plays a role in the development of anemia. The G allele of rs4820268 is associated with low serum iron levels.[104]

Vitamin B-12 deficiency has been linked to many complications, including increased macrocytic anemia risk. In total, 16 studies have identified single-nucleotide polymorphisms (SNPs) that exhibit significant associations with vitamin B-12 concentrations; of these SNPs, 59 are vitamin B-12-related gene polymorphisms, which are thus associated with vitamin B-12 status. However, most of the genes that could explain variations in vitamin B-12 concentrations have been identified in Caucasian populations.[105]

Megaloblastic anemia involves disturbed DNA synthesis, which results in morphologic and functional changes in erythrocytes, leukocytes, platelets, and their precursors in the blood and bone marrow. This type of anemia is characterized by the presence of large, immature, abnormal erythrocyte progenitors in the bone marrow, and 95% of megaloblastic anemia cases are attributable to folic acid or vitamin B-12 deficiency.[106]

Methylenetetrahydrofolate reductase (MTHFR) and methionine synthase reductase (MTRR) are two important folate-metabolizing enzymes involved in the remethylation of homocysteine into methionine as well as in the synthesis of DNA.[107] The common polymorphisms in *MTHFR* (C677T and A1298C) and *MTRR* (A66G) result in reduced in vivo MTHFR and MTRR activity and thus in folate metabolism impairment. Zhang et al[108] found that *MTHFR* (C677T) is strongly correlated with megaloblastic anemia and might participate in its pathogenesis.

The risk of low iron status has been assessed based on a combination of rs3811647 in the TF gene, rs7385804 in the TRF gene, and rs4820268 in *TMPRSS6*; that of low folate status was assessed using the two common *MTHFR* polymorphisms, C677T and A1298C;[108] and that of low vitamin B-12 status was evaluated using rs1801131, rs2298585, rs41281112, and rs3760776. Citrate lyase beta-like (*CLYBL*) encodes a human mitochondrial enzyme. The risk allele A of rs41281112 terminates the translation of *CLYBL*, resulting in the disruption of protein–metal ion binding and leading to vitamin B-12 malabsorption. The rs2298585 in *MS4A3* might disrupt intestinal and gastric epithelial cells rejuvenation as well as vitamin B-12 absorption.

Gastric pathogens reduce vitamin B-12 absorption in the gut. *FUT6* encodes fucosyl-transferase 6, which is involved in forming Lewis-associated antigens, which inhibit the adherence of gastric pathogens to the gastric mucosa. A study showed that rs3760775 in *FUT6* was associated with elevated vitamin B-12 levels.[105]

Iatrogenic anemia

Drugs can induce anemia via several pathways: immunohemolytic anemia, nonimmune hemolytic anemia, methemoglobinemia, megaloblastic anemia, sideroblastic anemia, aplastic anemia, and pure red cell aplasia. Immuno-hemolytic anemia due to the destruction caused by the reaction between antibodies and antigens in the erythrocyte membrane (e.g., penicillins and cephalosporins). Non-immune hemolytic anemia is hemolytic anemia that is typically caused by side effects of drugs such as primaquine and nitrofurantoin; in these cases, glucose-6-phosphate dehydrogenase deficiency is common. Methemoglobinemia, which is anemia due to excessive methemoglobin production, can be induced by several drugs that oxidize hemoglobin (e.g., phenazopyridine, dapsone, primaquine, local anesthetics, isobutyl nitrite). Acquired megaloblastic anemia can be caused by vitamin B-12 with or without folic acid deficiencies induced by drugs such as trimethoprim, pyrimethamine, sulfasalazine, phenytoin, and antiretrovirals. Drugs such as isoniazid, chloramphenicol, and linezolid can cause sideroblastic anemia by interfering with heme biosynthesis. Aplastic anemia—the failure to produce blood cells (hemoglobin, leukocyte, and platelet)—can be induced by chloramphenicol, sulfonamide, trimethoprim/sulfamethoxazole, and other drugs that can suppress bone marrow function. Pure red cell aplasia can be caused by azathioprine and other immunosuppressants, linezolid, isoniazid, rifampin, IFN-α, chloroquine, allopurinol, and other drugs.[109]

Iatrogenic anemia or hospital-acquired anemia occurs after blood loss due to medical procedures such as surgery, hemodilution due to excessive intravenous fluid administration, and phlebotomy. Surgery can cause blood loss in >20% cases, particularly in high-risk surgical procedures. Phlebotomy also contributes to hospital-acquired anemia.[110,111] Thavendiranathan et al[112] showed that every milliliter of blood drawn can reduce hemoglobin by 0.07±0.011 g/L.

CONCLUSIONS

Despite the many governmental measures, anemia remains a major public health problem in Indonesia. A possible reason for the failure of anemia intervention to reduce anemia prevalence is that the causes underlying anemia are not only nutritional but also non-nutritional. AI, the most common type of non-nutritional anemia, is associated with chronic infectious diseases and NCDs. IDA can also coexist in patients with chronic AI. Anemia in helminthiasis is another type of non-nutritional anemia. For comprehensive and successful mitigation of anemia prevalence in Indonesia, the causes of nutritional and non-nutritional anemia, including genetic and iatrogenic factors must be acknowledged and addressed.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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Review Article

Nutritional anemia: Limitations and consequences of Indonesian intervention policy restricted to iron and folic acid

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Background and Objective: Currently, anemia is a severe public health issue in Indonesia. The aim of this review was to examine policy measures and program implementation to reduce anemia attributed to iron deficiency in Indonesia. **Methods and Study Design**: A literature search was conducted using Google Search, Sciencedirect.com, and PubMed to retrieve relevant studies in the last three decades. Qualitative data were also obtained from service providers. The search yielded 141 articles, of which 32 were excluded, and further screening was conducted based on the type and scale of the intervention program. **Results**: In the iron–folic acid (IFA) supplementation programs studied, antenatal care and health personnel capacity information were limited. Implementation often did not correspond to standard operating procedures. Analysis, follow-up, and feedback on IFA tablet programs were lacking. Moreover, the IFA tablet supply was inadequate, facilities and infrastructure were insufficient, and counseling guidance, relevant material, and information media were lacking. In the national fortification program, wheat flour was used as a vehicle for anemia prevention. However, evidence from the Total Diet Study indicated that wheat noodles have limited value across the Indonesian archipelago. **Conclusion**: Programs to reduce the likelihood of anemia will be more successful if they are less dependent on nutrient-specific strategies and focus more on the pathogenetic complexity arising from personal behavior, sociocultural factors, dietary and health patterns, local community, and ecology. Partnerships between the community and government reflected in evidence-based policy will always be of value, but continued research is required to examine the factors contributing to the successful outcomes of such programs.

Key Words: iron deficiency anemia, Indonesia, program policy, supplementation, fortification

INTRODUCTION

In patients with anemia, the number and size of red blood cells or the hemoglobin concentration is below the established cut-off value, consequently impairing blood's oxygen-transporting capacity.[1-4] Anemia is an indicator of both poor nutrition and poor health.[5] Anemia, especially that due to iron deficiency (IDA), is the most common micronutrient deficiency, especially among children under 5 years and women of reproductive age.[6,7] It leads to a higher risk of infections as well as impaired cognitive function and physical work capacity. Moreover, maternal anemia is associated with intrauterine growth restrictions.[6] If treated early, anemia due to acute blood loss has a favorable prognosis. Iron supplementation is a relatively inexpensive intervention for treating and preventing anemia related to iron deficiency.[6,8,9]

According to the 2018 Global Nutrition Report, globally, the incidence of anemia has increased slightly to 32.8%.[10] In 2016, Indonesia had the highest anemia prevalence (42%) among pregnant women compared with that in neighboring countries such as Malaysia (37%), Singapore (32%), Brunei Darussalam (27%), Vietnam (37%), the Philippines (30%), and Thailand (40%).[11]

Anemia is considered a public health concern when the national anemia prevalence among women of reproductive age (15–49 years) is ≥20%. Public health concern related to anemia is categorized as mild, moderate, and severe when the prevalence is 5%–19%, 20%–39%, and >40%, respectively.[12] On the basis of the 2018 Basic Health Research project, the anemia prevalence among pregnant women in Indonesia increased from 37.1% in 2013 to 48.9% in 2018, and currently, it is a severe public health issue.[13]

In 2012, the World Health Assembly Resolution endorsed the implementation of a comprehensive plan for maternal, infant (younger than 1 year), and young-child nutrition;[14] a 50% reduction of anemia in reproductive-age women was specified as one of six global nutrition targets for 2025.[15] There has been an increase in the number and breadth of national nutrition policies and nutrition

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targets, and their financing and implementation are outstanding challenges. More countries are prioritizing nutrition by establishing national nutrition policies and action plans: 164 countries have such plans, 61% of which are multisectoral.[10] Public health strategies for anemia prevention and control include improvements to dietary diversity; food fortification with iron, folic acid, and other micronutrients; distribution of iron-containing supplements; and control of infections and malaria.[5]

For more than three decades, Indonesia has implemented an iron intervention program. Since the 2000s, iron has been added to wheat flour as mandatory fortification. This food-based approach has been promoted. However, currently, anemia is a severe public health and nutrition issue. This paper aims to review policy measures and program implementation to reduce anemia attributed to iron deficiency in Indonesia.

IRON DEFICIENCY ANEMIA IN INDONESIA

Anemia was listed as a public health burden worldwide in 2011; the World Health Organization (WHO) reported that the prevalence of anemia is the highest in children (42.6%) and the lowest in nonpregnant women (29.0%).[16] Anemia is currently among the most common and intractable nutritional problems globally. It is a global public health problem affecting both developing and developed countries, with major consequences for human health and social and economic development. WHO estimates the number of anemic people worldwide to be 2 billion in which 50% of all anemia cases attributable to iron deficiency. Iron deficiency anemia occurs at all stages of life but is more prevalent in pregnant women and young children. Adolescents, particularly girls, are vulnerable to iron deficiency. The 2002 World Health Report identified iron deficiency as one of the 10 most severe risks in countries with high infant and adult mortality.[17] A previous study also reported that addressing iron deficiency anemia is one of the most cost-effective public health interventions.[18]

The 2013 Basic Health Research in Indonesia showed that the prevalence of anemia in children aged 1–4, 5–14, and 15–24 years was 28.1%, 26.4%, and 18.4%, respectively.[19] The prevalence of anemia increased compared with that in the previous survey conducted in 2007, which was 27.7%, 9.4%, and 6.9% in children aged 1–4, 5–14, and 15–24 years, respectively.[20] In particular, the prevalence of anemia in school-age children and adolescents almost tripled. The Basic Health Research project also showed that the anemia prevalence was higher in the suburbs than in urban areas.[19]

Compared with anemia prevalence estimates in 1997, anemia prevalence estimates were lower in 2008 for all groups, with the greatest decline occurring in children aged 5 to 11 years (25.4%). The highest prevalence of anemia was observed in children aged 0–5 years, those aged 12–15 years, and nonpregnant and pregnant women in 2000. However, a chi-squared trend analysis revealed that the anemia prevalence declined significantly in all groups over the survey years (p=0.005 for pregnant women, p<0.0001 for all other groups). From this first-ever trend analysis of anemia in different populations in Indonesia, we concluded that the prevalence of anemia has decreased from 1997 to 2008 in all age and sex groups studied. Despite this progress, anemia remains a moderate public health problem in children aged <12 years and >15 years and in nonpregnant and pregnant women.[21]

In 1996, Muhilal reported that the prevalence of anemia among pregnant women in various parts of Indonesia ranged between 38.0% and 71.5%, and the average prevalence for the general population of Indonesia was approximately 63.5% (Table 1).

Unexpectedly, Java, the most developed part of Indonesia, was among the areas with the highest anemia prevalence of 57.8%–71.5%. Irian Jaya, one of the less developed areas, had the lowest prevalence (38%).[22] Moreover, the 1992 Household Health Survey showed that 63.5% of pregnant women and 55% of children under five had iron deficiency anemia. Similarly, the 1995 Household Health Survey showed that 50% of pregnant women had anemia. Pregnant women are the most at-risk population, and the prevalence of anemia (defined as hemoglobin <11 g/L) among this population is approximately 60% in Indonesia.[23] Among reproductive-age women, the prevalence of anemia in Indonesia is 30%–40%.[24]

In 1996, the prevalence of anemia in preschool children in various parts of Indonesia ranged between 35.8% and 60.6%, and the average prevalence at the national level was 55.5%. Similar to the situation for pregnant women, the lowest prevalence in preschool children was observed in Irian Jaya (35.8%). In Central Java, the prevalence in school children (44.9%) was the lowest, whereas the prevalence in pregnant women (62.5%) was the highest.[22] Nationally, the prevalence of anemia in children under 5 years was 28.1% and in children aged 5–14 years it was 26.4%.[19] Thus, with a cut off of anemia prevalence ≥40%, anemia has become a severe public health problem in Indonesia.

CURRENT POLICY AND IMPLEMENTATION

Iron Supplementation

Research on gardeners in Indonesia showed that the ad-

Table 1. Anemia prevalence in children, women, and men measured during the second, third, and fourth waves of the Indonesia Family Life Surveys (IFLS)

Group	Year	Anemia (%)
Children 0–4 y	1997/8	46.0
	2000	54.6
	2007/8	31.4
Children 5–11 y	1997/8	46.0
	2000	36.4
	2007/8	20.6
Children 12–15 y	1997/8	27.5
	2000	28.2
	2007/8	15.8
Women >15 y (nonpregnant)	1997/8	36.0
	2000	38.8
	2007/8	26.6
Women >15 y (pregnant)	1997/8	45.1
	2000	46.5
	2007/8	37.3
Men >15 y	1997/8	29.0
	2000	22.8
	2007/8	15.4

Source: Barkley, 2015 [21]

ministration of 100 mg iron for 60 days resulted in a significant improvement in hematological status, performance, work output, and morbidity among anemic workers.[25] This result endorses the WHO recommendation of an iron supplementation program for pregnant mothers.

Supplementation with daily oral iron and folic acid is recommended by WHO as a part of antenatal care to reduce the risks of low birth weight, maternal anemia, and iron deficiency (strong recommendation). Management of major nutrition deficiency in Indonesia, including nutritional anemia, is an important part of the effort to reduce infant and toddler mortality. Hence, since 1985 several activities related to Family Nutrition Improvement Efforts (*Upaya Perbaikan Gizi Keluarga-UPGK),* such as toddler weight measurement, mother and child nutrition counseling, vitamin A supplementation, iron tablets, and oral rehydration salt administration, were conducted in *Posyandu* (Integrated Healthcare Center) as an integrated service. In the first 3 years of REPELITA (Five-Year Development Plan) IV, more than 2 million pregnant mothers had received iron tablets: 150,000 individuals in 1984/85; 660,000 individuals in 1985/86; and more than a million individuals in 1986/87.[26]

Jus'at demonstrated that the iron folic acid supplementation program (iron–folic acid [IFA] tablets) implemented in collaboration with the Religious Office (*Kantor Urusan Agama-KUA*), accompanied by the provision of education (KIE) on the importance of IFA tablets and their early consumption prior to pregnancy, reduced anemia prevalence from 23.8% to 14.0% during the program.[27] The research findings caused the release of PERMENKES RI (The Minister of Health of Republic of Indonesia Regulation) Number 97 of 2014 on Health Services Prior to Pregnancy, which aims to eradicate anemia problems.

The Regulation of Minister of Health Number 97 of 2014 on Health Service During Pregnancy states that every pregnant mother should receive a minimum of 90 IFA tablets during pregnancy from the first contact and must also be provided counseling and education on the benefits, side effects, storing instruction, and methods of consuming IFA tablets. Moreover, PERMENKES RI Number 88 of 2014 on Iron Folic Acid Tablets Standard for Reproductive Women and Pregnant Mothers and PERMENKES RI Number 51 of 2016 on Standard Nutritional Supplementation Product were established.

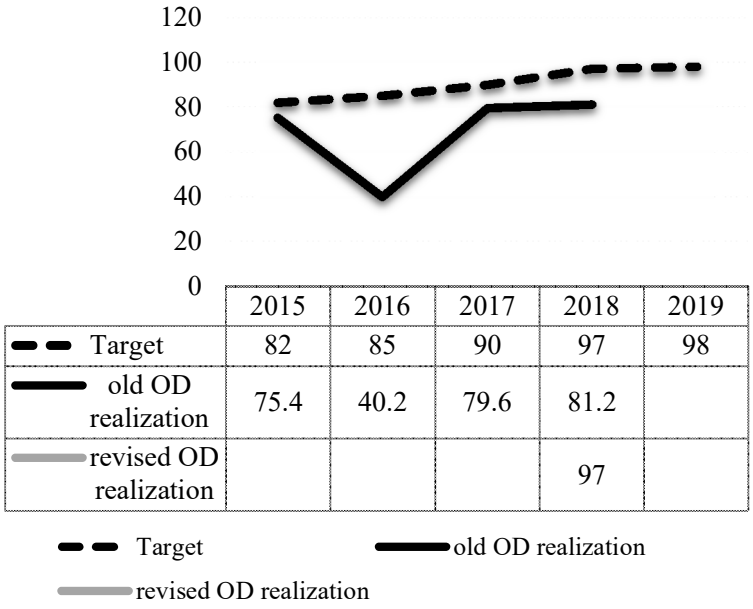
The Ministry of Health (MoH) through PERMENKES RI Number 88 of 2014 released the new technical specification for IFA tablets, which was valid from 2016. This new technical specification regulates the composition, dosage, and packaging of IFA tablets with the aim of increasing the effectiveness of IFA tablet administration. Each IFA tablet consists of ferrous fumarate iron equal to 60 mg elemental iron and 0.400 mg folic acid. The dosage specification is in accordance with the WHO recommendation.[28]

PERMENKES RI Number 51 of 2016 on Standard Nutritional Supplementation Products mentioned that for iron and folic acid tablets, iron is added in the form of a ferrous fumarate compound to increase the effectiveness of IFA tablet administration. However, Toto Sudargo, Dewanti, and Vista Ari Rahmawati showed that Fe-fumarate IFA tablets had reduced compliance among pregnant mothers in Yogyakarta, whereas commercial IFA tablets had higher compliance rates because of their preferable flavor, smaller tablet size, and fewer side effects.[29] Fitriana evaluated IFA tablet program adherence in female adolescents in East Sempaja, Palu, in which Kimia Farma IFA tablets were replaced with Hemafort Pharos; female adolescents preferred Hemafort Pharos IFA tablets.[30] Both types of IFA tablets are Fe-fumarate, but Hemafort Pharos tablets contain multinutrients, whereas Kimia Farma IFA tablets contain only iron and folic acid. IFA tablets with multinutrients tend to be more favored and could have higher compliance (in terms of IFA tablet consumption) than IFA tablets, which contain only folic acid and iron (regardless of whether it is Fe-Fumarate or not).

According to the 2018 Basic Health Research project, the proportion of female adolescents receiving IFA tablets was as low as 22.9%, whereas the proportion was 48.5% in the Performance Report of the Directorate of Community Nutrition of the MoH. This discrepancy is caused by the data collection methods. The percentage of girls who receive IFA tablets (TTD) was determined as the percentage of girls aged 12–18 years in junior high/high school or equivalent who receive regular iron tablets every week. Each teenage girl is expected to receive 52 iron tablets for 1 year.[31] On the basis of the survey results, the main reasons why female adolescents did not consume IFA tablets were the bad taste and smell of IFA tablets and because they believed that it was unnecessary to consume the tablets.[13]

The 2018 Basic Health Research project revealed that the percentage of pregnant women who received IFA tablets was 73.2%, which is slightly lower than the percentage of pregnant women who received IFA tablets in the 2018 Performance Report of the Directorate of Community Nutrition, MoH (81.2%). A positive trend was found for the percentage of pregnant women who received 90 IFA tablets during pregnancy from 2015 to 2018, even though it was still below the target (Figure 1). Moreover, the level of compliance of pregnant women in consuming ≥90 iron tablets during pregnancy only reached 38.1%.[13,32] Generally, the main reasons for noncompliance with IFA consumption by pregnant women were dislike, boredom, forgetfulness, feeling nauseous, and/or vomiting due to pregnancy.[13]

Tablet consumption was defined as the taking of IFA tablets containing iron and folic acid, both from the program and independently, by adolescent girls or pregnant women. This definition does not accurately describe the government's capacity to cover the requirements of IFA tablets in the supplementation program. On the basis of information related to the realization of iron supplement availability from the Directorate of Public Medicines and Health Supplies, the Directorate General of Pharmacy and Health Equipment, MoH, the iron supplement supply in 2017 was only 75% due to budget efficiency measures. Starting from 2019 to 2020, each region in Indonesia outside the stunting locus (priority area of stunting) was required to procure IFA tablets using Health Special Allocation Funds (DAK). IFA tablets for regions in the stunting locus were procured using the central budget. For 2021, the procurement of all iron supplements (in regions both in the stunting locus and outside the stunting locus) will be conducted by the center.



	2015	2016	2017	2018	2019
Target	82	85	90	97	98
old OD realization	75.4	40.2	79.6	81.2	
revised OD realization				97	

Figure 1. Percentage of pregnant women who received 90 IFA tablets during pregnancy (2015–2018). Source: Directorate of Community Nutrition of the MoH, 2018.[32]

Table 2 provides a summary of IFA tablet supplementation program evaluation in various areas in Indonesia. In general, the quality of antenatal care was low; the capacity of health personnel was low; IFA tablet program implementation did not correspond to the SOP; analyses, follow-up, and feedback were lacking in IFA tablet program reports; facilities and infrastructure were insufficient; counseling guidance was lacking; and counseling material, information media, and IFA tablet supply were insufficient.

On the basis of the Directorate of Community Nutrition's 2018 Budget Realization Report, the available budget for procuring IFA tablets for pregnant women was Rp 6,283,713,000, and Rp 5,810,354,524 of this amount has been spent (amounting to 92.47% of the total budget).[32] According to the results of an inspection, the Audit Board of the Republic of Indonesia (BPK-RI) concluded that the MoH of the Republic of Indonesia was not effective in managing funds for goods in 2018. Rp 6.13 billion of state money was wasteful spending; IFA tablets remained undistributed throughout 2018 until the expiration date in 2019. The MoH has not conducted adequate planning for delivering goods to local governments. The calculation for planning the need of goods was not carried out with the adequate basic variables for the central and regional governments. The variables used in the calculation at the provincial health office differ between the program implementing division and the pharmaceutical installation division. This has resulted in an inconsistency in the planning calculations for IFA tablet (TTD) procurement by provincial health offices; these calculations are used in the joint preparation of the drug given nationally. An examination of the dropping realization due to this inappropriate planning showed that a proportion of vitamin A tablets and IFA tablets for pregnant women and teenage girls was not used by the expiration date, resulting in a loss of IDR 6.13 billion.[33]

Supplementation is generally effective on a small scale. However, when it is implemented on a larger or national scale, its effectiveness is influenced by four aspects: appropriate planning for procurement and distribution, preparation of health service providers and communication with mothers, quality control and effective product traceability, and intensive monitoring and supervision.[34] WHO guidance for iron and folic acid supplementation has already emphasized the following:

"The implementation of a behavior change communication strategy to communicate the benefits of the intervention and management of side effects is vital to improving the acceptability of and adherence to recommended supplementation schemes".[6]

Iron fortification

For reducing anemia, the fortification program is considered cheaper and more effective than the supplementation program. WHO recommends iron fortification in various compound categories, including water-soluble, poorly water-soluble but soluble in dilute acid, water-insoluble, and poorly soluble in dilute acid, and encapsulated forms. The selection of the iron fortificant depends on the type of food vehicle targeted for fortification because it influences the effectiveness of iron fortification in terms of iron availability.[35] The iron compounds recommended by WHO to fortify cereals are ferrous sulfate, ferrous fumarate, ferric pyrophosphate, and electrolytic iron.[36]

In 1993, the New Order Government established the State Ministry of Food Affair and initiated a policy on food fortification and strengthened it in REPELITA III in one of the chapters of Food Law of 1996 Article 27. Chapter III on Food Quality and Nutrition in Article 27 of the Law states the following: "In terms of deficiency or decrease in society's nutritional status, the government can set requirements for improvement and enrichment of certain circulated food nutrient." The term nutrient enrichment means fortification. In response to the effectuation of this food law, the MoH issued a ministerial decree dated

Table 2. Evaluation studies of the iron supplementation program for adolescent girls and pregnant women in various regions of Indonesia

No	Authors (year)	Title	Location	Method	Result	Suggestion
1	Siekmans et al. (2018)[79]	Barriers and enablers of IFA supplementation for pregnant women	Afghanistan, Bangladesh, Indonesia, Ethiopia, Kenya, Nigeria, Senegal	Formative research was conducted using mixed qualitative and quantitative methods. Indonesia: FGD: PW or PPW (n=6 groups), influential persons (n=6 groups); IDI: PW or PPW (n=24), key influencers (n=24), village health workers—midwives or nurses (n=6), facility health workers (n=12), TBA (n=8), cadres or CHWs (n=8), community leaders (n=12), district and provincial level (n=18)	Opportunity: All pregnant mothers and health care workers understand the description of anemia symptoms. Hindrance: - Pregnant mothers do not think that they are at risk. - The low access and quality of ANC services reduce the scope of and compliance with IFA tablet consumption: a. Inadequacy of IFA tablet provision b. Insufficiency of counseling to encourage compliance with IFA tablet consumption	- Community-based delivery and counseling of IFA and referral to ANC - Improve ANC access and quality - Renewed investment in training for service providers - Ensure effective behavioral changes
2	Natalia et al. (2017)[80]	The scope of ANC and Fe tablets, their relationship with anemia prevalence in East Java	21 Regencies/ Cities in East Java	Quantitative study using secondary data from a regency/city on anemia prevalence in pregnant mothers with Hb level of <11 g/dL registered in the Nutrition and Family Health Section of East Java Province Health Services. Data analysis was through Pearson correlation.	- There was no correlation between ANC coverage and Fe tablets and anemia prevalence (p>0.05). - The coverage of Fe tablet administration to pregnant mothers through ANC services did not describe high or low anemia prevalence in pregnant mothers.	
3	Toto Sudargo, Dewanti, Vista Ari Rahmawati (2020)[29]	Comparing the efficiency between commercial and governmental iron-folic acid (IFA) supplement among pregnant women in Yogyakarta and Sleman	Yogyakarta City and Sleman Regency within the Yogyakarta Province	Using the mixed-method approach, the study evaluated and compared the efficiency between commercial IFA and IFA provided free by the government to pregnant women across all community health centers (Puskesmas). Hemoglobin was measured using a rapid test kit to determine anemia status. An interview was conducted to qualitatively evaluate participants' perception toward both types of supplementation.	- Yogyakarta had the highest prevalence of anemia (35.49%), whereas the prevalence was 8.90% in Sleman. - Yogyakarta City has preferably been using commercial IFA, replacing supplements provided by the government, since 2006, whereas in Sleman Regency, a similar change was noted between 2015 and 2018. However, in 2019, modified IFA was introduced in Sleman with Fe-Fumarate as the iron compound, replacing Fe-Sulfate. This has caused a decrease in compliance, leading to a return to the use of commercial IFA. - In Yogyakarta City, total coverage (100%) was achieved with commercial IFA in Puskesmas Danurejan 2, whereas the lowest coverage (66.9%) was found in Puskesmas Mantrijeron. In Sleman Regency, the highest and lowest coverage was 99.14% (Puskesmas Depok 2) and 77.68% (Puskesmas Pakem), respectively. - The use of commercial IFA has resulted in higher compliance as it has a more preferable taste and flavor, smaller size, and fewer side effects.	The use of commercial IFA in the government supplementation program to improve compliance and acceptance among pregnant women.

PPW: postpartum women; PW: pregnant women; CHW: community health worker; FGD: focus group discussion; IDI: in-depth interview; IFA: iron–folic acid; TBA: traditional birth attendant; ANC: antenatal care; IDA: iron deficiency anemia; IFE: internal factor evaluation; EFE: external factor evaluation; SWOT: strengths, weaknesses, opportunities, and threats; AHP: analytical hierarchy process; SOP: standard operating procedure; Hb: Hemoglobin.

Table 2. Evaluation studies of the iron supplementation program for adolescent girls and pregnant women in various regions of Indonesia (cont.)

No	Authors (year)	Title	Location	Method	Result	Suggestion
4	Rahmiati et al. (2018)[81]	Qualitative study about factors and strategy improvement of iron supplementation on pregnant woman in Tasikmalaya District	Tasikmalaya Regency	Cross sectional study and in-depth interview with the head of the IDA tablet program stakeholder. IFE and EFE analyses were used to reveal the situation of IDA supplementation. A SWOT analysis was used to provide an alternative strategy, and the AHP was used to determine the priority of strategies.	- An IFE score of 2.14 demonstrates that internally, the program did not optimize the strengths and did not improve the weaknesses. - EFE score of 2.10 indicates that the program did not optimize opportunities and did not improved the weakness.	- The alternative strategy involved the improvement of commitment, roles, and partnerships among stakeholders; the improvement of the action program; the improvement of facilities and infrastructure; and the improvement of health worker capacity.
5	Permatasari et al. (2018)[82]	The effectiveness of an iron supplementation program among adolescent girls in Bogor City	Bogor City, West Java Province	Quasi-experiment, pre–post intervention, effectiveness study. This study was performed parallel to the Prevention and Management Program of IDA on Junior High School and High School Adolescent Girls that was conducted by the Health Service of Bogor City (by administering iron supplement tablets; 60 mg of elemental iron and 0.25 mg of folic acid) for 16 weeks, with weekly supplementation and 10 tablets during the menstrual period. Tablets that must be consumed were 52 in total.	- The anemia prevalence among adolescent girls decreased after the intervention. The most influential factor for the increase in the Hb level in this study was the initial status of Hb. - The IDA Prevention Program was considered as ineffective, though there was a decrease in prevalence. The level of IFA tablet consumption compliance was still low.	- The IFA tablet administration program should be conducted by ensuring that participants consume the tablets together on the appointed day to increase compliance and place their compliance card on the shelf in their classroom. - The popularization of IFA tablet consumption for parents should be conducted so that students can obtain support and parents can understand the importance of consuming IFA tablets and provide food that is rich in iron, particularly animal-derived food, which is rarely consumed by participants (meat, chicken, liver, and fish).

PPW: postpartum women; PW: pregnant women; CHW: community health worker; FGD: focus group discussion; IDI: in-depth interview; IFA: iron–folic acid; TBA: traditional birth attendant; ANC: antenatal care; IDA: iron deficiency anemia; IFE: internal factor evaluation; EFE: external factor evaluation; SWOT: strengths, weaknesses, opportunities, and threats; AHP: analytical hierarchy process; SOP: standard operating procedure; Hb: Hemoglobin.

Table 2. Evaluation studies of the iron supplementation program for adolescent girls and pregnant women in various regions of Indonesia(cont.)

No	Authors (year)	Title	Location	Method	Result	Suggestion
6	Briawan et al. (2009)[83]	The determinant of success iron supplementation program for school students	Bekasi	The intended success of the program is determined based on a change in anemia status and increase in hemoglobin level. The brand of the capsules provided for the IDA Prevention Program by Bekasi Health Service was Diabion. The analyzed variables were capsule consumption compliance, health status, and initial status of anemia, age, nutritional status, and hand-washing habits as well as animal food consumption frequency.	- Overall, anemia prevalence was reduced, but a difference was noted between the change pattern of anemia prevalence of high school girls, which was increasing, and that of junior high school girls, which was also increasing. - The average compliance level of capsule consumption was 84.9% (good) presumably due to the absence of side effects - A relationship was found between initial anemia status, menstruation status, hand-washing habit, animal food consumption frequency, and increase in hemoglobin level. - The determinants of the iron supplementation program (the anemia status change and the increase in the hemoglobin level) were hand-washing habits and initial status of anemia.	The frequency of students' consumption of animal food was very low; this should be of concern to parents.
7	Dahlia et al. (2013)[84]	The evaluation of iron tablet administration program for pregnant mothers at Binamu Community Health Center, Binamu Subdistrict, Jeneponto Regency	The area of Binamu Community Health Center, Binamu Subdistrict, Jeneponto Regency.	This was a descriptive survey study describing the IFA tablet program implementation for pregnant mothers in terms of input, process, and output through interviews and observations.	- The availability of IFA tablets was not sufficient. - No technical guidance was available. - In the planning process (Health Office Work Unit Budget Plan), planning for IFA tablet accessibility based on the target/beneficiary was not conducted.	
8	Tuju et al. (2013)[85]	The analysis of IFA administration program implementation by midwife in community health center in the area of South Minahasa Regency Community Health Center	17 subdistricts of South Minahasa Regency	The type of research was observational descriptive analytic and cross-sectional.	- The variable affecting the implementation of the IFA tablet program was bureaucracy - The implementation of the IFA tablet program did not follow the existing SOP.	- Provision of education for midwives regarding the benefits in complying with the SOP of IFA tablet administration. - Give incentives to midwives who must implement the program in accordance with standards that fulfill coverage requirements.

PPW: postpartum women; PW: pregnant women; CHW: community health worker; FGD: focus group discussion; IDI: in-depth interview; IFA: iron–folic acid; TBA: traditional birth attendant; ANC: antenatal care; IDA: iron deficiency anemia; IFE: internal factor evaluation; EFE: external factor evaluation; SWOT: strengths, weaknesses, opportunities, and threats; AHP: analytical hierarchy process; SOP: standard operating procedure; Hb: Hemoglobin.

Table 2. Evaluation studies of the iron supplementation program for adolescent girls and pregnant women in various regions of Indonesia (cont.)

No	Authors (year)	Title	Location	Method	Result	Suggestion
9	Secapramana (2015)[86]	Fe tablet administration at Klari Subdistrict Community Health Center, Karawang Regency, West Java.	Klari Subdistrict Community Health Center, Karawang Regency, West Java	An evaluation was conducted by comparing the coverage of the Fe tablet administration program for pregnant mothers in Klari Subdistrict Community Health Center, Karawang Regency, West Java, from January to December 2015 using the standard system approach.	- The need for Fe tablets in Klari Community Health Center, Kawarang Regency, was 277,200 Fe tablets. The provision of Fe tablets was conducted by the government and a private party. - Leaflets and posters for education were absent. - Transportation was available, but there were some areas that could be reached by car. - The majority of the population in Klari subdistrict, Karawang Regency, have low education, and many pregnant mothers had not checked their pregnancy status regularly, and some of them were purposely not taking the Fe tablet or not consuming them. - In the planning of the program, no written data were available. - Planning for the designated service for Fe distribution does not exist. - No recording or reporting was performed.	NA
10	Maitri et al. (2017)[87]	The Evaluation of iron folic acid (IDA) tablet administration as the preventive and curative effort for anemia among pregnant women at Kraton Community Health Center in Yogyakarta City.	Kraton Community Health Center in Yogyakarta City	Data were obtained from secondary data and an in-depth interview with the chief of the Community Health Center, KIA staff, nutrition staff, pharmaceutical personnel, the cadre of pregnant mothers' companions, and pregnant mothers; also, interviews were conducted using questionnaire to determine the knowledge level of pregnant mothers.	- The level of IFA tablet consumption compliance was good. Education related to IFA tablets from midwives was good, and there were high levels of knowledge, self-motivation, and family support, with an absence of side effects from consuming IFA tablets. The high prevalence of anemia in pregnant women in 2016 (33%), was caused by the following: - The lack of IFA tablet distribution. - The consumption of various IFA tablets from the market with an IFA content that did not meet the standard - IFA tablet administration was not performed from the beginning of the pregnancy. - The consumption pattern of pregnant mothers was not appropriate.	NA
11	Fitriana and Dwi Pramardika (2019)[30]	Evaluation of iron folic acid tablet program for female adolescents	Bengkuring Community Health Center, East Sempaja, Palu	Evaluation research using the qualitative research method in the form of in-depth interviews followed by content analysis. The quantitative method was performed to examine Hb level.	- As many as 3 of 10 female adolescents in the Integrated Service Unit Community Health Center of Bengkuring had anemia. - The replacement of IFA tablet Kimia Farma (2018) with Hemafort Pharos (2019) increased compliance among female adolescents in the IFA tablet program. - Facilities and infrastructure were lacking in the anemia and IFA tablet program. - There was a discrepancy in distribution, which was performed once a month at Bengkuring Community Health Center. - Monitoring of IFA tablet consumption compliance and hemoglobin levels in female adolescents was not performed.	NA

PPW: postpartum women; PW: pregnant women; CHW: community health worker; FGD: focus group discussion; IDI: in-depth interview; IFA: iron–folic acid; TBA: traditional birth attendant; ANC: antenatal care; IDA: iron deficiency anemia; IFE: internal factor evaluation; EFE: external factor evaluation; SWOT: strengths, weaknesses, opportunities, and threats; AHP: analytical hierarchy process; SOP: standard operating procedure; Hb: Hemoglobin.

Table 2. Evaluation studies of the iron supplementation program for adolescent girls and pregnant women in various regions of Indonesia (cont.)

No	Authors (year)	Title	Location	Method	Result	Suggestion
11	Fitriana and Dwi Pramardika (2019)[30]	Evaluation of iron folic acid tablet program for female adolescents	Bengkuring Community Health Center, East Sempaja, Palu	Evaluation research using the qualitative research method in the form of IDI followed by content analysis. The quantitative method was performed to examine Hb level.	- The data on IFA tablet program were not recorded in the report book by the school. - No analysis or follow-up was conducted, and feedback was not available in the IFA tablet program report from schools, community health centers, or Samarinda Health Services. - There was an inconsistency between the aim and objective of the IFA tablet program of the community health center.	NA
12	Triana Mutmainah et al. (2014)[88]	Analysis of the differences between the implementation of and iron tablet supplementation program for pregnant mothers by the nutrition officer of a high-coverage community health center and by the nutrition officer of a low-coverage community health center in Kendal Regency Area.		Qualitative design presented in a descriptive, exploratory manner with the type of case study through IDI and observations.	- A specific bureaucratic structure does not exist - No SOP was available. - The coverage was still much lower than the minimum service standard. - The implementer was not aware that IFA tablet supplementation is important. - The delivery of information and education to pregnant mothers was not considered as an important part of the program because the program had been running for a long time. - The specific promotional material and information media for the IFA tablet supplementation program for pregnant mothers were not available. - All of the community health centers do not have counseling guidance and implementation instructions for the IFA tablet supplementation program.	NA

PPW: postpartum women; PW: pregnant women; CHW: community health worker; FGD: focus group discussion; IDI: in-depth interview; IFA: iron–folic acid; TBA: traditional birth attendant; ANC: antenatal care; IDA: iron deficiency anemia; IFE: internal factor evaluation; EFE: external factor evaluation; SWOT: strengths, weaknesses, opportunities, and threats; AHP: analytical hierarchy process; SOP: standard operating procedure; Hb: Hemoglobin.

Table 3. Average levels of nutrients to be added to fortified wheat flour based on extraction, fortificant compound, and estimated per capita flour availability

Nutrient	Flour extraction rate	Compound	Level of nutrient to be added in parts per million (ppm) by estimated average per capita wheat flour availability (g/day)†			
			<75‡	75–149	150–300	>300
Iron	Low	NaFeEDTA	40	40	20	15
		Ferrous sulfate	60	60	30	20
		Ferrous fumarate	60	60	30	20
		Electrolytic iron	NR§	NR§	60	40
	High	NaFeEDTA	40	40	20	15
Folic acid	Low or high	Folic acid	5	2.6	1.3	1
Vitamin B-12	Low or high	Cyanocobalamin	0.04	0.02	0.01	0.008
Vitamin A	Low or high	Vitamin A palmitate	5.9	3	1.5	1
Zinc¶	Low	Zinc oxide	95	55	40	30
	High	Zinc oxide	100	100	80	70

†These estimated levels account for only wheat flour as the main fortification vehicle in a public health program. If other mass-fortification programs with other food vehicles are implemented effectively, these suggested fortification levels may need to be adjusted downwards as required.
‡Estimated per capita consumption of <75 g/day does not allow for the addition of a sufficient level of fortificant to cover the micronutrient needs of women of childbearing age. Fortification of additional food vehicles and other interventions should be considered.
§NR: Not recommended because very high levels of electrolytic iron could negatively affect the sensory properties of fortified flour.
¶For these zinc fortification levels, 5-mg zinc intake and no additional phytate intake from other dietary sources are assumed.
Source: WHO, 2009.[40]

June 16th, 1996 regarding Wheat Flour Fortification.

The State Ministry of Food Affair formed the cross-sector Fortification Commission with active support from UNICEF. A national-level discussion, namely National Workshop on Food and Nutrition (Widyakarya Nasional Pangan dan Gizi) VI, was held in 1998. Since then, various experiments on wheat flour fortification started, and the implementation of wheat flour fortification began in 1998 in a wheat flour factory in Jakarta. Finally, on January 14, 1999, the wheat flour fortification program was officially launched by the government.

Two years later, wheat flour fortification with iron, zinc, folic acid, vitamin B-1, and B-2 became mandatory after the release of Decree of the Minister of Industry Trade number 153 in 2001 (Indonesian National Standard; Standar Nasional Indonesia [SNI]) for wheat flour. In February 2008, the mandatory wheat flour fortification program by SNI was once withdrawn by the government because wheat flour fortification was thought to be one of the causes of a dramatic increase in staple food prices, including the price of wheat flour. After several interministerial consultations, SNI wheat flour fortification was re-implemented in 2009. Twenty-six rules have been established for the food fortification policy in Indonesia. There are 10 general rules and 16 specific rules for mandatory fortification, among which 10 are specific fortification rules for wheat flour.[37]

The requirements for fortificant addition to wheat flour products as food vehicles in SNI 3751-2009 are described in the Decree of the Minister of Health, Republic of Indonesia No. 1452/Menkes/SK/X/2003. It is mentioned that produced, imported, or circulated wheat flour in Indonesia should be fortified to contain iron at a minimum of 50 mg/kg, zinc at a minimum of 30 mg/kg, vitamin B-1 (thiamine) at a minimum of 2.5 mg/kg, vitamin B-2 (riboflavin) at a minimum of 4 mg/kg, and folic acid at a minimum of 2 mg/kg.

From January to December 2011, the Laboratory of Balai Besar Industri Agro (Center for Agro-based Industry) analyzed 583 samples of wheat flour from various wheat flour companies considering that the period from January to December 2011 was the transition period for the application of mandatory SNI 3751-2009 in accordance with the Regulation of the Minister of Industry of Republic of Indonesia Number 35/M-IND/PER/3/2011, which was valid from March 22, 2012. According to the test results of 583 samples, the majority (95.85%) of samples complied with the requirements of SNI 3751-2009, whereas the remaining 4.15% did not fulfill the requirements of SNI 3751-2009. It can be assumed that in 2011, wheat flour products as food commodities that were circulated and marketed in Indonesia already met the SNI requirements according to the applied regulation.[38]

The National Standardization Agency of Indonesia requires fortification with iron of a minimum concentration of 50 ppm without any iron compound specified.[39] For iron fortification, manufacturers in Indonesia use elemental iron because it costs less and causes few, if any, sensory changes.

In 2004, a Center for Disease Control and Prevention (CDC) expert group in Cuernavaca, Mexico, made global recommendations for the type and level of different iron compounds (Table 3) to be added to wheat flour.[40] WHO recommended the same iron compounds but suggested that each country should estimate the level of fortification that would provide the required iron lacking in the traditional diet.[35]

Because elemental iron powders are organoleptically inert, they are widely used for wheat flour fortification. In 2002, a SUSTAIN task force evaluated the usefulness of the different elemental iron powders commonly employed in wheat flour fortification.[41] On the basis of in vitro, rat, and human studies, the task force recommended that electrolytic iron should be the only elemental iron powder used and that its amount added should be twice the iron level of ferrous sulfate, as its absorption capacity is approximately

half of that of iron. They also recommended that carbon monoxide–reduced iron should not be used because of unacceptably low absorption. Furthermore, they indicated that more studies of carbonyl- and hydrogen-reduced iron powders are required before a recommendation can be made. It was subsequently found that another form of reduced iron (i.e., atomized iron powder) is widely used for wheat flour fortification because of its low cost. However, because of its low solubility in dilute acid under standardized conditions and its low absorption in rat hemoglobin repletion studies and human iron tolerance tests, atomized, reduced iron powder is not recommended for wheat flour fortification.[42]

The analysis results of the 2014 Indonesian Total Diet Study showed that among cereal groups, rice was the most consumed product by the majority of the Indonesian population (97.7%), with a consumption of 201.3 g per capita per day, followed by wheat and its products consumed by approximately 30.2% of the population (51.6 g per capita per day). A similar consumption pattern for cereal groups was found based on age, with rice consumption and its products as the highest consumed product followed by wheat and its products. The 51.6-g consumption of wheat and its products comprised wheat flour (9.4 g), wheat flour products (9.6 g), and noodles (32.6 g). Noodles were the third most consumed (by 23.4% of the population) cereal food commodity, with an average consumption of 32.6 g per capita per day.[43]

We compiled a list of wheat flour-based food products. Table 4 provides the estimates of iron content (mg) in wheat flour and its derivative products. Given that the average consumption of wheat flour and its derivative products in Indonesia is only 51.6 g per person per day and the estimated iron content is 8.8 mg (in 100 g per serving), the additional iron obtained from average wheat flour consumption is estimated to be 4.5 mg per capita per day. For noodles, as one of the most common wheat products consumed, the estimated iron content is as high as 5.5 mg per instant noodle serving (Table 4); thus, the iron content acquired from noodles is approximately 2.6 mg iron per capita per day.

The average amount of additional iron from fortified wheat flour is 4.5 mg per capita per day. The lowest dose of electrolytic iron with a significant impact on iron status is 10 mg. However, in a trial, electrolytic iron was shown to be less efficacious than ferrous sulfate in reducing iron deficiency, and no reduction was demonstrated in the percentage of participants with anemia.[44] Moreover, iron deficiency anemia remained in 60% of children in China after a 6-month trial using more than twice this 10-mg dose.[45] Because of the uncertainty regarding the lowest effective dose of electrolytic iron, the recommendation from the Cuernavaca Workshop should not be changed; this groups recommends that electrolytic iron twice the concentration of ferrous sulfate should be added.[35]

However, the wheat consumption range in Indonesia is below 75 g/day; as per the WHO recommendation (2009), electrolytic iron is not recommended when the average consumption of wheat flour is below 75 g/day because high levels of electrolytic iron could negatively affect the sensory properties of fortified flour.

The iron compounds that are recommended when wheat consumption is below 75 g/day are Na Fe-EDTA, ferrous sulfate, and ferrous fumarate. The results of experimental studies in animal and human models demonstrated that regardless of how beneficial the iron fortificant may be, its intake in combination with enhancers and inhibitors determines the final effect.[36] All the fortified condiments have been used in cereal-based diets high in phytic acid; therefore, Na Fe-EDTA is more preferable than ferrous sulfate and ferrous fumarate, and the enhanced iron absorption through EDTA in the presence of phytate is expected to reduce the variability in iron status responses caused by differences in overall meal bioavailability.[42]

Fe fortification using Fe-sulfate, Fe-fumarate, and Na Fe-EDTA in wheat flour does not significantly affect the sensory properties of breads and baozi. Na Fe-EDTA slightly affects the texture (slightly harder) of cookies. For noodles and macaroni, Fe-sulfate and Na-Fe-EDTA affect the color of products (darker color). Fe-fumarate is recommended for the iron fortification of wheat flour, with the lowest effect on the sensory properties of wheat products.[39]

The national wheat flour fortification program appears to use fortification levels that are too low in relation to the wheat flour consumption pattern, or the coverage of the program is limited. No study has investigated the effectiveness of iron compounds used in fortification in Indonesia, except for the Family Life Survey analysis series on anemia by Kendrick et al.[46] Kendrick et al concluded that wheat flour fortification has not significantly reduced the anemia prevalence among reproductive-age women in Indonesia.[47] Therefore, it seems unlikely that a meaningful reduction in the national prevalence of iron deficiency would be achieved through wheat flour fortification unless current practices are changed. The nine countries that can expect a positive impact from wheat flour fortification programs use ferrous sulfate: Argentina, Chile, Egypt, Iran, Jordan, Lebanon, Syria, Turkmenistan, and Uruguay. They could provide an average of 5.4–9.6 mg of additional iron per day through fortified flour, with optimal coverage.[42]

Quality monitoring for the wheat flour fortification program is lacking; quality monitoring is crucial because there are still reports of falsified fortification labels and the existence of low-quality, unfortified wheat flour in market circulation. Some local governments do not realize the importance of fortification; thus, the regional regulations that have been issued are ineffective.

Regarding the fortification of wheat flour, the government must immediately conduct an effectiveness test to determine its impact on reducing the prevalence of anemia. The replacement of supplementation with fortification results in savings in the state budget because the fortification program is cheaper and more effective than supplementation.

An effective and continuous food fortification program could enhance the nutrition status of vulnerable groups when the fortified food is consumed regularly, and the micronutrient substances added to the food vehicle are based on the daily average food intake per capita. The adequately fortified food must be consumed consistently by the majority of the population (approximately >80%).

Table 4. Iron content in flour and its products on the market

No.	Category	Brand Name	RDA† (%)	Iron content‡ (mg)
1	Flour	Bogasari Kunci Biru (Untuk Kue Kering, Cake, dan Biskuit)	40	8.8
2	Flour	Bogasari Segitiga Biru (Untuk Aneka Makanan)	50	11
4	Flour	Bogasari Cakra Kembar (Untuk Roti & Mie)	60	13.2
5	Flour	MILA Serbaguna	25	5.5
6	Flour	Golden Eagle	25	5.5
7	Flour	Hana Emas	60	13.2
8	Instant noodles	Indomie Rasa Soto Mie	25	5.5
9	Instant noodles	Indomie Goreng Rasa Rendang	20	4.4
10	Instant noodles	Indomie Mie Goreng Jumbo	35	7.7
11	Instant noodles	Indomie Rasa Ayam Bawang	15	3.3
12	Instant noodles	Indomie Mie Goreng	25	5.5
13	Instant noodles	Indomie Mie Goreng Iga Penyet	15	3.3
14	Instant noodles	Indomie Mie Goreng Sambal Rica-Rica	35	7.7
15	Instant noodles	Indomie Mie Goreng Pedas	45	9.9
16	Instant noodles	Indomie Mie Keriting Goreng Spesial	15	3.3
17	Instant noodles	Indomie Mie Keriting Rasa Ayam Panggang	20	4.4
18	Instant noodles	Indomie Mi Goreng Aceh	20	4.4
19	Instant noodles	Indomie Mi Goreng Rasa Ayam Geprek	30	6.6
20	Instant noodles	Indomie Rasa Seblak Hot Jeletot	30	6.6
21	Instant noodles	Mie Sedaap Rasa Ayam Spesial	10	2.2
22	Instant noodles	Mie Sedaap Rasa White Curry	15	3.3
23	Instant noodles	Mie Sedaap Rasa Kari Ayam	10	2.2
24	Instant noodles	Mie Sedaap Rasa Ayam Bawang	10	2.2
25	Instant noodles	Mie Sedaap Rasa Baso Spesial	10	2.2
26	Instant noodles	Mie Sedaap Rasa Soto	25	5.5
27	Instant noodles	Mie Sedaap Rasa Kari Spesial	10	2.2
28	Instant noodles	Mie Sedaap Goreng Ayam Krispi	10	2.2
29	Instant noodles	Mie Sedaap Mi Goreng	10	2.2
30	Instant noodles	Mie Sedaap Korean Spicy Chicken	10	2.2
31	Instant noodles	Mie Sedaap Cup Rasa Baso Spesial	10	2.2
32	Instant noodles	Mie Sedaap Cup Rasa Ayam Bawang Telur	10	2.2
33	Instant noodles	Mie Sedaap Cup Rasa Soto	10	2.2
34	Instant noodles	Mie Sedaap Cup Mi Goreng	10	2.2
35	White bread	Sari Roti Double Soft	10	2.2
36	White bread	Sari Roti Tawar Kupas	20	4.4
37	Biscuit	Lucky Stick Strawberry	10	2.2
38	Biscuit	Hello Panda Rasa Susu	6	1.32
39	Biscuit	Hello Panda Cookies & Cream	8	1.76
40	Biscuit	Biskuat Original	4	0.88
41	Biscuit	Belvita Breakfast Rasa Pisang & Sereal	20	4.4

†BPOM (National Agency of Drug and Food Control) RDA label reference: 2150 calories with 22 mg iron.
‡Estimated value
Weight per service for the flour category is generally 100 g and for instant noodles it is 70 g.
Source: Market survey compilation by author, 2020.

Therefore, the latest data on the target of food consumption to be fortified are crucial for determining the national standard.

Iron fortification of rice should be considered, which is a food commodity widely (97.7%) consumed by the Indonesian population, with an average consumption as high as 201.3 g per capita per day, which is much higher than the consumption level of wheat flour and its products. In a previous study, biofortified high-iron rice provided benefits for iron-deficient populations by increasing iron stores; this food also maintained the iron stores in populations without deficiency. From this feeding trial, it can be concluded that biofortified rice has the potential to improve the diets of the low-income population in developing countries.[48]

In the 1940s, the Philippines government started to fortify rice with thiamin, niacin, and iron and succeeded in decreasing the beriberi incidence, which, at that time, was a severe health problem caused by a lack of thiamine. In 1952, the Philippines government established laws on rice fortification that required all rice mills and wholesalers to fortify the rice milled and sold.

In the last decade, significant developments have been made in low-cost rice fortification technology, which have contributed to the reduction of micronutrient deficiency. The technology can affordably generate fortified rice having the same shape, smell, and taste as unfortified rice.

According to WFP (2018), nine studies have shown that fortifying rice with iron (alone or in combined with other micronutrients) can increase iron status (evidence of moderate certainty), other studies have shown small effect on iron status. One study demonstrated that fortified rice can increase the hookworm infection risk (evidence with low certainty).[8]

In Indonesia, to overcome the problem of anemia, a pilot project of fortification with iron and other substances in *Raskin* (rice for low-income individuals) was conducted in

2011. The feasibility of rice fortification was also examined in terms of cost and its impact on iron deficiency anemia (IDA). The fortification project was executed in 80 villages in Karawang and 15 villages in Bekasi using 14000 tons of *Raskin*. The monthly production amount of 1167 tons of *Raskin* was fortified for 3 years (2010–2012), costing US$2,220,440, with a possible time extension until 2013. The existing technology was assumed to be able to produce premix (artificial rice with a high iron content) with an identical shape and color as actual rice. At that time, no funding was available to conduct a premix trial and other necessary tests; thus, the cheapest premix was imported from India. The best and the most expensive premix was from the Philippines.[49]

In 2014, *BULOG* (Indonesian Bureau of Logistics) was involved in the development of the Rice Fortification for Poor Families pilot project in collaboration with the government and the Asian Development Bank using the Japan Fund for Poverty Reduction. The Indonesian Bureau of Logistics was actively involved, particularly in fortified *Raskin* production and distribution. The Southeast Asian Food and Agricultural Science and Technology Center of Bogor Agricultural University/IPB University conducted a fortified rice acceptance trial; the results showed that fortified rice was well accepted by the consumer because the fortification did not alter the color, taste, and smell of the rice. Moreover, 100 g of *Raskin* in 2014 comprised iron (8 mg), folic acid (20 μg), vitamin B-1 (0.64 mg), vitamin B-12 (1.0 μg), niacin (6 mg), and zinc (3 mg).

In 2015, a rice fortification program was conducted by the private producer AMARTA with the aim of fulfilling society's daily nutritional requirements. The nutritional components in 100 g of rice were folic acid (125 mcg), vitamin A (200 mcg), vitamin B-1 (thiamine; 0.4 mg), vitamin B-2 (riboflavin; 0.5 mg), vitamin B-3 (niacin; 6 mg), vitamin B-6 (pyridoxine; 0.6 mg), vitamin B-12 (cobalamin; 2 mcg), vitamin D (cholecalciferol; 1.5 mcg), vitamin E (tocopherol; 3 mg), vitamin K; 25 mcg), iron (5 mg), magnesium (30 mg), calcium (100 mg), iodine (50 mcg), zinc (5 mg). The rice cost was approximately Rp 20,000 per kg, and the rice was available in 5-, 10-, and 25-kg packs.[50]

In 2019, *BULOG* introduced rice containing vitamins (fortified) under the brand Fortivit, which does not require rinsing. The rice was enriched with vitamins and minerals. Specifically, 100 g of rice contained 195 μg of vitamin A, 0.65 mg of vitamin B-1 (thiamine), 9.1 mg of vitamin B-3 (niacin), 0.78 mg of vitamin B-6, 169 μg of vitamin B-9 (folic acid), 4 mg of iron (Fe), and 6 mg of zinc (Zn). This rice was developed in collaboration with the Kernel fortificant provider company, and it would be sold for IDR 20,000 per kg under the premium category and IDR 12,000 under the medium category.[51]

The consumption of micronutrient powder containing iron has some potential side effects in babies and children. In a recent study of children in Kenya, the administration of micronutrient powder containing iron (12.5 mg iron as ferrous fumarate) caused the development of intestinal inflammation (the increase of fecal calprotectin concentration) and an increase in the number of enteropathogens (including *Shigella*, *Escherichia coli*, and *Clostridium*) compared with micronutrient powder without iron.[52,53]

The adverse effects of micronutrient iron on intestinal microbiota can be reduced through the addition of prebiotic galacto-oligosaccharides to micronutrient powder, although further studies are required to confirm this. Thus, compared with iron interventions such as oral iron supplementation or fortification with micronutrient powder containing iron, rice fortification is preferred, as it is associated with a lower risk of infectious diseases in individuals with high or adequate iron intake. The daily iron dosage from the consumption of iron fortificant in the amount of rice is commonly lower and limited per person. In addition, iron fortificant is added to the food matrix thus reduces the potency of transferrin-bound iron accumulation in blood.

Therefore, the success of rice fortification interventions depends on the population and context as well as the prevalence of anemia. This is because iron deficiency can have other causes. The potential damage of fortified rice is low considering the low daily iron dosage and the limit on how much rice an individual can consume. More studies should be conducted to examine the possible biological and clinical adverse effects of iron-fortified rice from excess iron intake.

A study found that the fortification of cooking oil may be an alternative method of increasing vitamin A intake in mothers and children, especially in rural communities.[54] Mean oil consumption ranges from 2.4 mL/capita per day for infants aged 6–11 months to 31.5 mL/capita per day for lactating mothers. Moreover, the Recommended Nutrient Intake (daily) of vitamin A from fortified oil ranged from 26% in children aged 12–23 months to 35%–40% in older children and nonlactating women.[55] The increased intake of vitamin A is also attributed to the consumption of various foods that improve serum retinol in preschool children.[56]

Food-based approach

The International Conference on Nutrition was convened in 1992 for the development of food-based dietary guidelines (FBDGs) to promote appropriate diets and healthy lifestyles. In total, 159 heads of state committed to a plan of action on nutrition.[57] The popularization of nutrition messages started in the 1950s when a highly regarded nutrition expert in Indonesia, Prof. Poerwo Soedarmo MD, developed the slogan "Four Healthy Five Perfect" (locally known as Empat Sehat Lima Sempurna [ESLS] to educate people about the importance of nutrition. The message is a modification of the United States slogan "Basic seven and basic four."[58,59] This slogan is presented in a circlular form, with staple (carbohydrate source), side dish (protein and fat sources), vegetables, and fruits (vitamin and mineral sources) on the outside and milk in the middle. In the subsequent 25 years, ESLS became preferred in nutrition education and is widely known, especially among school-age children. It is well-known by the public even today.[60]

ESLS, which unintentionally provided a higher value for milk, produced a problematic situation for the governments of developing nations because of the unavailability of milk locally and its high price.[61] The government of Indonesia introduced the Guide to a Balanced Diet in 1993 (locally known as Pedoman Umum Gizi Seimbang [PUGS]). This was a result of the commitment of countries to the International Conference on Nutrition in 1992. In

1995, the guide was launched by the MoH and formally incorporated in the nutrition policy and program of REPELITA VI (1994–1998).[62] The guidelines were developed based on the results of research by the Nutrition Center for Research and Development, MoH. The guide has 13 messages: (1) food biodiversity, (2) eat food with sufficient energy, (3) consume complex carbohydrates for energy, (4) energy from fat and oil should only provide 25% of total energy, (5) use only iodized salt, (6) eat iron-rich foods, (7) exclusively give breast milk to infants 0–4 months (now 0–6 months), (8) eat breakfast daily, (9) drink sufficient clean and safe water, (10) do physical activity and exercise regularly, (11) avoid alcoholic drinks, (12) eat clean and safe food, and (13) always read food labels.[61]

The illustrative representation (as a cone) of the guidelines is a pyramid with three layers: (1) bottom layer: energy sources, (2) middle layer: fruit and vegetables, (3) top layer: foods that are sources of animal and plant protein. In 2002, the cone was altered to four layers, with energy source foods, vegetables and fruit, animal and plant protein, and sugar and salt from the bottom to top layers separately. Additionally, the following revisions were made: (1) separation between animal and plant proteins, in which milk is incorporated into the animal protein group, (2) addition of sugar and salt, (3) insertion of the recommended amount for consumption (servings), (4) fats and oils were excluded in the guide, and (5) message no. 7 was revised to "provide only breast milk for the baby until 4 months old, after which breast milk should be supplemented with complementary foods." In the next 8 years, no attempt was to modify the guidelines or popularize healthy eating and physical well-being.[63]

For children younger than 5 years, in addition to iron intake, the intake of zinc and calcium was consistently found to be limited in young children's diets, especially during the complementary feeding period.[64,65] However, the current FBDG messages do not specifically address the need to increase the density of these nutrients or to incorporate foods fortified with these nutrients. The anemia prevalence over the last 10 years has indicated that balanced nutrition has not yet been applied by the majority of individuals. Research on iron-rich food in Indonesia is lacking. An analysis of iron-rich food intake has been conducted by evaluating the consumption of animal protein source food, which is recognized as a good source of highly available iron.

Effect of optimal nutrition promotion and education on anemia status

The protein intake of the Indonesian population is still dominated by plant foods. For the prevention of anemia, protein and iron from animal foods are much more effective. Animal protein has high available iron, partly through the hem iron content of animals, and iron content is mostly unaffected by interactions with other food components.[36] The Deputy for Food and Agriculture of the Coordinating Ministry for Economic Affairs revealed that the consumption of animal protein in the country is only 8%, which is far below that in Malaysia (28%), the Philippines (21%), and Thailand (20%).[66]

On the basis of the Total Diet Study,[43] the meat most consumed by the population of Indonesia is poultry, with a consumption rate of 21.5% for all ages, followed by processed beef and buffalo, which are consumed by approximately 8.1% of the population. The 19–55 and 5–12 year age groups have the highest consumption of chicken (22.5%) and processed beef (13.8%), respectively.

Based on data from the Central Bureau of Statistics of Indonesia, the average daily per capita protein consumption decreased slightly from 47.25% in early 2011 to 45.21% in 2012 and continued to decline until it increased again at the end of 2015 (45.32%), reaching the highest at the end of 2016 (48.56%) and then stabilizing at 47.8% at the end of 2018.[67] This same pattern was identified for the consumption of processed foods.

The Executive Summary of Indonesian Population Expenditure and Consumption[67] revealed that the lower protein consumption may be the result of the low income level of the Indonesian population. Another problem is the quality of protein consumed because quality protein sources, such as livestock products, are expensive compared with vegetable protein sources.

In September 2018, the average daily protein consumption of every Indonesian citizen was 64.64 g, which is sufficient (in terms of quantity) based on the protein adequacy rate (2018 Indonesian protein adequacy rate is 57 g/capita/day). However, the largest contributor to protein consumption is grains (19.51 g), which makes up approximately 30% of total protein consumption. Consumption of protein in the form of fish, meat, egg, and milk is 16.67 g, or approximately one-quarter of total protein consumption. This amount is still less than the consumption of protein from whole grains. This finding in is in line with the conclusions of Harper, who researched the proportion of food ingredients commonly consumed in Indonesia and in other Asian countries.[68] According to Harper, most residents consume protein derived from plants. He also suggested increasing the consumption of animal protein if the income level of the population increases.[69]

According to Sediaoetama, the recommendation for animal protein consumption in the daily diet is 30% of total protein consumption.[70] Even if the quantity of protein consumed is sufficient in the Indonesian diet, its composition is still dominated by vegetable protein, whereas the proportion of animal protein consumed is still below the recommended level.

In terms of each group of animal protein, the maximum protein consumption is from fish compared with meat, eggs, and milk. On average, each Indonesian resident consumes 8.78 g of protein a day from fish. Protein consumption from meat is 4.46 g, half of the protein consumption from fish. Moreover, protein consumption from eggs and milk is only 3.43 g per capita a day.[67]

In the first quintile, protein consumption from eggs and milk (20.32%) is higher than that from meat (17.48%; Figure 2). This indicates that eggs and milk are more popular and affordable for low-income individuals. However, milk and eggs are not good sources of iron. Iron in egg yolk is poorly absorbed because of the presence of phosvitin.[71]

The emphasis on protein for evaluating nutritional quality has become counter-productive, as food product development is encouraged on this basis alone, without regard to the wider spectrum of food characteristics necessary for

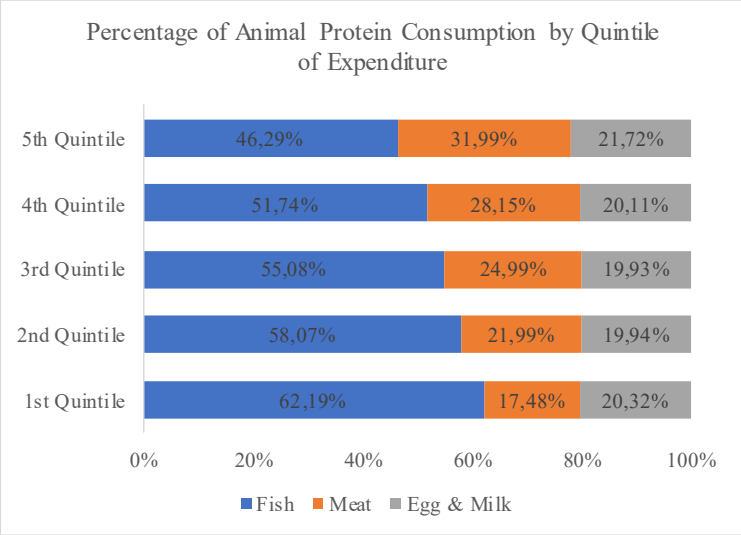


Figure 2. Proportion of animal protein consumption by quintile of expenditure. Source: BPS, 2018.[67]

optimal nutrition. Food intake biodiversity is a preferable measure of dietary quality and a basis of the prevention of nutritional anemia. It is now recommended by FAO as an index of food security[72,73] and in health outcome evaluation[74] and costs.[75,76]

Food production, supply, and distribution

The supply, availability, and distribution of animal protein sources is still uneven in all regions of Indonesia. The livestock sector in each region should be increased through local wisdom. According to the National Socioeconomic Survey, the consumption of animal protein at the provincial level varies between 11 and 27 g per capita a day.[77] The province with the highest average consumption of animal protein is the Riau Islands (27.12 g). More than 50% of the total consumption of animal protein in the Riau Islands is from fish (52.75%). By contrast, East Nusa Tenggara has the lowest protein consumption, which is 11.11 g per capita a day or less than half the protein consumption of the Riau Islands.

In general, in all provinces, the consumption of protein from fish is greater than that from meat, egg, and milk, except in the province of DI Yogyakarta. The consumption of protein from meat in Yogyakarta is 5.70 g per capita a day, the consumption of protein from eggs and milk is 3.89 g, and that from fish is 3.58 g. In addition, in terms of the proportion of the total animal protein consumption of each province, DI Yogyakarta has the highest proportion of protein consumption from meat (43.27%).[77]

CONCLUSION

Small-scale iron supplementation interventions are occasionally effective; however, regarding iron supplementation interventions on a larger scale, many regions in Indonesia had inadequate IFA tablet supply and ineffective implementation. Fortification should provide budgetary savings, but this concept may be ill-conceived or misplaced. Indonesian manufacturers add electrolytic iron to wheat flour, but wheat consumption is below the required 75 g/day in Indonesia, negating its effectiveness. The average amount of additional iron in fortified wheat flour is below the lowest dose of electrolytic iron necessary for a significant impact on iron status. WHO recommends that electrolytic iron should not be used when the average wheat flour consumption is below 75 g/day. Iron fortification of rice, a staple more widely consumed by Indonesians (rather than wheat flour), is a preferable alternative.

A feasibility study on iron-fortified cooking oil is recommended since its consumption level is relatively stable across life stages. The mean oil consumption ranges from 2.4 mL/capita per day for infants aged 6–11 months to 31.5 mL/capita per day for lactating mothers. However, no evaluation of its benefit and risk has been conducted, so the widespread use in this industry, where unintended consequences such as increased consumption of energy-dense fried foods would be encouraged, among other risks and costs.[78]

Although iron and folic acid supplementation has been implemented since the 1980s, iron fortification has been mandatory for two decades as a national intervention in Indonesia, and dietary modification has been promoted by the government. On the basis of the anemia prevalence among pregnant women, anemia is still a severe public health problem. Poor-quality diets, lack of food biodiversity, and compromised optimal nutrition and nutrient bioavailability, with adverse consequences for food security and health including nutritional anemia, are causes of iron deficiency and have an effect on its complex pathogenesis. Vulnerable life stages, such as the reproductive life span of women, childhood, and later life, and adverse socioeconomic circumstances are associated with the high prevalence of nutritional anemia, including that attributed to iron deficiency. Programs to reduce the likelihood of anemia in these settings will be more successful if they are less dependent on nutrient-specific strategies and focus more on the pathogenetic complexity arising from personal behavior, sociocultural factors, dietary and health patterns, local community, and ecology. Partnerships between the community and government reflected in evidence-based policy will always be of value, but continued research is required to examine the factors contributing to the successful outcomes of such programs.

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AUTHOR DISCLOSURES

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(Revised October 2020)

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The aims of the *Asia Pacific Journal of Clinical Nutrition* (*APJCN*) are to publish high quality clinical nutrition relevant research findings which can build the capacity of clinical nutritionists in the region and enhance the practice of human nutrition and related disciplines for health promotion and disease prevention. *APJCN* will publish original research reports, reviews, short communications and case reports. News, book reviews and other items will also be included. The acceptance criteria for all papers are the quality and originality of the research and its significance to our readership. Except where otherwise stated, manuscripts are peer-reviewed by at least two anonymous reviewers and the Editor. The Editorial Board reserves the right to refuse any material for publication and advises that authors should retain copies of submitted manuscripts and correspondence as material cannot be returned. Final acceptance or rejection rests with the Editorial Board.

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Book

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Chapter in a Book

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ANCOVA (analysis of covariance)
ANOVA (analysis of variance)
BMI (body mass index)
BMR (basal metabolic rate)
CHD (coronary heart disease)
CI (confidence interval)
CVD (cardiovascular disease)
df (degrees of freedom)
DHA (docosahexaenoic acid)
DNA (deoxyribonucleic acid)
DRIs (dietary reference intakes)
EDTA (ethylenediamine tetra-acetic acid)
ELISA (enzyme-linked immunosorbent assay)
EPA (eicosapentaenoic acid)
FAO (Food and Agriculture Organization) (except when used as an author)
FFQ (food-frequency questionnaire)
GC (gas chromatography)
Hb (haemoglobin)
HDL (high-density lipoprotein)
HIV (human immunodeficiency virus)
HPLC (high-performance liquid chromatography)
IHD (ischaemic heart disease)
LDL (low-density lipoprotein)
MRI (magnetic resonance imaging)
MUFA (monounsaturated fatty acids)
NS (not significant)
OR (odds ratio)
PCR (polymerase chain reaction)
PUFA (polyunsaturated fatty acids)
RDA (recommended dietary allowance)
RER (respiratory exchange ratio)
RIA (radioimmunoassay)
RMR (resting metabolic rate)
RNA, mRNA etc. ribonucleic acid, messenger RNA etc.
SFA (saturated fatty acids)
SNP (single nucleotide polymorphism)
UN (United Nations) (except when used as an author)
UNICEF (United Nations International Children's Emergency Fund)

UV (ultra violet)
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ATTACHMENT 5

Infographic Projects

- Tanjungsari Cohort Study Infographic Publication titled “Maternal Contributors to Intergenerational Nutrition, Health, and Well-being: Revisiting the Tanjungsari Cohort Study for Effective Policy and Action in Indonesia.”
- Sweetened-Condensed Milk Infographic Publication titled “Consumption Patterns of Sweetened Condensed Milk (SCM) in the Diet of Young Indonesian Children and Its Potential Nutritional Health Consequences.”

MATERNAL CONTRIBUTORS TO INTERGENERATIONAL NUTRITION, HEALTH, AND WELL-BEING:

Revisiting The Tanjungsari Cohort Study for Effective Policy and Action in Indonesia

DANONEINSTITUTE

MATERNAL CONTRIBUTORS TO INTERGENERATIONAL NUTRITION, HEALTH, AND WELL-BEING: Revisiting The Tanjungsari Cohort Study For Effective Policy And Action In Indonesia

HEALTH, NUTRITION, AND WELLBEING OF INDONESIANS

Malnutrition, including stunting, remains one of the main challenges in Indonesian public health sector.

WHY TANJUNGSARI COHORT STUDY (TSC)?

Available data can be reanalyzed for evidence-based policy development.

THE IMPORTANCE OF IUGR FOR MALNUTRITION AND STUNTING RISK ASSESSMENT

IUGR predicts Low Birth Weight (LBW), growth retardation and mortality of infants.

MATERNAL & ENVIRONMENTAL DETERMINANT FOR GROWTH FALTERING IN THE FIRST 5 YEARS

Risk factors of shortness/stunting in under-five children (based on univariable binary logistic regression).

DETERMINANT OF SHORTNESS IN ADOLESCENT

Adolescent shortness in half of the cohort; Predictors of shortness in adolescent.

METABOLIC & COGNITIVE FUNCTION OF ADULTS WITH HISTORY OF LBW

Weight catch-up in the first 2 years may be a modulating factor for metabolic and cognitive performance.

LESSONS LEARNED

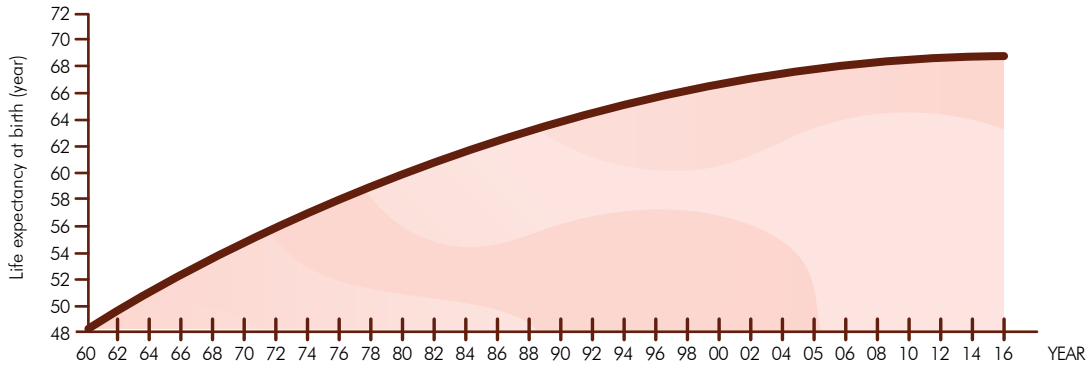
Pregnancy; infancy; adolescence; adulthood; social aspect.

RECOMMENDATIONS

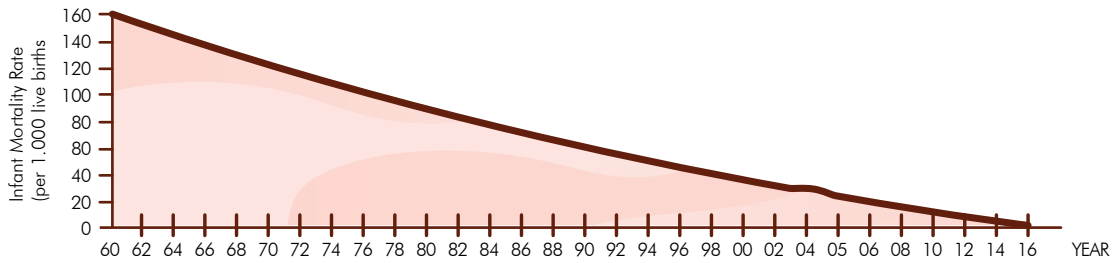
IUGR assessment; intervention for catch-up growth; nutritional adequacy through complementary feeding; education on exclusive breastfeeding & maternal nutrition; the role of women in community.

HEALTH, NUTRITION, AND WELLBEING OF INDONESIANS

- The advancement of health, nutrition, and well-being among Indonesians, while impressive over the period 1960-2017 for life expectancy and infant mortality remains variable across the nation and problematic overall.



A Indonesian life expectancy at birth (years) by year



B Indonesian infant mortality rate (per 1,000 live births) by year

	GDP (in constant 2010 USD)			
	1995 2,219.81	**2007** 2,750.62	**2013** 3,560.11	**2018** 4,130.66
Life expectancy at birth (years)	65.03	67.58	68.68	69.19 (2016)
IMR per 1,000 live births	50.4	30.9	24.5	21.4 (2017)
LBW (%)	10.3 (1997)	11.5	10.2	6.2
Underweight (%)	30.3	18.4	19.6	17.7
Wasting (%)	14.9 (1995)	13.6	12.1	10.2
Stunting (%)	48.1 (1995)	36.8	37.2	30.8

- Progress with nutritionally-related disease (NRD) has been claimed in the 2018 Baseline Health Research report (Riskesdas), with a further slight decline in infant mortality rate, prevalence of low birth weight, and underfive malnutrition. In contrast, there has been a significant increase in GDP during the same time frame as indicated in the above table. This shows **the nutritional issue has not received enough attention as much as the economic growth in Indonesia.**

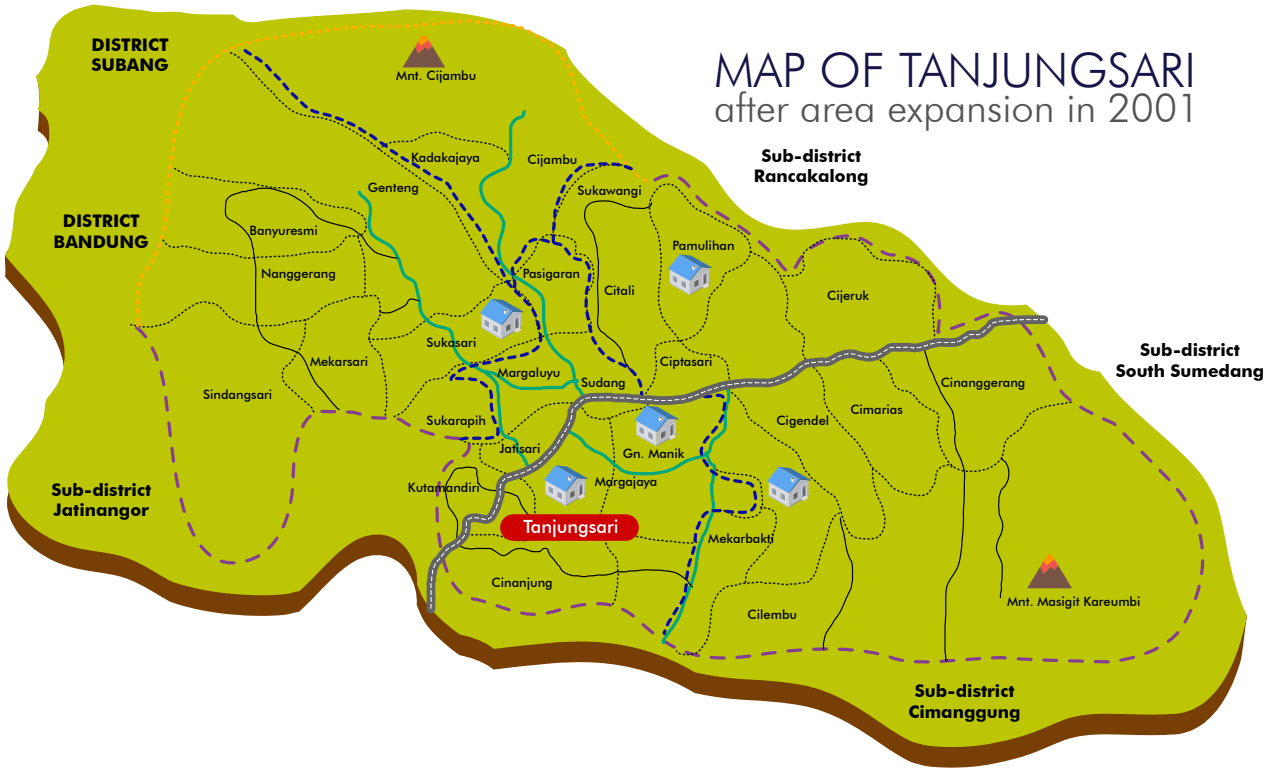
- **Malnutrition,** in any of its forms-underweight, wasting, and shortness or stunting (pathological shortness), and in any of the recognised at-risk populations-pregnant women, the newborn, and under-five children-**remains one of the main challenges for Indonesian public health sector that urgently need to be resolved.**

SECTION 1

WHY TANJUNGSARI COHORT STUDY?

TCS is a longitudinal study that started with the RAS (Risk Approach Strategy by Traditional Birth Attendants) research project in October 1987-December 1989.

A birth cohort was established in 1988–1990 in the Tanjungsari subdistrict (West Java, Indonesia). It intended to design and implement evidence-based policy to reduce pathological shortness (stunting) in under-five children in Indonesia.



SECTION 1

WHY TANJUNGSARI COHORT STUDY?

TCS focuses on the factors that affect the growth and development of under-five and young children, including later life, cognitive function, and metabolic profile.

Cohort observation for 21 years (1988-2009) thus covering three generations (from grandmother to grandchildren). Additionally, further observation on later life was extended until 2017.

HISTORY OF THE SAMPLE SIZE OF TANJUNGSARI COHORT STUDY:

Jan 1988 - Dec 1989
4,440 pregnant women (G1)
4,108 singleton births (G2)

continued recruitment

March 1990
additional 590 singletons
Total: 4,698 singleton births (G2)

3,890 children with data for 2-month follow-up

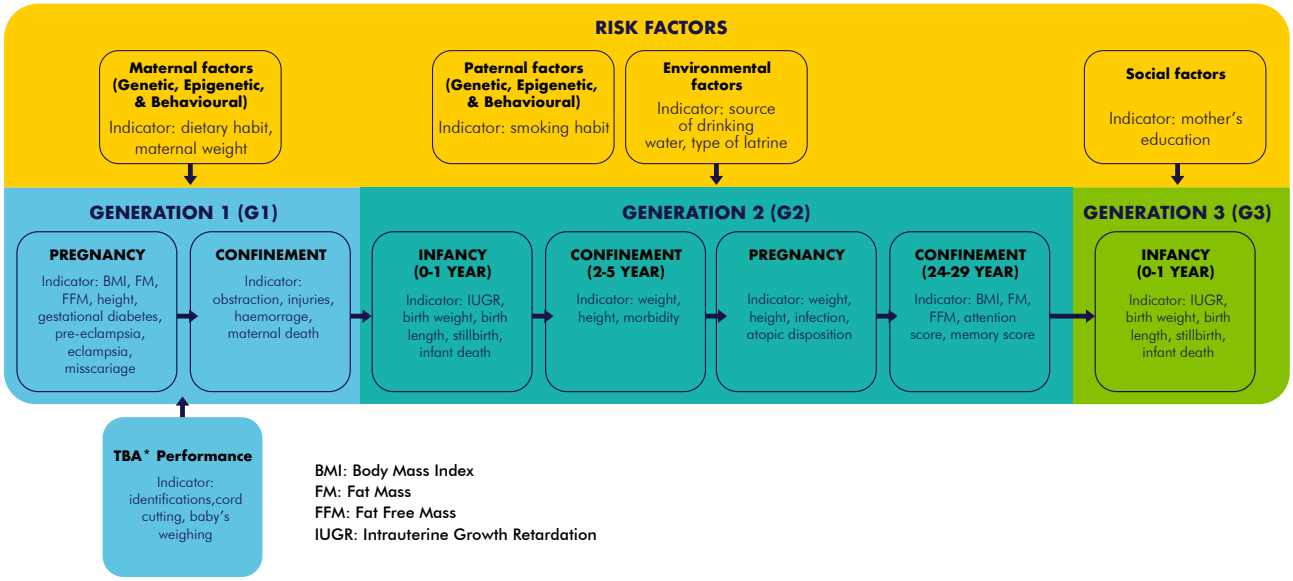
1991-1992
3,144 children two years old

1994-1995
3,795 children with data for 5-years follow up

2001-2002
3,148 12 years old children

2009-2012
(Fetal Origins of Adult Disease or FOAD Studies)
Samples from 3,548 adult (G2)

Conceptual Framework for the intra- and inter-generational TCS of maternal and child health with example indicators



BMI: Body Mass Index
FM: Fat Mass
FFM: Fat Free Mass
IUGR: Intrauterine Growth Retardation

- The Tanjungsari Cohort Study merits revisitation for at least 3 reasons: (1) Observation of 3 generations since 1988; (2) re-analysis for potential links between ecological factors and nutritionally-related health (NDR) outcomes; (3) Valuable insights into public health and nutritional policy across the lifespan may be provided.

SECTION 2

THE IMPORTANCE OF INTRAUTERINE GROWTH RETARDATION (IUGR) FOR MALNUTRITION AND STUNTING RISK ASSESSMENT

WHY IUGR?

An important indicator
for child growth and development, intellectual potential, as well as its sequences in later life.

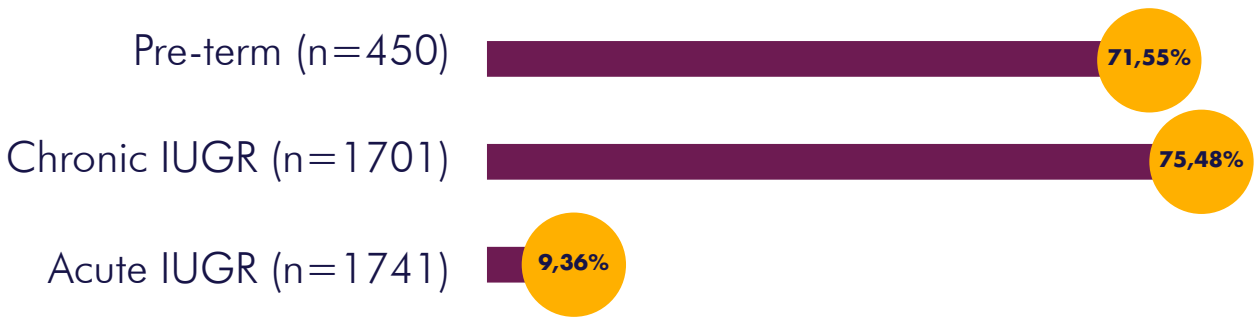
IUGR might contribute to the development of non-communicable disorders in adult life
(e.g. obesity, type 2 diabetes, hypertension, heart disease, etc.)

It leads to the development of less potent cellular immunity
thus higher risk of severe infectious disease in children.

IUGR Percentage in Tanjungsari Cohort Study

(Alisjahbana et al., 2019)

Chronic IUGR, Acute IUGR, and Pre-term based on Body Weight and Body Lenght
(Alisjahbana et al., 2019)



Due to the large variation in weight and length at particular gestational age, Alisjahbana et al. developed another means of classifying infants as non-IUGR or IUGR using only BW and BL. **Newborns are considered to have impaired fetal growth (IUGR) in two circumstances:**

1. A combination of BW <2700 g with a normal BL of ≥ 48 cm was considered to imply acute IUGR.
2. A combination of BW <3000 g and BL < 48 cm implies chronic IUGR.

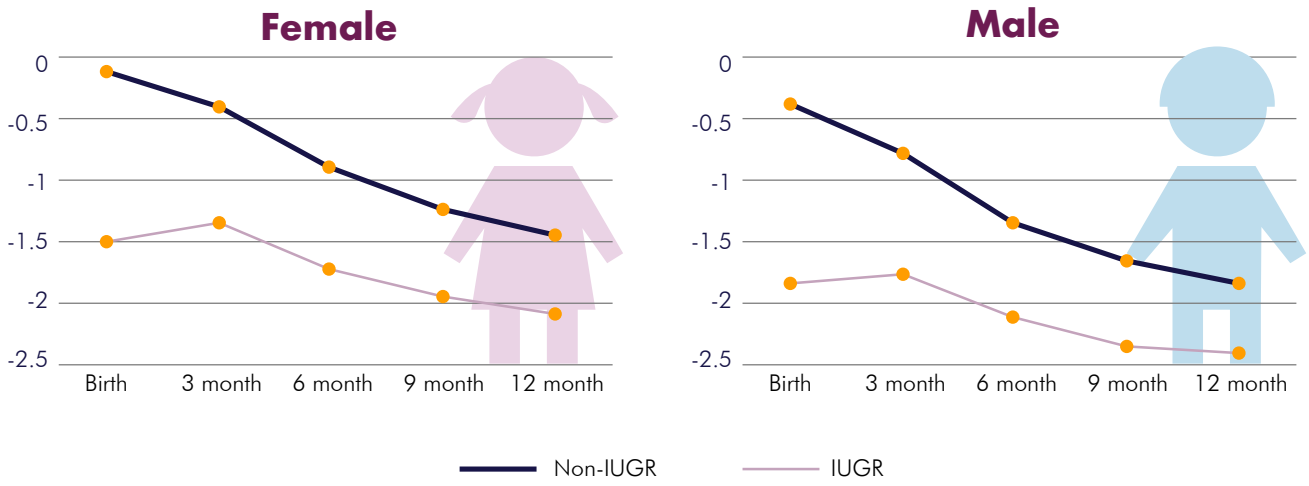
IUGR based on BW and BL identifies a larger group of at-risk infants. Including BL as a determinant factor has contributed in optimizing nutritional status in the first 1,000 days of life.

IUGR is different from Pre-term!

- IUGR: A condition in which an unborn baby is smaller than it should be as it is not growing at a normal rate inside the womb.
- Pre-term: Birth occurring earlier than 37 weeks gestational age.

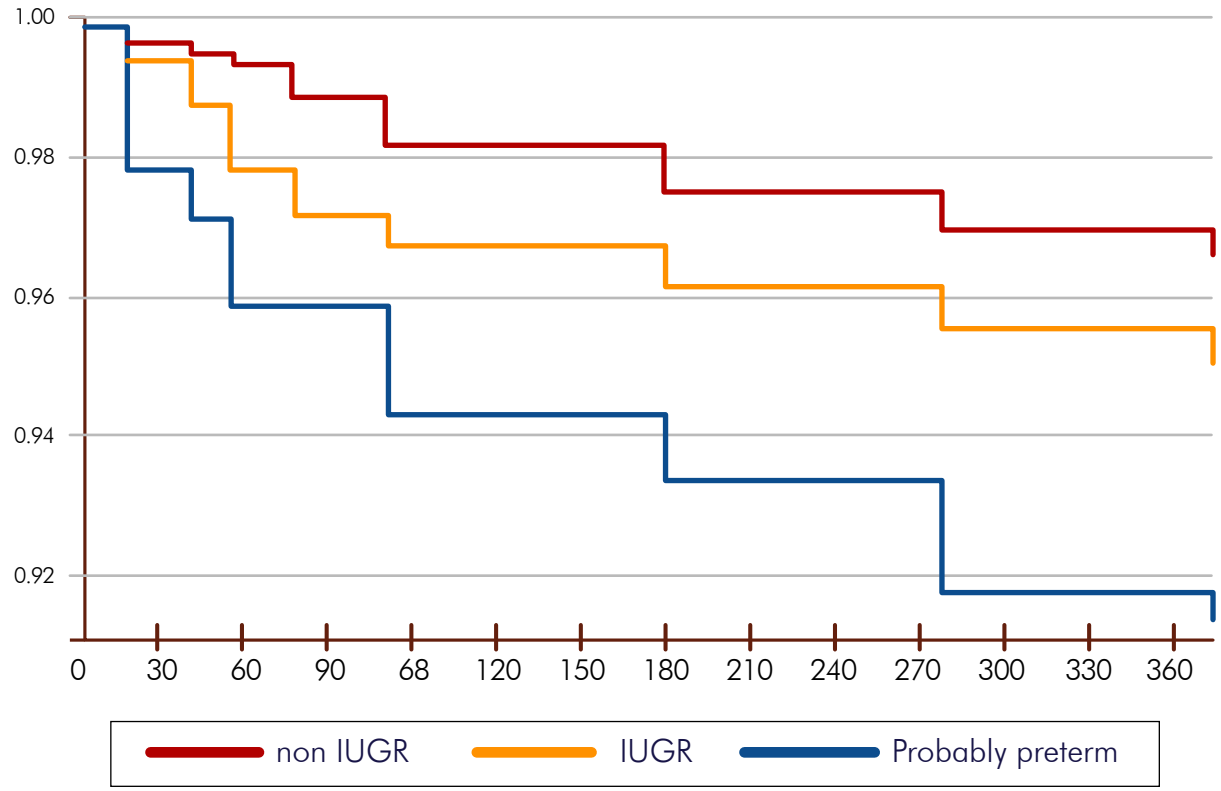
Comparation between the growth of IUGR and non-IUGR infants (based on mean WAZ and HAZ in the first year) (Source: Alisjahbana et al., 2019)

The growth curves for the IUGR infants were consistently below those of the non-IUGR infants, both in females and males. After 3 months, the growth in both groups began to progressively falter until the age of 12 months. In the Non-IUGR and IUGR groups, the HAZ was different between genders. In fact, the mean HAZ deviated by a larger extent than did the WAZ. Below are the figures for HAZ in infancy for both female and male in the non-IUGR and IUGR groups.



HAZ in infancy for female and male in the non-IUGR (n=691; 886) and IUGR (n=754; 693)

Infant mortality based on IUGR



Kaplan-Meier survival curve of infants in the first year of life by IUGR category.

Throughout infancy, the survival curve on non-IUGR infants was better than the IUGR infants, whereas preterm infants (which can also include infants with birth weights of 2,500-2,700 g) had the highest probability of death.

Within the IUGR and preterm categories, significant differences in the survival curve were identified:

1. At 3 months of age, the risk of death for the LBW babies was 3.1x higher than the normal birth weight (≥2,500 g) babies.
2. At 3 months of age, the risk of death for the preterm babies were 2.9x higher than the non-IUGR babies.
3. The risk for IUGR babies was 1.7 higher than the non-IUGR babies.

The Hazard Ratio of Risk Factors for Infant Mortality
(Source: Alisjahbana et al., 2019)

The risk of IUGR and other determinants of infant mortality are calculated using hazard ratio and/or adjusted hazard ratio (aHR). Among the most significant factors are **IUGR, sex, education, and latrine.** Maternal education of less than 6 years and latrine usage type are significantly associated with mortality in the crude HRs, but not when adjusted for sex and IUGR.

44% **Latrine**
Unimproved latrine condition increases the risk of infant mortality by 44%

51% **Maternal Education**
Maternal education less than 6 years increases the risk of infant mortality by 51 %

60% **IUGR**
The IUGR infant is at risk of death by 60%

70% **Sex**
A male infant is at risk of death by 70%

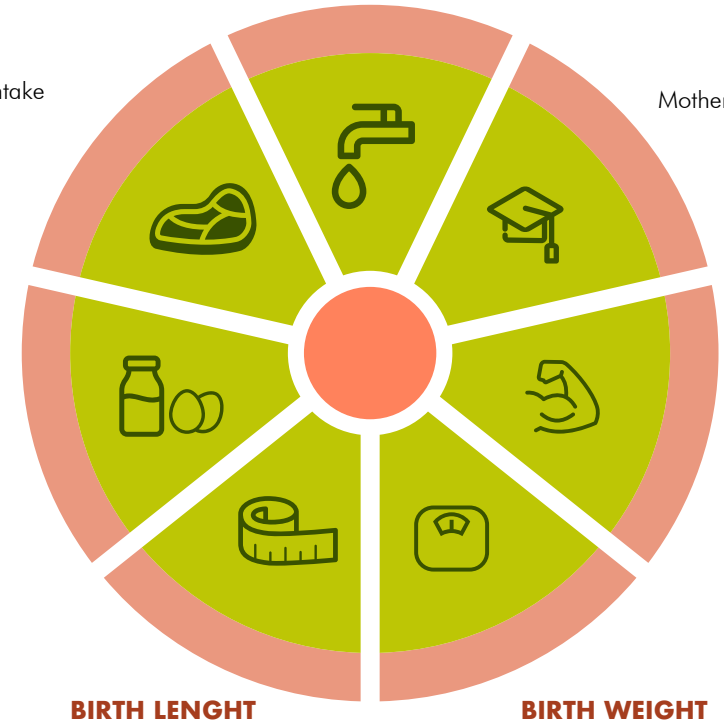
SECTION 3

MATERNAL & ENVIRONMENTAL DETERMINANT FOR GROWTH FALTERING IN THE FIRST 5 YEARS

Risk factors of shortness/stunting in under-five children based on univariable binary logistic regression
(Sofiatin et al, 2019)

WATER
Unimproved source of drinking water
= 1,5x risk of shortness/stunting.

PROTEIN INTAKE (6-24 MONTHS)
No additional protein intake 6-24 months (MP-ASI)
= 1,45x risk of shortness/stunting.



EDUCATION
Mother formal education ,6 years
= 1,25x risk of shortness/stunting.

PROTEIN INTAKE (0-6 MONTHS)
No additional protein intake 0-6 months
= 1,3x risk of shortness/stunting.

MUAC
MUAC of Mother
= 1,43x risk of shortness/stunting.

BIRTH LENGHT
Short Birth Weight
= 2,43x risk of shortness/stunting.

BIRTH WEIGHT
Low Birth Weight
= 2,38x risk shortness/stunting.

SECTION 4

DETERMINANT OF SHORTNESS IN ADOLESCENT

The 12-year tracking of maternal-child dyads in the rural Tanjungsari in Indonesia reveals that a combination of intrauterine, maternal education, environmental and interval growth performance factors are associated with severe shortness or stunting in early adolescence at age 12 (Sasongko et al., 2019).

Adolescent shortness was found in almost half of the cohort followed from birth. It was associated, among others, with birth weight as well as several individual, maternal and environmental factors evident at age 2, along with atopic disposition at age 12. Nevertheless, stature itself may not constitute a health risk over and above the associated socio-environmental conditions.
Shortness is not necessarily a nutritional problem and may represent nutritional adaptation.

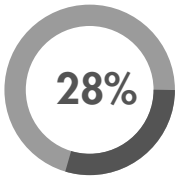
SECTION 4

DETERMINANT OF SHORTNESS IN ADOLESCENT

Bivariate and Multivariate analysis of predictors of shortness in adolescent (12 years old):

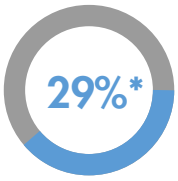
Complementary Feeding

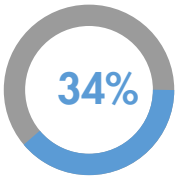
Consumption of complementary feeding in the form of milk at age 2 years reduced the risk of stunting by 22%, indicating the importance of nutritional adequacy.



Infectious Disease Risk

History of infectious disease at age 12 years increased the risk of shortness by 28%.



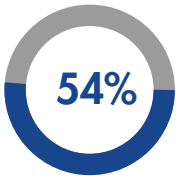


Atopic Disease Risk

History of atopic disease at age 12 years increased the risk of shortness by 34% or 29%*.

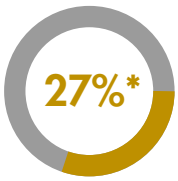
Low Birth Weight

History of Low Birth Weight increased the risk of shortness by 61% or 64%*.



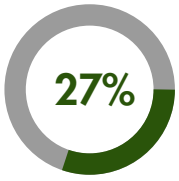
Shortness at Age 2

Shortness at age 2 increased the risk of shortness in adolescent by 54%.



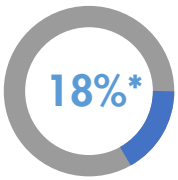
Drinking Water

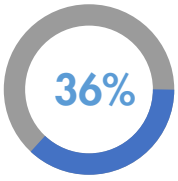
Unimproved source of drinking water increased the risk of shortness in adolescent for 45% or 27%*.



Maternal Literacy

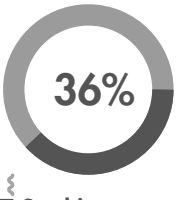
Mothers who were illiterate / had <6 schooling years increased the chance of having stunted children by 27% or 19%*.





Latrine

Unimproved latrine increased the risk of shortness in adolescent by 36% or 18%*.



Smoking Exposure

Exposure to smoke increased the risk of shortness in adolescent by 36%.

Breastfeeding

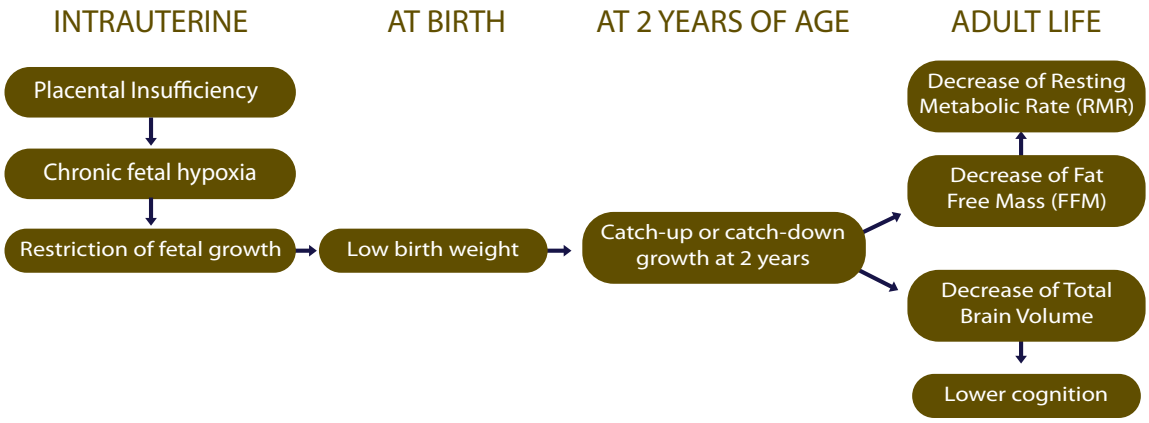
Stop breastfeeding at age 2 years might decrease the risk of shortness in adolescent by 19%.

Note: *Percentage based on multivariate analysis.

SECTION 5

METABOLIC & COGNITIVE FUNCTION OF ADULTS WITH HISTORY OF LBW

TSC Conceptual Framework for birth weight, growth at 2 years, resting metabolic rate (RMR) and cognition:



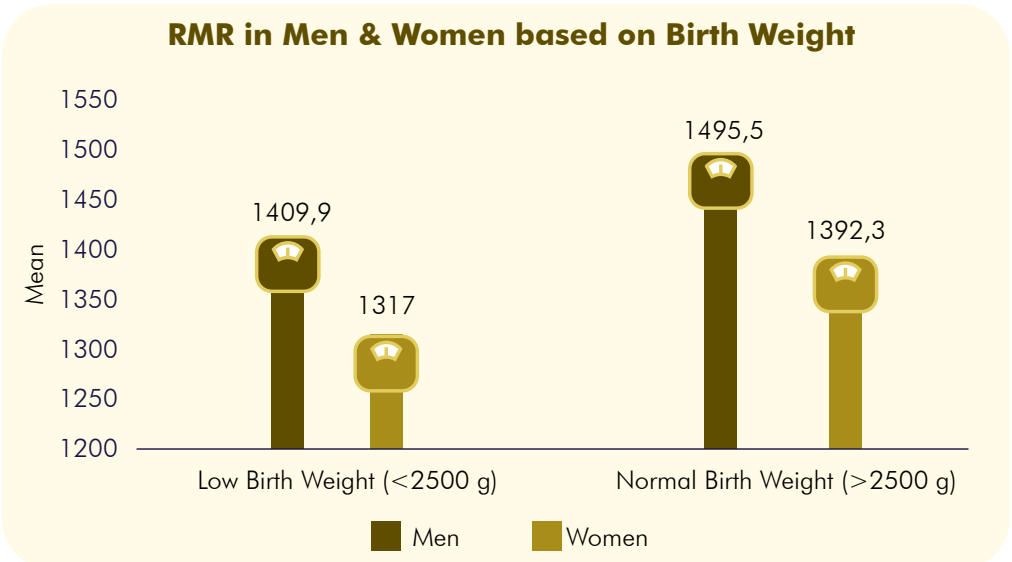
RMR is positively associated with birth weight, body weight at 2 years age, body mass index, and fat-free mass in adult life (Nugraha et al., 2019).

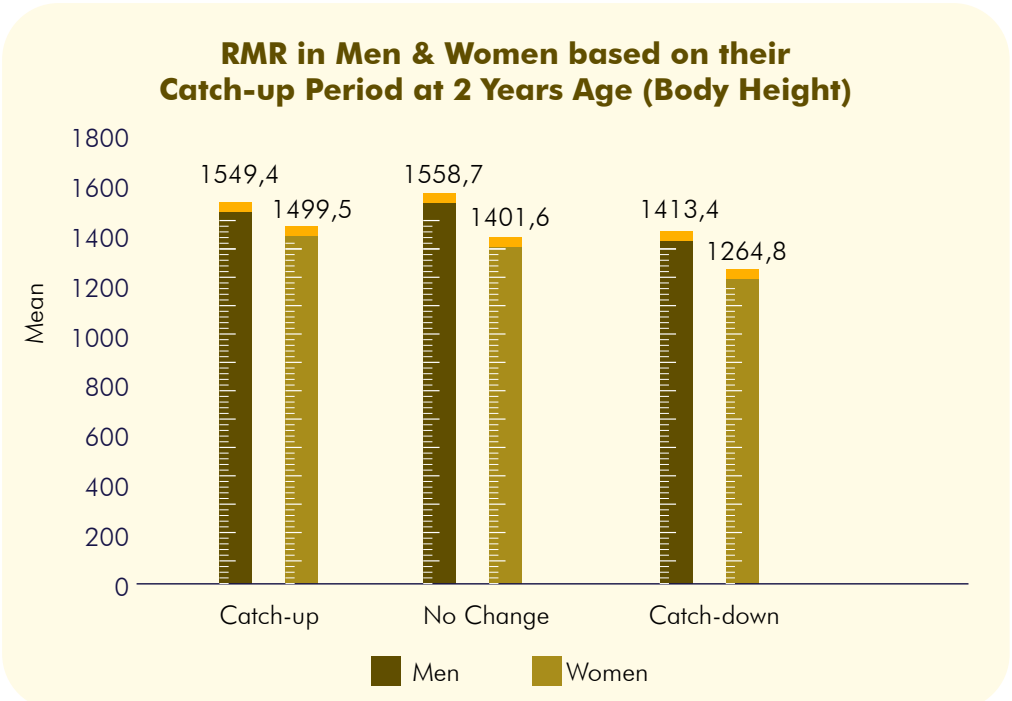
How the RMR was measured?

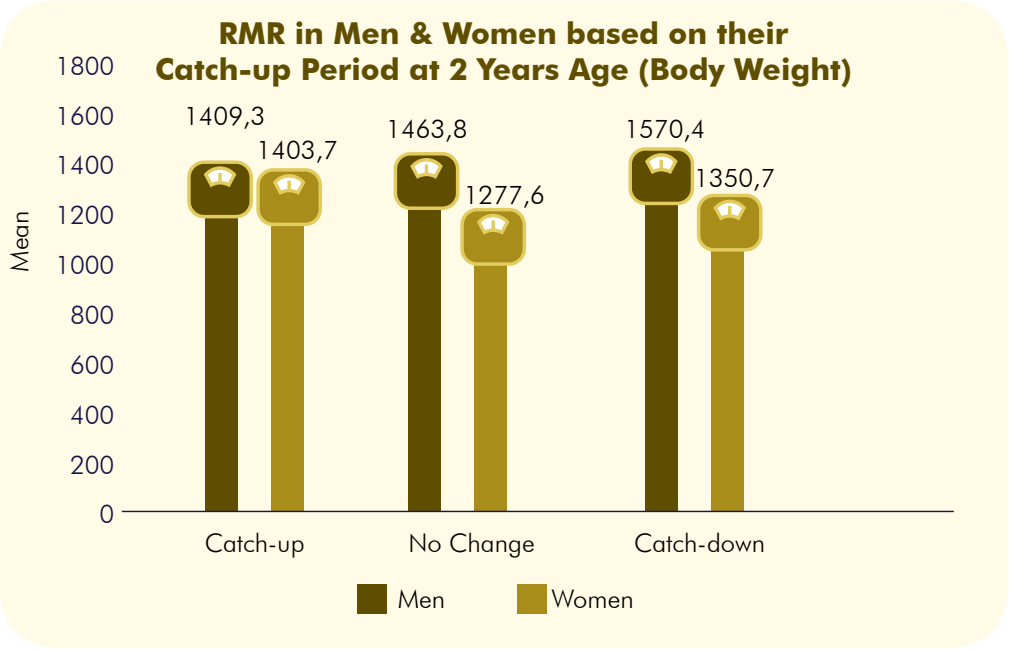
RMR was measured using indirect calorimetry (QUARK RMR, Cosmed, Rome, Italy). Measurements were recorded at 5-s intervals for 16 minutes. Calibration was performed prior to every examination. Oxygen consumption (VO2) and the production of carbon dioxide (VCO2) in litres per minute, as well as the tidal volume, were measured. RMR values were obtained in kilocalories (kcal) per day by using the Weir Formula: [3.941 (VO2) + 1.106 (VCO2)] x 1440.

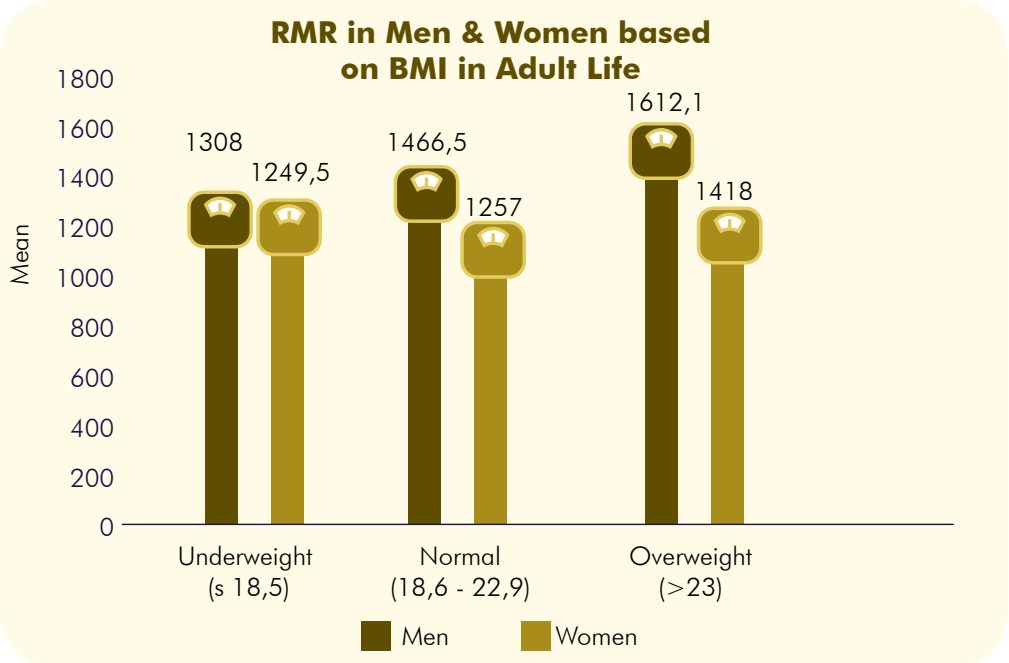
MR (kcal/24 h) in men and women according to birth weight, catch-up at 2 years, and BMI in adult life

(Nugraha et al., 2019)





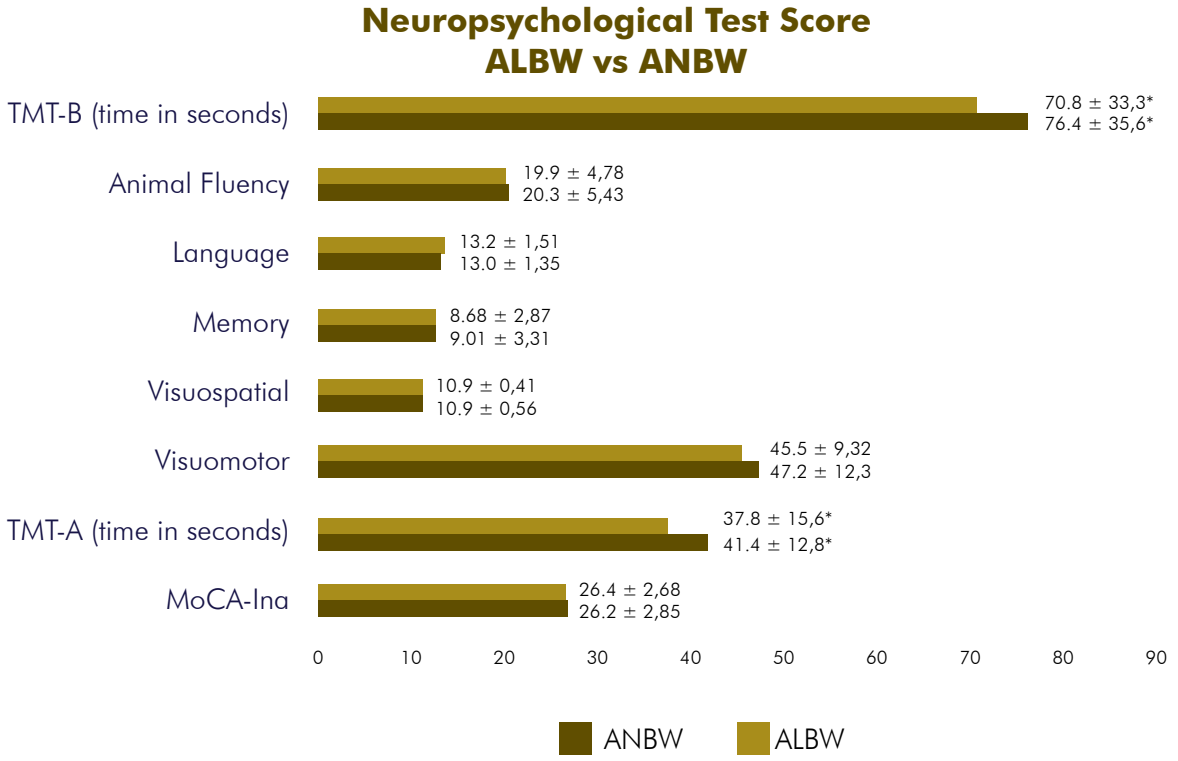




Based on the statistic above, no significant difference was discovered in the RMR between birth weight groups among the men or women. At 2 years age height was associated with RMR; in adulthood, BMI was associated with RMR.

Body size (weight and height/length) at 2 years of age is a crucial factor in determining RMR during adulthood. Therefore, improving nutritional status that affects body size (catch-up) may independently affect RMR in adulthood regardless of birth weight.

Comparison of neuropsychological test scores between Adulth with history of Low Birth Weight (ALBW) and Adulth with history of Normal Birth Weight (ANBW) groups (Nugraha et al., 2019)



In this study, ALBW participants have the same level of education, employment, monthly income, and marital status compare to ANBW participants. It is supposed that all ALBW participants might have a much milder cognitive deficit and managed to catch-up in education and social-economic attainment in adult life.

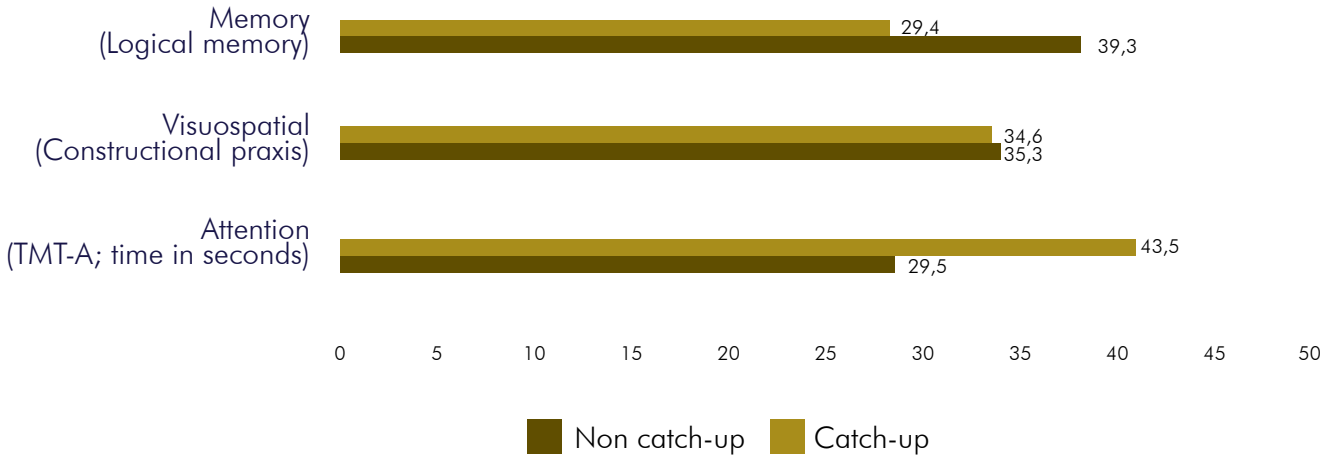
Even though ALBW participants have the same achievement for educational level, socioeconomic attainment, and the global cognitive screening test compared to ANBW participants, ALBW participants still have lower scores for specific cognitive domain tests of attention compared to those with ANBW. This subtle cognitive deficits in attention (TMT-A) are significant in adult life (41,4 ± 12,8 vs 37,8 ± 15,6). It takes a much longer time for ALBW participants to finish the test compared to those of ANBW groups.

***TMT-A and TMT-B are valued based on time per second. The faster the processing time, the better the test result.**

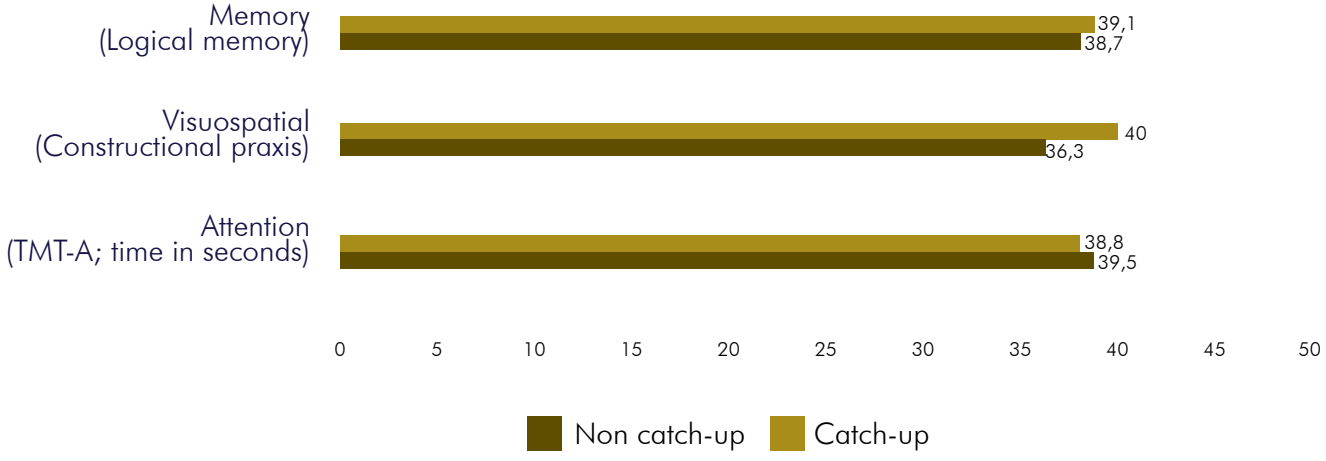
Comparison of neuropsychological test scores between catch-up and non-catch-up subjects

(Nugraha et al., 2019)

Neurophysical Test Score Comparison between Catch-up & Non Catch-up in ALBW Group



Neurophysical Test Score Comparison between Catch-up & Non Catch-up in ANBW Group



The catch-up period has a role in influencing cognitive achievement such as memory, visuospatial, and attention. In the ALBW group, catch-up is associated with superior attention and memory function compared with their counterparts who do not experience catch-up growth. This is reflected in the shorter time catch-up subjects take to finish the TMT-A test and by the higher score that the catch-up participants obtained on the logical memory test. By contrast, the catch-up subjects in the ANBW group show poorer visuospatial function, as reflected by their lower score on the constructional praxis test. These findings indicated that weight catch-up may be a modulating factor for birth weight and cognitive achievement.

SECTION 6

LESSONS LEARNED

PREGNANCY

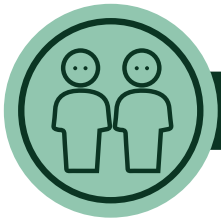
- IUGR classification based on a combination of body weight and body length identified a larger group of infants at health risk compared with Low Birth Weight. **Only 23.6% of infant mortality may be avoided if health programmes concentrate solely on infants with Low Birth Weight; while targeting interventions to preterm and IUGR newborns could potentially prevent more than 60.2% of infant death.**

INFANCY

- **Growth-retarded infant never reaches their growth potential** and remain smaller and lighter than their peers.
- **The first week, first month and first 90 days after birth** were the most vulnerable age periods regarding infant mortality.
- Low Birth Weight is a risk factor for shortness/stunting. **Adding complementary protein at 6-24 months may prevent shortness/stunting.**

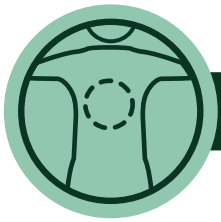
SECTION 6

LESSONS LEARNED



ADOLESCENCE

- Shortness/stunting in adolescents presumably reflects the **cumulative effects of poor nutrition, infection and environmental factors** operative from the fetal period through young adulthood.
- More attention should be paid to adolescent girls who are short/stunted because of the **possible adverse consequences in the event of pregnancy,** where intergenerational nutritional disorders may occur.
- **Shortness/stunting at age 2 years is a risk factor for shortness/stunting in adolescence.** Children who were stunted at 2 years are more likely to remain stunted and not recover.



ADULTHOOD

- Adult with history of low birth weight has a poorer **attention span** compared to adult with history of normal birth weight.
- **Clinical characteristics associated with RMR:** birth weight, weight at 2 years of age, BMI, and fat-free mass in adult life.
- Weight gain and catch up are associated with superior memory performance in adults with history of low birth weight. However, even though the TCS study indicates that there are cognitive benefits with weight catch-up at 2 years of age, caution should be taken in interpreting this because **catch-up may also increase vascular risk factors** such as high levels of sugar in blood (hyperglycemia) and increased waist circumference, as well as Body Mass Index.

SOCIAL ASPECT

- The habit of prioritizing men during the meal is still practiced in rural areas, thus affecting the quality of the mother's nutritional intake. Therefore, the **promotion of exclusive breastfeeding should be complemented by educating the family on the importance of maternal nutrition.**
- Female community health volunteer is the key to strengthen the healthcare system in rural settings, especially with regards to mother and child's nutrition.

SECTION 7

RECOMMENDATIONS

1. IUGR assessment at the Puskesmas level should be conducted.
2. Strengthening intervention during Window Opportunity for Catch-Up Growth at different ages.
3. More attention should be addressed to under-five children with history of Low Birth Weight, especially nutritional adequacy through consumption of, amongst others, complementary feeding in milk form aiming to reduce the risk of shortness/stunting.
4. The promotion of exclusive breastfeeding should be accompanied by educating the family on the importance of good maternal nutritional status.
5. Continuous support should be given to the education of women and the role of women in community development as it pertains to child growth and development.

GLOSSARY

- ALBW: Adult with history of Low Birth Weight
- ANBW: Adult with history of Normal Birth Weight
- BMI: Body Mass Index
- FFM: Fat Free Mass
- HAZ: Height for Age Z-score
- IMR: Infant Mortality Rate (per 1,000 lives births)
- IUGR: Intrauterine Growth Retardation
- MoCa-Ina: Indonesian version of Montreal Cognitive Assessment
- MUAC: Middle-Upper Arm Circumference
- Puskesmas: Pusat Kesehatan Masyarakat (Public Health Center)
- RMR: Resting Metabolic Rate; energy required by the body in a resting condition
- TMT-A/B: Trail Making Test Part A/B; cognitive function test
- WAZ: Weight for Age Z-score

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Gizi untuk Anak Bangsa

CONSUMPTION PATTERNS OF SWEETENED CONDENSED MILK (SCM)

in the Diet of Young Indonesian Children and Its Potential Nutritional Health Consequences

Mohammad Juffrie, MD, PhD, Ratu Ayu Dewi Sartika MSc, PhD, Roy Alexander Sparringa MAppSC, PhD, Lindawati Wibowo SSi, MSc, Widjaja Lukito MD, PhD

FACTS & FIGURES

Approximately 90% of the Indonesian population prefer consuming SCM, milk powder, or ultra-high-temperature (UHT) milk than fresh milk (DG of Livestock and Animal Health, 2012).

58.9% of children who consumed SCM were from families with a low socioeconomic status (Sugito et al, 2008).

A survey in Jakarta found that 22.1% of children 12-38 months were given SCM in combination with breast milk (Martha E. et al, 2017).

A few cases where infants were given SCM as breastfeeding substitute were found in some studies, either among normal (0.25%; Palupi E., 2015) or underweight infants (2,2%; Adriani M. & Kartika V., 2011).

30% of caregivers of preschoolers (aged 3-5 years) in urban Yogyakarta maintained their children's milk consumption by substituting the growing-up formula/milk with SCM, especially when children grew older (Prawirohartono et al, 2015).

SCM should not be given to young children as either breast milk or formula milk substitutes. Yet, indications of such improper utilization of SCM have been repeatedly documented in several independent studies mostly conducted in urban and semiurban areas in Indonesia (UNICEF, 2005; Martha E et al, 2017; Sugito FS et al, 2008; Prawirohartono EP et al, 2015).

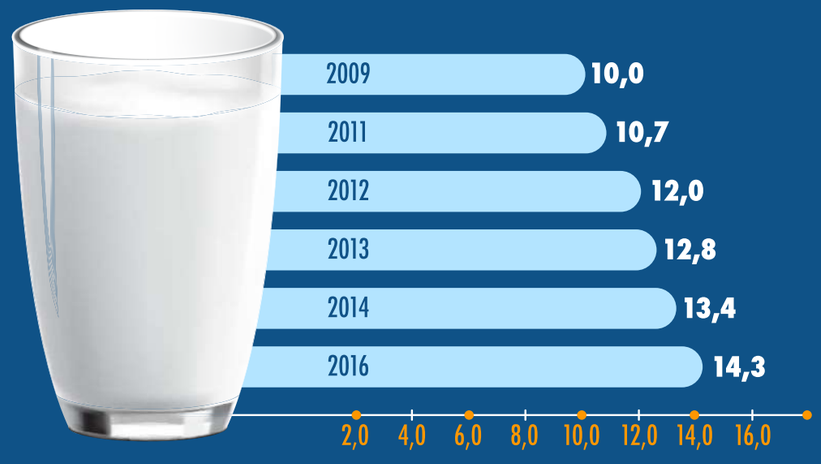
Caregivers, especially those from families with low socioeconomic status, perceived that SCM is nutritionally sufficient to support growth of a toddler (Martha E et al, 2017; Sugito FS et al, 2008).

Parents' education, particularly the mother's, is also associated with the preference to administer SCM to children. (Palupi E, 2015; Sartika RAD & Ruswandi RBI, unpublished data).

SWEETENED CONDENSED MILK IN INDONESIA

Indonesia is still categorized as a country with low milk consumption, with an estimated country-specific intake of less than 30 kg or 29.1 L per capita/year. It is the lowest among other ASEAN countries, including the Philippines, Malaysia, and Thailand.

Annual milk consumption (L per capita) of Indonesians

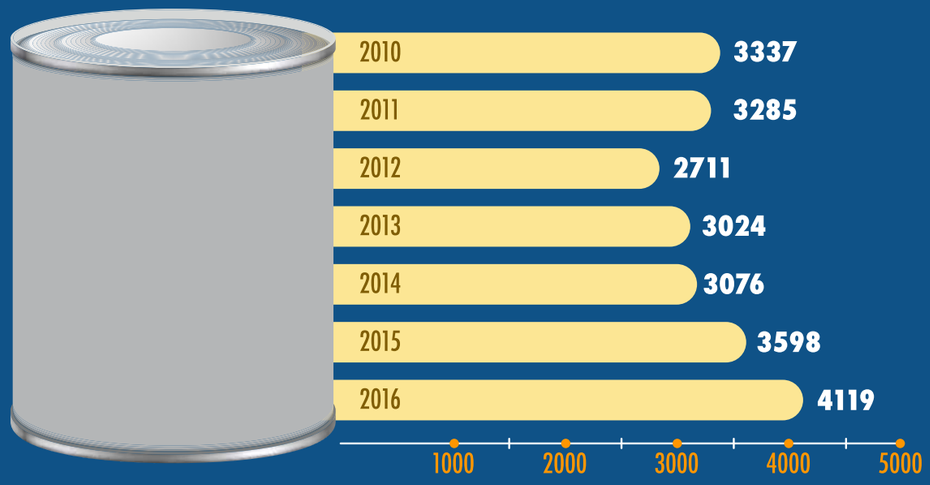


Philippines
22.1 L per capita/year

Malaysia
50.9 L per capita/year

Thailand
33.7 L per capita/year

Annual consumption of SCM and its product analogs in Indonesia per capita from 2010 to 2016 (Ministry of Agriculture, 2017) (in 397 g per unit)



SCM MARKET IN INDONESIA

Annual SCM production capacity ±812,000 tons

Local SCM industries obtain fresh milk supplies from > 100,000 dairy farmers equivalent to an invesment value Rp 5,5 trillion

SCM industries employ 6,652 workers.

The annual market for SCM grew steadily by 4.74% (USDA, 2017). The much cheaper price and the ease of bulk transportation without the need for cold chain management make the market distributin of SCM widespread within the country.

Supplies used for processing SCM include low-grade local fresh milk containing high amount of bacteria and low protein. In the evaporation process, fresh milk is pasteurized, which can remove pathogens and inactive vegetative spoilage bacteria and enzymes, but not bacterial spores (USDA Foreign Agricultural Service GAIN Report, 2009-2013).

Local manufacturers rely on imported Whole Milk Powder (WMP), as one of SCM ingredients, from New Zealand (53%-65%), Australia (15%-16%), the UK (7%), and very limited quantities from the US.

SCM, with a market share of 35% sustainably dominates the national market together with liquid ready-to-drink milk (26%) and powdered milk (39%) (USDA Foreign Agricultural Services, 2009-2015).

DETERMINANT FACTORS OF SCM CONSUMPTION

The preference for dairy products for consumption is attributable to some interlinked factors related to product characteristics (taste, aroma, etc.) and socioeconomic variables. Data have shown that SCM in sachets is favorable to be administered to toddlers because the product is easy to obtain, very affordable, has an enjoyable taste, needs no storage with only a one-serving portion per sachet, and can be prepared whenever the child wants it (Martha E. et al, 2017; Prawirohartono EP et al, 2015). This might explain why product characteristics of SCM appear to matter more than its nutritional value, particularly within certain population segments (i.e. underprivileged, poor, or less educated).

PATTERNS OF SCM CONSUMPTION AMONG INDONESIAN CHILDREN

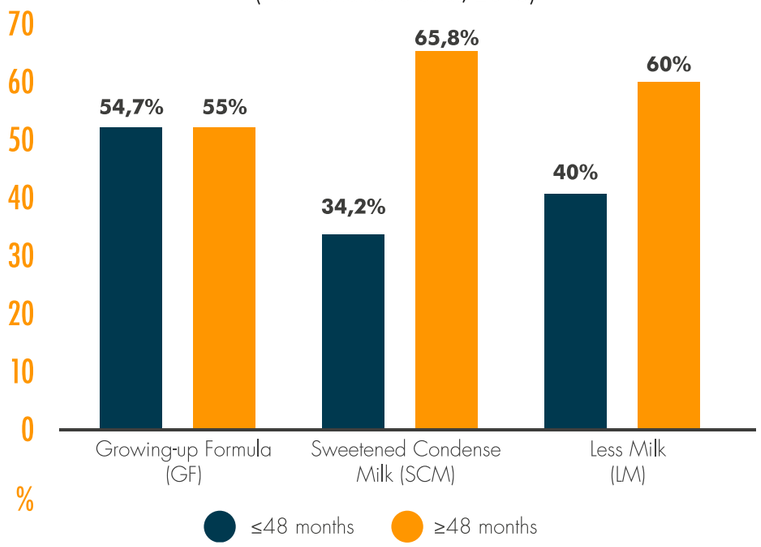
Studies in urban Yogyakarta, Bogor, and West Jakarta have consistently **found gradual increases in the proportion of children consuming SCM** in analyses stratified by age group. These studies also show that economic variables—family income and parent's education—are consistently associated with child milk consumption patterns.

Urban Yogyakarta (Prawirohartono et al, 2015)

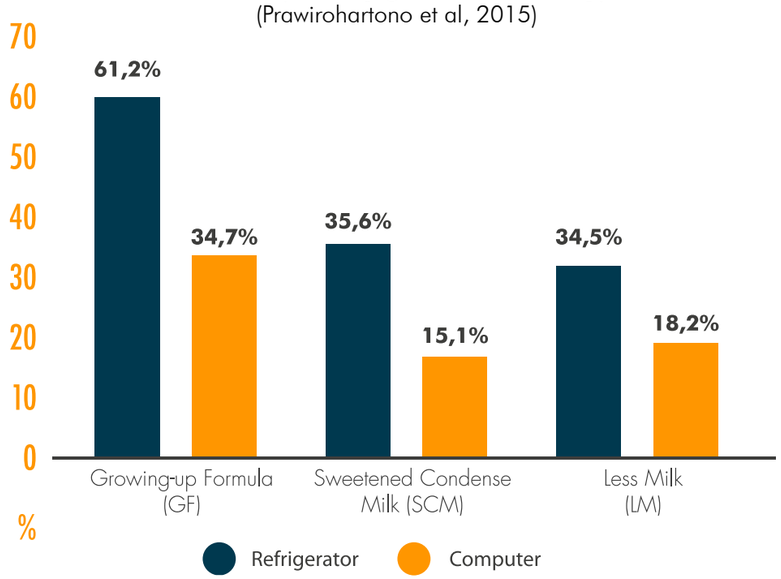
Method: 3-day food recall

Subjects: 249 children aged 3-5 years; compared between those who consumed growing-up formula (GF), sweetened condensed milk (SCM), less milk (LM)

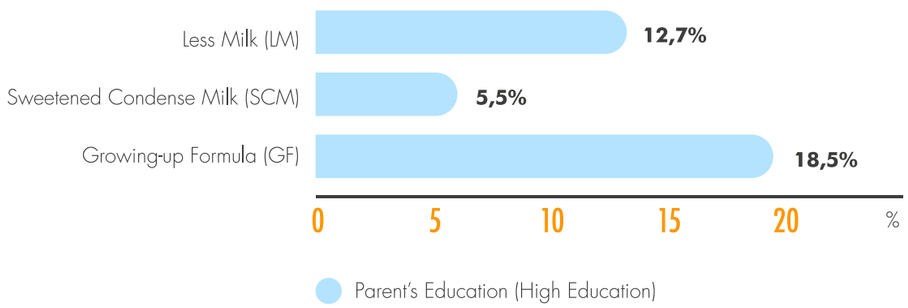
Proportion of children in urban Yogyakarta consuming GF, SCM, and LM based on child age groups
(Prawirohartono et al, 2015)



Proportion of children in urban Yogyakarta consuming GF, SCM, and LM based on family income (tertiary goods availability)
(Prawirohartono et al, 2015)



Proportion of children in urban Yogyakarta consuming GF, SCM, and LM based on parent's education (high education)
(Prawirohartono et al, 2015)

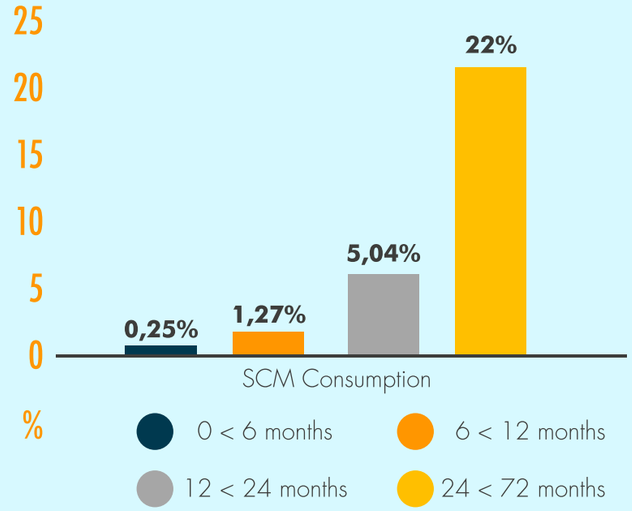


Bogor City (Palupi E., 2015)

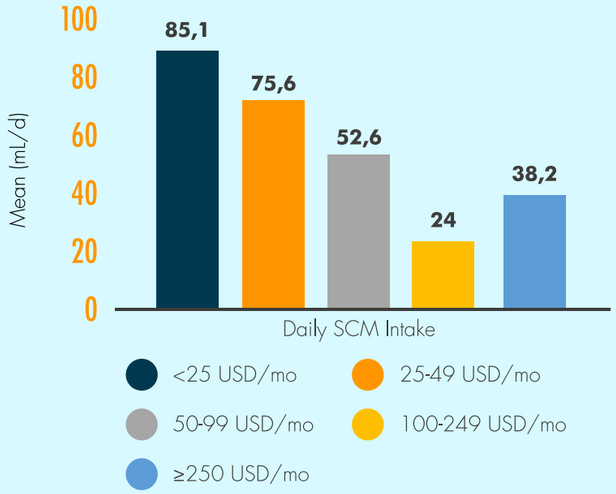
Method: History of breastfeeding & milk consumption, milk consumption frequency, 2-day food recall

Subjects: 221 children at ages 5 to 6

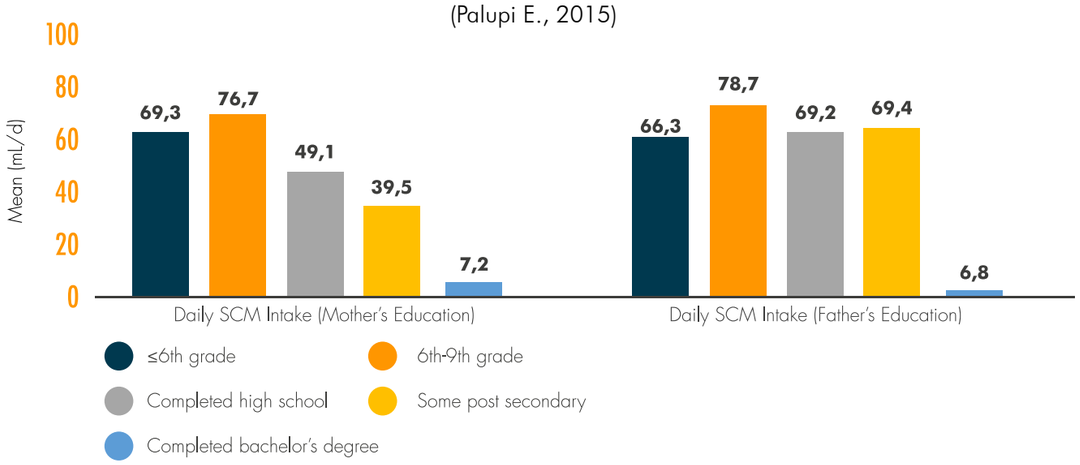
Proportion of children in Bogor City consuming SCM based on child age groups
(Palupi E., 2015)



Proportion of children in Bogor City consuming SCM based on family income
(Palupi E., 2015)



Proportion of children in Bogor City consuming SCM based on parent's education
(Palupi E., 2015)

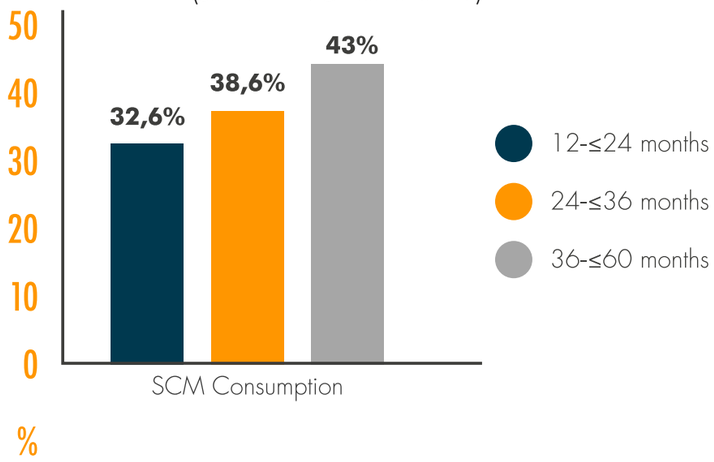


West Jakarta (Sartika RAD & Ruswandi RBI, unpublished data)

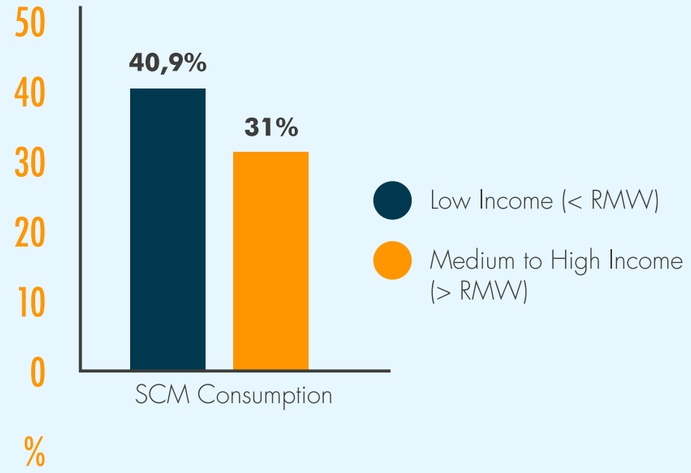
Method: 2-day food recall

Subjects: : 200 children aged 12-<60 months

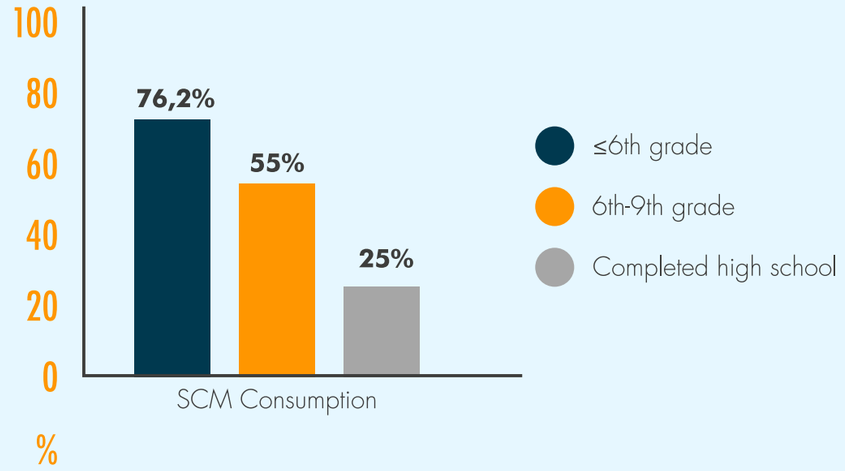
Proportion of children in West Jakarta consuming SCM based on children age groups
(Sartika RAD & Ruswandi RBI)



Proportion of children in West Jakarta consuming SCM based on family income
(Sartika RAD & Ruswandi RBI)

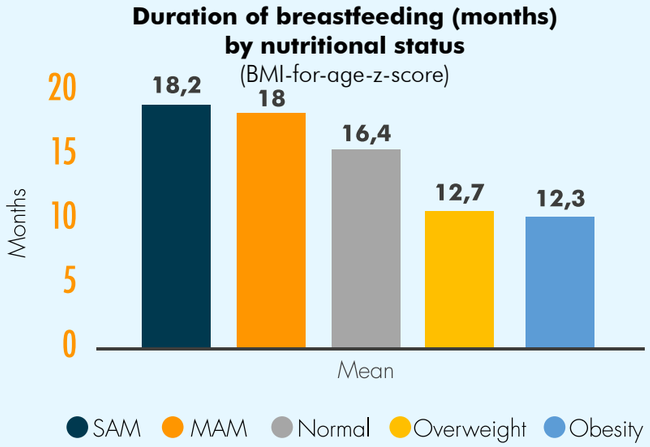


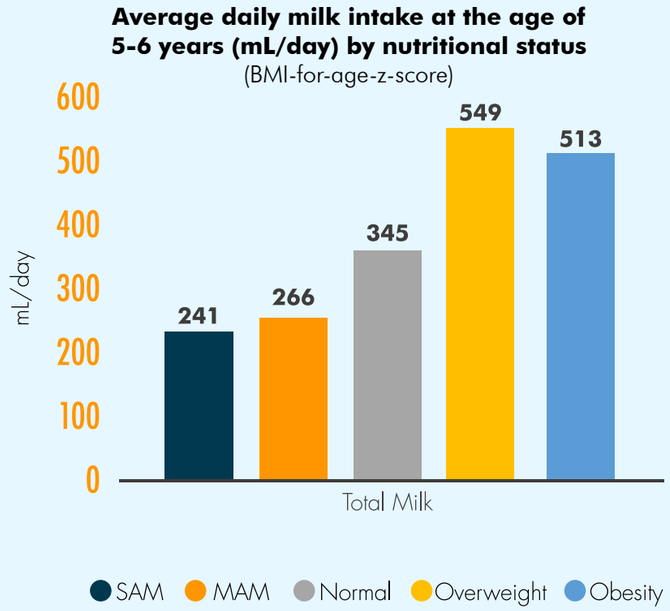
Proportion of children in West Jakarta consuming SCM based on mother's education
(Sartika RAD & Ruswandi RBI)

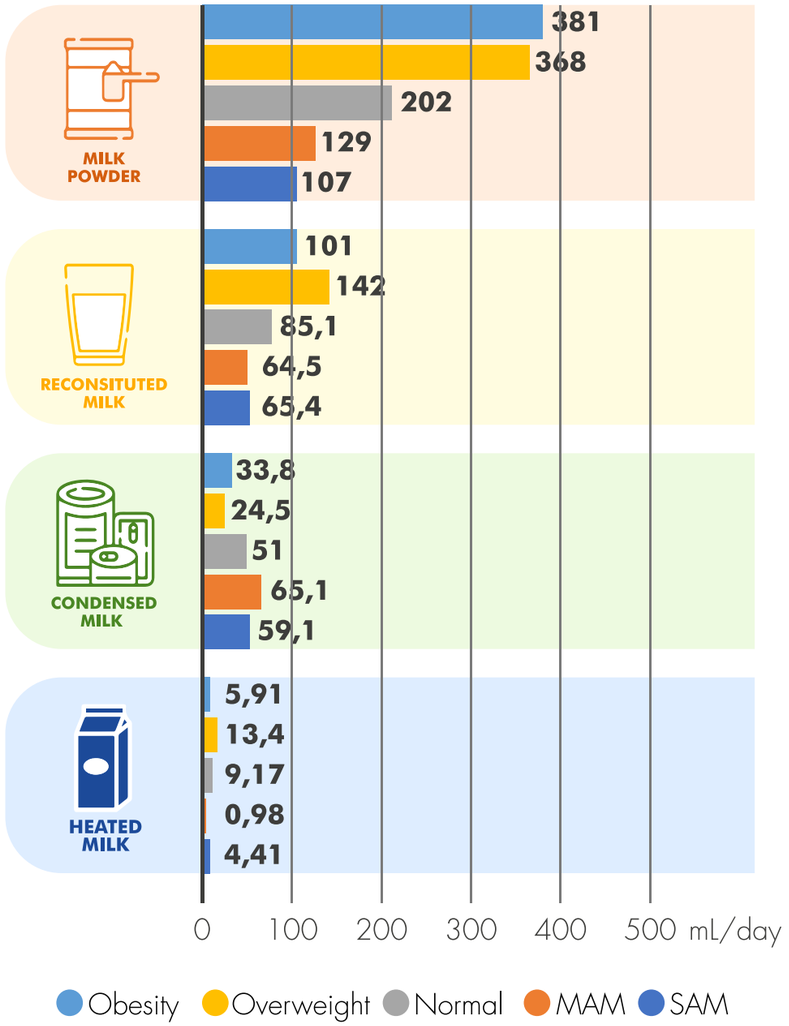


EVIDENCE ON THE ASSOCIATION BETWEEN (REGULAR) CONSUMPTION OF SCM AND HEALTH MEASURES

Duration of breastfeeding and usual daily milk intake at age of 5-6 years by nutritional status (Palupi E., 2015)



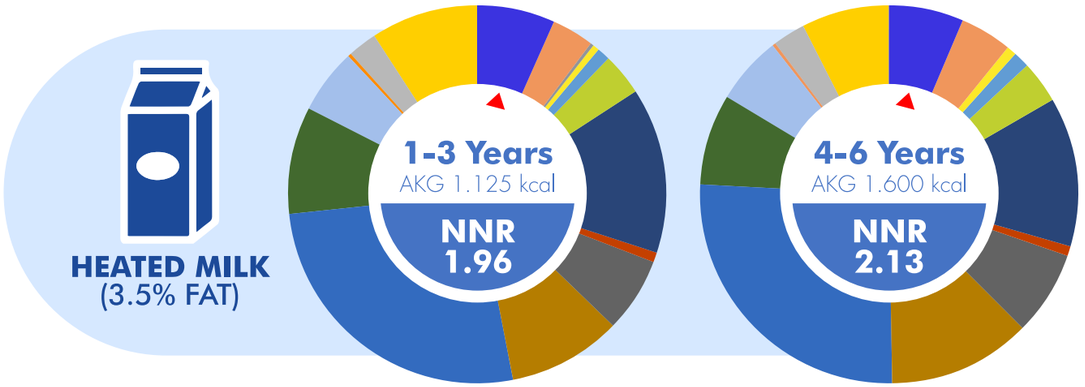


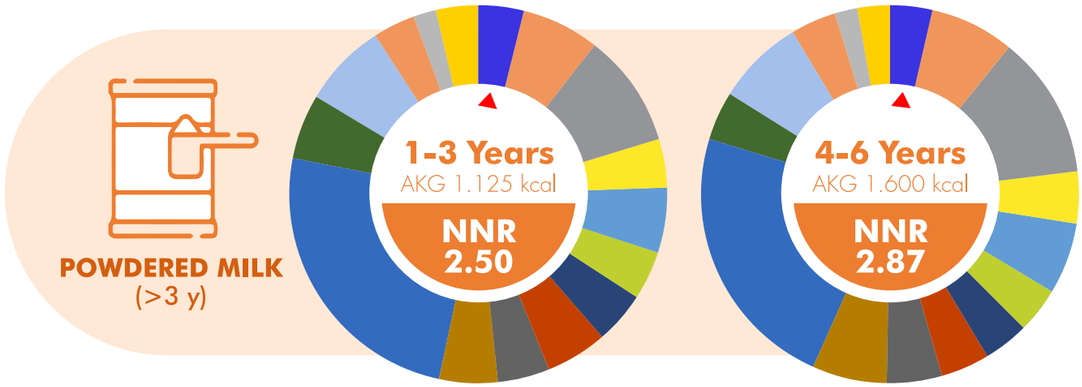


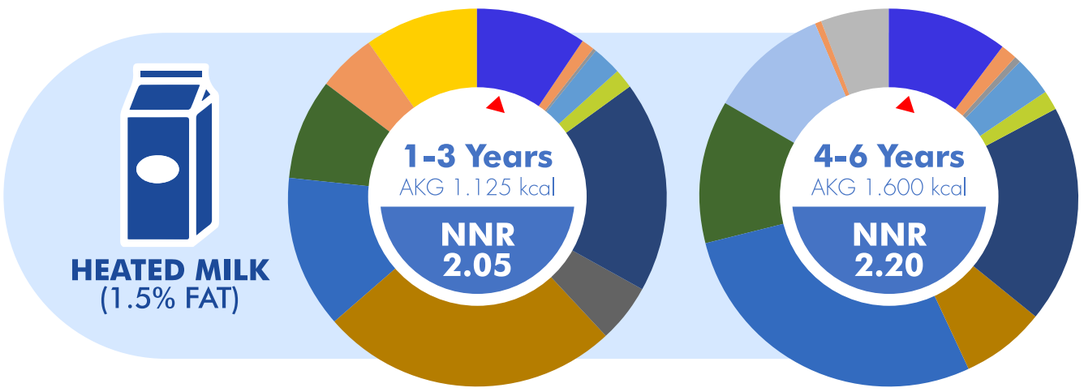
NOTE: BMI: body mass index in kg/m2; N: number of respondents; BMIfz: BMI-for-age z-score; SAM: severe acute malnutrition (BMIfz <-3, N=60); MAM: moderate acute malnutrition ($-2<$BMIfz≤-3, N=61); Nor-mal: $-2\leq$MBIfz≤1, N=163; Overweight: $1<$BMIfz≤-2, N=43; Obesity: BMIfz>2, N=60; Mean: usual daily intake of milk calculated by the multiple source method (MSM).

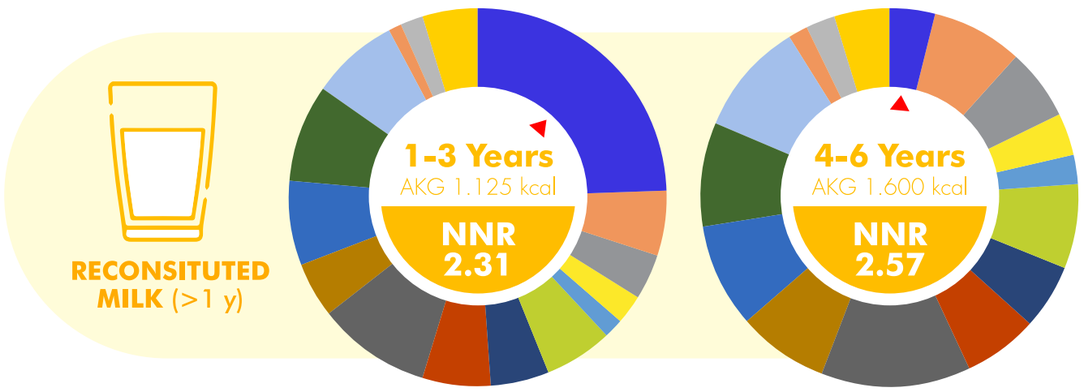
The BMIfz of children at ages 5-6 years had positive associations with daily formula and reconstituted milk consumption but have negative associations with SCM and breastmilk intake. SCM could hardly be a full substitute for any other milk across different nutritional status groups, but it is consumed more by undernourished group.

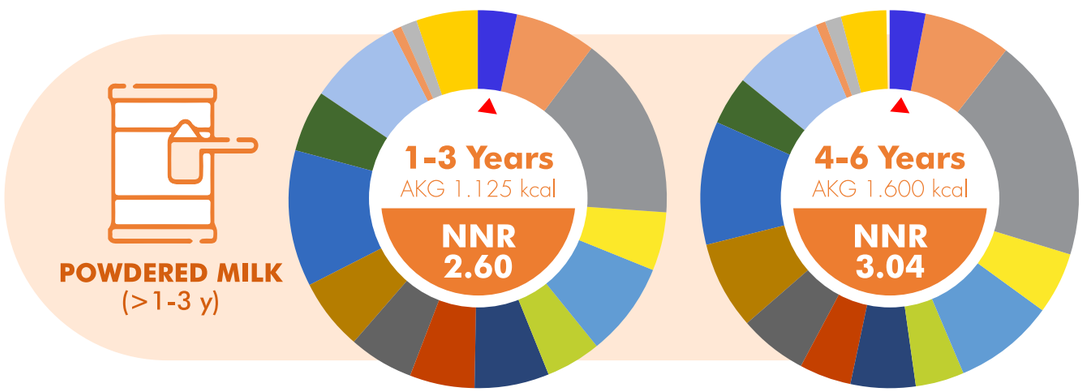
Based on its naturally nutrient rich (NNR) score, **SCM has the lowest nutritional value as compared with the other types of milk,** which makes it less ideal for young children to consume (Palupi E., 2015).

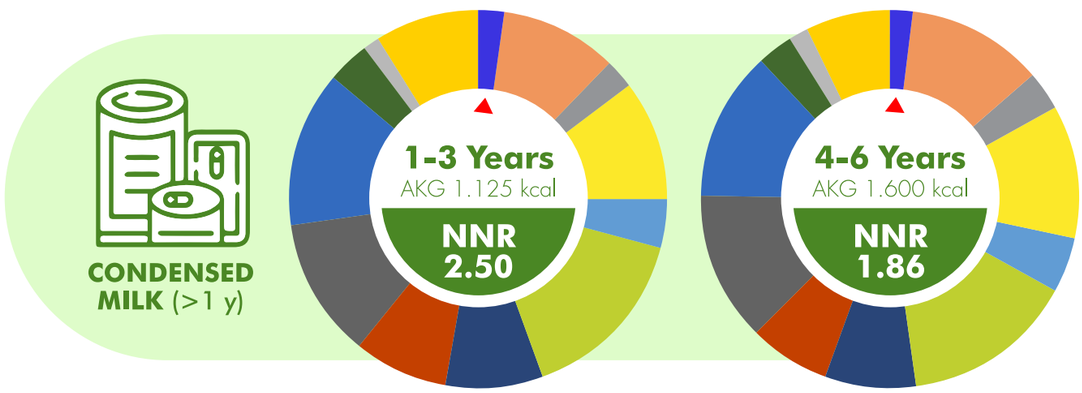












Health risks of SBB or SCM consumption by young Indonesian children aged less than 5 years:

1. As a product with low nutritional value but with high added sugar, SCM may be associated with the risk of undernutrition among young children with poor dietary patterns if the energy from sugar causes "voluntary reduction in the intake of other foods/drinks." Futher study must be conducted better understand the direction of the association: whether SCM intake increases the risk of undernutrition or whether undernourished children consume SCM more due to other reasons (i.e., poverty, poor feeding, energy compensation, or maternal education).

    - SSB in any form might also be one of the major sources of free sugar for children aged less than 5 years because 43.6% of them have been exposed to it (Ruswandi RBI, 2017).
    - Children aged < 5 years who consumed SSB (not specifically SCM) had a 3.8-fold higher risk of being underweight than those who did not consume SSB after controlling for mother's education, total child energy intake, and the interaction between SSB consumption and mother's education (Ruswandi RBI, 2017).

2. As one of the SSB variants, the health risks of high SCM consumption might also be linked to its high sugar content. The public health recommendation to limit free sugar consumption from any sources is fundamental for the prevention of health disorders, such as type 2 diabetes mellitus and dental caries.

3. Conclusions could not be drawn for risk factors; health outcomes; measures such as HDL-cholesterol, body weight, weight gain, body fat percentage, fat distribution, and energy intake (children); and conditions including coronary events, stroke, incident hypertension, glycemia, insulinemia, insulin resistance/sensitivity, and oral cancer due to insufficient evidence for the relationship with SSB (WHO, 2015).

EXISTING POLICIES THAT REGULATE THE MARKETING AND PROMOTION, INCLUDING RISK COMMUNICATION, OF SCM FOR CHILDREN

PerkaBPOM No. 1 Year 2015 & PerkaBPOM No. 21 Year 2016
(Food Category)

- SCM with milk fat content <8% and protein content not less than 6.5% is further classified into four product analogs: [1] sweetened skimmed milk (fat content not less than 8%), [2] vegetable-fat SCM (milk fat content not more than 1%), [3] creamed SCM (milk fat content not less than 45% and total solid not less than 65%), and [4] creamer SCM.
- These products, with the exception of creamer SCM, were regulated for milk fat and protein contents, but not for total fat content.

Circular Letter No. HK.06.5.51.511.05.18.2000 Year 2018
(Label and Advertisement of Condensed Milk and the Analogue Food Category 01.3)

- National polemics of 2017 and 2018 resulted in the issuance of a circular letter followed by a new Indonesian FDA regulation.

PerkaBPOM No. 31 Year 2018
(Processed Food Label)

- New regulation reinforces the correct labeling and advertisement of SCM (including its analogs) as "not suitable product for infant."
- Product labeling follows the Codex Alimentarius. However, information on the content of sugar used as the product preservative is not mandatory in labelling.
- Monitoring of products post marketing still relies on the provision of an external official complaint by consumers to enable a special team within the FDA to react to the problem of product overclaims.

RECOMMENDATIONS TO CONTROL SCM CONSUMPTION

1. The behavior of reading food labels by caregivers should be promoted to correctly understand which products are safe to be consumed by young children.

2. Limiting free sugar consumption from any sources, including SSB and SCM, is still highly recommended despite the lacking evidence.

3. Understanding and applying a balanced diet as the core of young child feeding.

4. Active monitoring of product advertisements, enforcement of regulations, and provision of effective customer education as corrective measures to the nonideal SCM consumption among young children in Indonesia.

List of Abbreviations

BMIfz : Body Mass Index-for-age-z-score
BPOM : Badan Pengawas Obat dan Makanan / The National Agency of Drug and Food Control
DRI : Dietary Reference Intake
GF : Growing-up Formula
IFCS : Individual Food Consumption Survey
LM : Less Milk
MAM : Moderate Acute Malnutrition
NNR : Naturally Nutrient Rich
RMW : Regional Minimum Wage
SAM : Severe Acute Malnutrition
SCM : Sweetened Condensed Milk
SSB : Sugar-Sweetened Beverages
WMP : Whole Milk Powder

ACKNOWLEDGMENT

The Indonesian Danone Institute Foundation is an independent non-profit organization that was established in 2007 (No.: C-3394.HT.01.02. TH 2007) and operates in accordance to the laws of the Republic of Indonesia.


Yayasan
INSTITUT DANONE
Gizi untuk Anak Bangsa
INDONESIA

ATTACHMENT 6

Website Management Report

- Website Maintenance Annual Report 2020
- New Website Design for the Indonesian Danone Institute Foundation

Website Maintenance ANNUAL REPORT 2020

Indonesia Danone Institute Foundation

TABLE OF CONTENTS

NEW WEBSITE

Why Build A New Website?

The first website of Indonesian Danone Institute Foundation (IDIF) was launched in 2009. Every year since 2015 the number of mobile users who access DII's website had been steadily increasing, from 28.68% in 2015 to 59.57% in 2019.

Almost all Internet users in Indonesia use mobile devices. In 2020, mobile Internet users in Indonesia are recorded at 171 million or 98 percent of total Internet users. The desktop version of a site might be difficult to view and use on a mobile device. This means a website should be easy to view and navigate on both desktop and mobile. The easiest way to do that is with a responsive website. This kind of site adjusts content to fit on a variety of screen sizes.

With mobile search becoming more popular than desktop, searchers have seen a number of mobile sites, and will not stay for long on a site they find outdated. Given 15 minutes to consume content, two-thirds of people would rather read something beautifully designed than something plain.

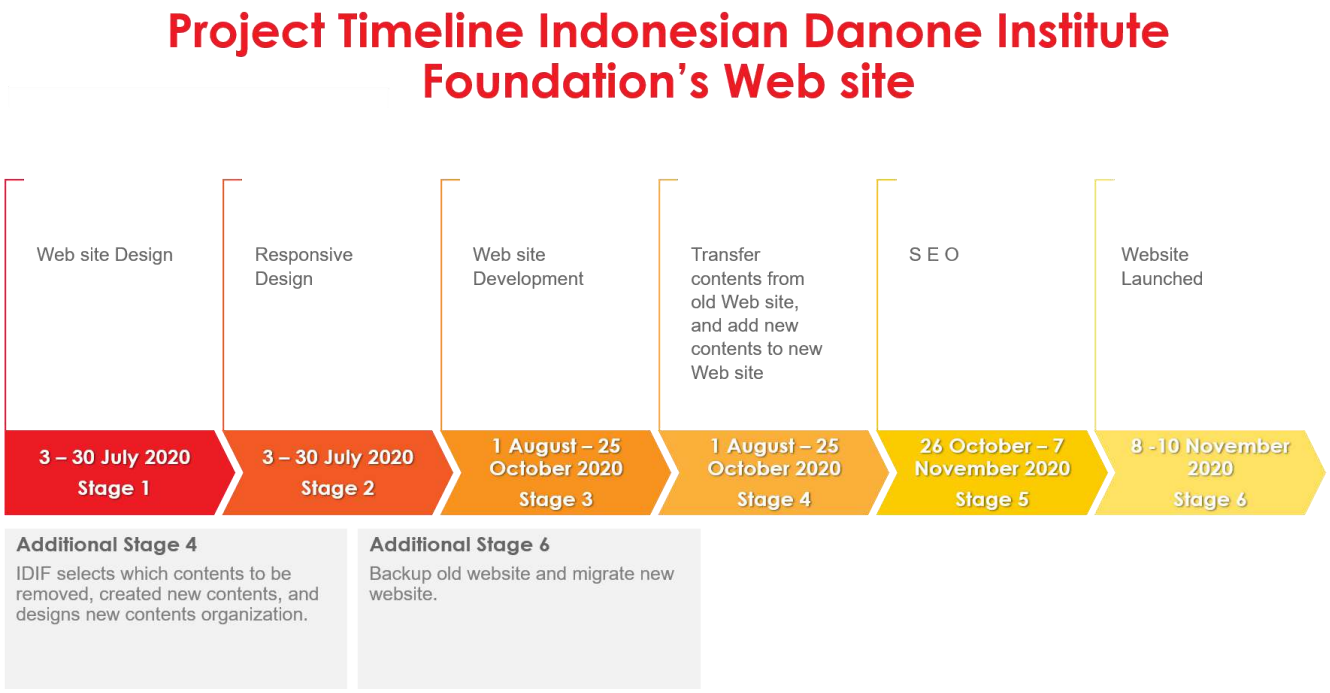
In fact, starting in late 2016, Google has begun experiments to primarily use the mobile version of a site's content for ranking, parsing structured data, and generating snippets.

In January 2020, IDIF initiated to have a new website.

The New Website

The design of IDIF's website follows the website of Danone Institute International (DII). The organization of website contents have changed, where the contents prior to 2015 are placed under the main menu of History. Newest contents which are placed on the homepage consist of 60% of IDIF's contents and 40% of DII's contents. There is one new feature called "SUBSCRIBE" which was not available in the old website. This feature will inform newest contents to subscribers which will be sent to their emails.

Project Timeline



DII Websites Documentation

The old and new websites have been archived for offline viewing and considered as documentation. The offline DII websites can be downloaded from: https://drive.google.com/file/d/1udPRgB2-M5q2Sowcpmxu0kGyI0CBUuEn/view?usp=sharing Double click the folder "Offline DII Websites". Double click the file index.html. Choose old website or new website.

WEBSITE USE ANALYSIS

Website use reports of danonenutrindo.org are facilitated by Google Analytics. The reports compare year 2020 with year 2019.The date range is January 1st - December 23rd, because the 2020 annual report was asked to be completed on that date.

Audience Overview

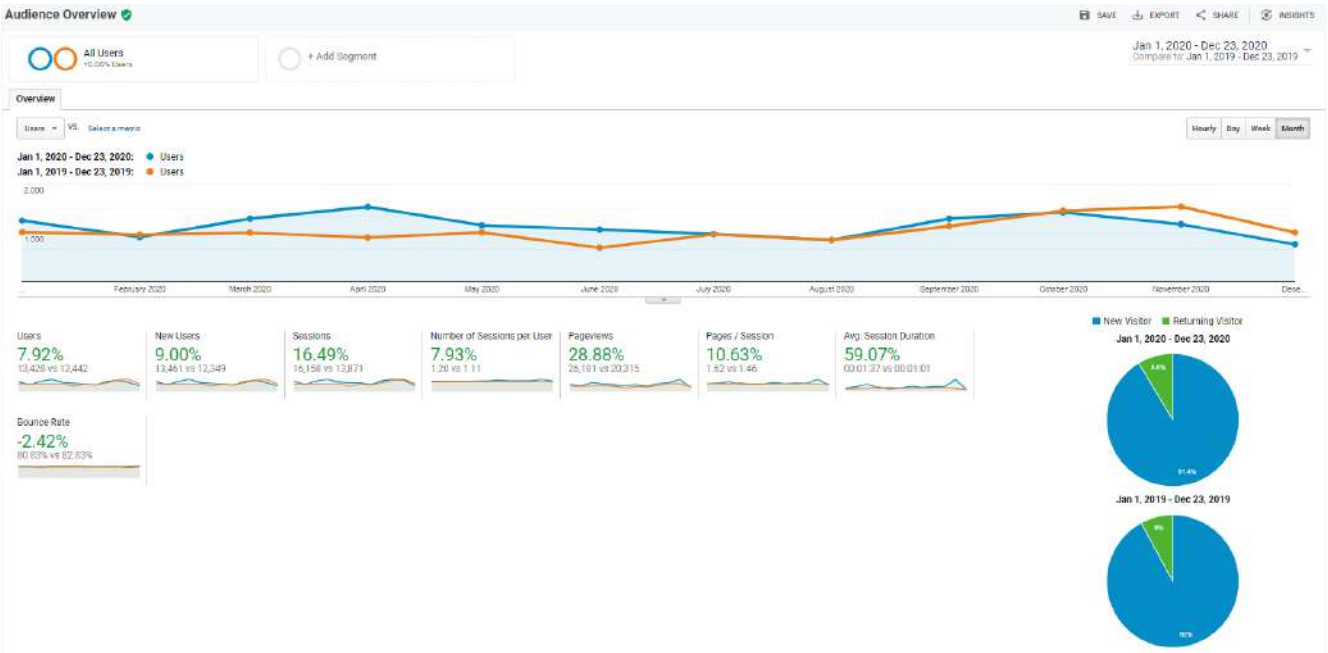


Chart 1

Chart 1 shows site visits has increased by 16.49% compared to 2019. All the metrics (quantitative measurements e.g., Users, New Users, Sessions, etc.) have increased. Notably the increase happened from March to June 2020. This increase is further explained from chart 2 and chart 3.

Pages

Page Title	Pageviews	Unique Pageviews	Avg. Time on Page
	28.89% 29,194 vs 20,315	20.59% 20,416 vs 16,930	19.12% 00:02:36 vs 00:02:11
1. Tentang Gizi Seimbang			
Jan 1, 2020 - Dec 23, 2020	5,353 (20.44%)	4,544 (22.26%)	00:04:42
Jan 1, 2019 - Dec 23, 2019	4,796 (23.61%)	4,044 (23.89%)	00:04:27
% Change	11.61%	12.36%	5.29%
2. Welcome to Indonesian Danone Institute Foundation			
Jan 1, 2020 - Dec 23, 2020	2,782 (10.62%)	1,838 (9.00%)	00:02:15
Jan 1, 2019 - Dec 23, 2019	1,855 (9.13%)	1,525 (9.01%)	00:01:26
% Change	49.97%	20.52%	57.58%
3. Prinsip 4: Pentingnya Menjaga Berat Badan Ideal Bagi Lansia			
Jan 1, 2020 - Dec 23, 2020	1,782 (6.81%)	1,544 (7.56%)	00:04:48
Jan 1, 2019 - Dec 23, 2019	1,618 (7.96%)	1,436 (8.48%)	00:03:31
% Change	10.14%	7.52%	36.45%
4. Prinsip 1: Pentingnya Makan Makanan Beraneka Ragam			
Jan 1, 2020 - Dec 23, 2020	1,479 (5.65%)	1,181 (5.78%)	00:02:14
Jan 1, 2019 - Dec 23, 2019	946 (4.66%)	772 (4.56%)	00:02:12
% Change	56.34%	52.98%	1.76%
5. Sejarah Gizi Seimbang			
Jan 1, 2020 - Dec 23, 2020	1,107 (4.23%)	923 (4.52%)	00:04:06
Jan 1, 2019 - Dec 23, 2019	701 (3.45%)	586 (3.46%)	00:04:49
% Change	57.92%	57.51%	-14.85%
6. Prinsip 1: Pentingnya Makan Makanan Yang Beraneka Ragam - Untuk Orang Dewasa			
Jan 1, 2020 - Dec 23, 2020	1,030 (3.96%)	877 (4.30%)	00:04:33
Jan 1, 2019 - Dec 23, 2019	676 (3.33%)	585 (3.46%)	00:03:09
% Change	52.25%	49.91%	44.07%
7. Beranda Gizi Seimbang (BGS)			
Jan 1, 2020 - Dec 23, 2020	898 (3.43%)	484 (2.37%)	00:00:44
Jan 1, 2019 - Dec 23, 2019	624 (3.07%)	338 (2.00%)	00:00:29
% Change	43.91%	43.20%	51.25%

Chart 2

What pages did the users visit? Chart 2 shows that “Tentang Gizi Seimbang” was the most viewed page, which was 20.44% of the total number (20,315) of pages viewed. A visitor spent 4 minutes and 42 seconds on average when visiting the page. The homepage was the second most viewed page. “Pentingnya Menjaga Berat Badan Ideal Bagi Lansia” was the third viewed page.

The number of viewed pages, and the average time spent on pages have increased on all the pages. All the 6 pages relate to the topic of Gizi Seimbang. As a reminder, on March 2nd, 2020, Indonesian President Joko Widodo announced the first two confirmed covid-19 cases in Indonesia. People were searching information in their effort to stay healthy to prevent covid-19.

Landing Pages

Landing Page	Acquisition Sessions
	16.56% 16,158 vs 13,871
1. /tentang_gizi_seimbang.php	
Jan 1, 2020 - Dec 23, 2020	4,671 (28.89%)
Jan 1, 2019 - Dec 23, 2019	4,300 (31.00%)
% Change	8.63%
2. /prinsip4_lansia.php	
Jan 1, 2020 - Dec 23, 2020	1,610 (9.96%)
Jan 1, 2019 - Dec 23, 2019	1,559 (11.24%)
% Change	3.27%
3. /index.php	
Jan 1, 2020 - Dec 23, 2020	1,361 (8.42%)
Jan 1, 2019 - Dec 23, 2019	1,271 (9.16%)
% Change	7.08%
4. /prinsip1_pentingnya_makan_makanan_beraneka_ragam.php	
Jan 1, 2020 - Dec 23, 2020	1,127 (6.97%)
Jan 1, 2019 - Dec 23, 2019	751 (5.41%)
% Change	50.07%
5. /sejarah_gizi_seimbang.php	
Jan 1, 2020 - Dec 23, 2020	863 (5.34%)
Jan 1, 2019 - Dec 23, 2019	572 (4.12%)
% Change	50.87%
6. /prinsip1_dewasa.php	
Jan 1, 2020 - Dec 23, 2020	851 (5.26%)
Jan 1, 2019 - Dec 23, 2019	590 (4.25%)
% Change	44.24%
7. /prinsip2_pentingnya_hidup_bersih.php	
Jan 1, 2020 - Dec 23, 2020	485 (3.00%)
Jan 1, 2019 - Dec 23, 2019	244 (1.76%)
% Change	98.77%
8. /contact_us.php	
Jan 1, 2020 - Dec 23, 2020	454 (2.81%)
Jan 1, 2019 - Dec 23, 2019	537 (3.87%)
% Change	-15.46%
9. /prinsip4_dewasa.php	
Jan 1, 2020 - Dec 23, 2020	434 (2.68%)
Jan 1, 2019 - Dec 23, 2019	82 (0.59%)
% Change	429.27%
10. /prinsip3_ibu_hamil.php	
Jan 1, 2020 - Dec 23, 2020	415 (2.57%)
Jan 1, 2019 - Dec 23, 2019	522 (3.76%)
% Change	-20.50%

Chart 3

Chart 3 shows, in 2020, 28.89% of visitors entered the site through the page "Tentang Gizi Seimbang", and 9.96% of visitors entered the site through “Pentingnya Menjaga Berat Badan Ideal Bagi Lansia”.

Chart 3 also shows that the number of visitors entered the site through the pages of “Pentingnya Makan Makanan Beraneka Beragam”, “Sejarah Gizi Berimbang”, “Pentingnya Makan Makanan Beraneka Beragam - Untuk Orang Dewasa”, “Pentingnya Menjalankan Pola Hidup Bersih”, and “Pentingnya Menjaga Berat Badan Ideal Bagi Orang Dewasa” have increased significantly compared to 2019. The increasing number varies from 44.24% to 429.27%.

Exit Pages

	Page	Exits
		16,171 % of Total: 100.00% (16,171)
1.	/tentang_gizi_seimbang.php	4,607 (28.49%)
2.	/prinsip4_lansia.php	1,602 (9.91%)
3.	/prinsip1_pentingnya_makan_makanan_beraneka_ragam.php	1,104 (6.83%)
4.	/index.php	1,043 (6.45%)
5.	/sejarah_gizi_seimbang.php	859 (5.31%)
6.	/prinsip1_dewasa.php	847 (5.24%)
7.	/contact_us.php	511 (3.16%)
8.	/prinsip2_pentingnya_hidup_bersih.php	483 (2.99%)
9.	/prinsip4_dewasa.php	435 (2.69%)
10.	/prinsip3_ibu_hamil.php	413 (2.55%)

Chart 4

Exit is the number of times visitors exited the site from a specified page. Chart 4 shows that visitors exited 28.49% from the page "Tentang Gizi Seimbang", and 9.91% from “Pentingnya Menjaga Berat Badan Ideal Bagi Lansia”.

Channels

Default Channel Grouping	Acquisition		
	Users	New Users	Sessions
	13,432 % of Total: 100.00% (13,432)	13,473 % of Total: 100.03% (13,469)	16,172 % of Total: 100.00% (16,172)
1. Organic Search	10,522 (78.13%)	10,544 (78.26%)	12,121 (74.95%)
2. Direct	2,781 (20.65%)	2,774 (20.59%)	3,662 (22.64%)
3. Referral	137 (1.02%)	130 (0.96%)	355 (2.20%)
4. Social	28 (0.21%)	25 (0.19%)	34 (0.21%)

Chart 5

How did danonenutrindo.org acquire users? Chart 5 shows ways visitors got to the site. 74.95% was through search engines, 22.64% visitors typed URL directly into their browsers, 2.20% visitors arrived on the site through other sources, and the rest 0.21% arrived on the site through social networks.

Mobile Overview

Device Category	Acquisition		
	Users ↓	New Users	Sessions
	13,432 % of Total: 100.00% (13,432)	13,473 % of Total: 100.03% (13,469)	16,172 % of Total: 100.00% (16,172)
1. mobile	**8,087** (60.33%)	8,161 (60.57%)	9,229 (57.07%)
2. desktop	**5,245** (39.13%)	5,241 (38.90%)	6,839 (42.29%)
3. tablet	**73** (0.54%)	71 (0.53%)	104 (0.64%)

Chart 6

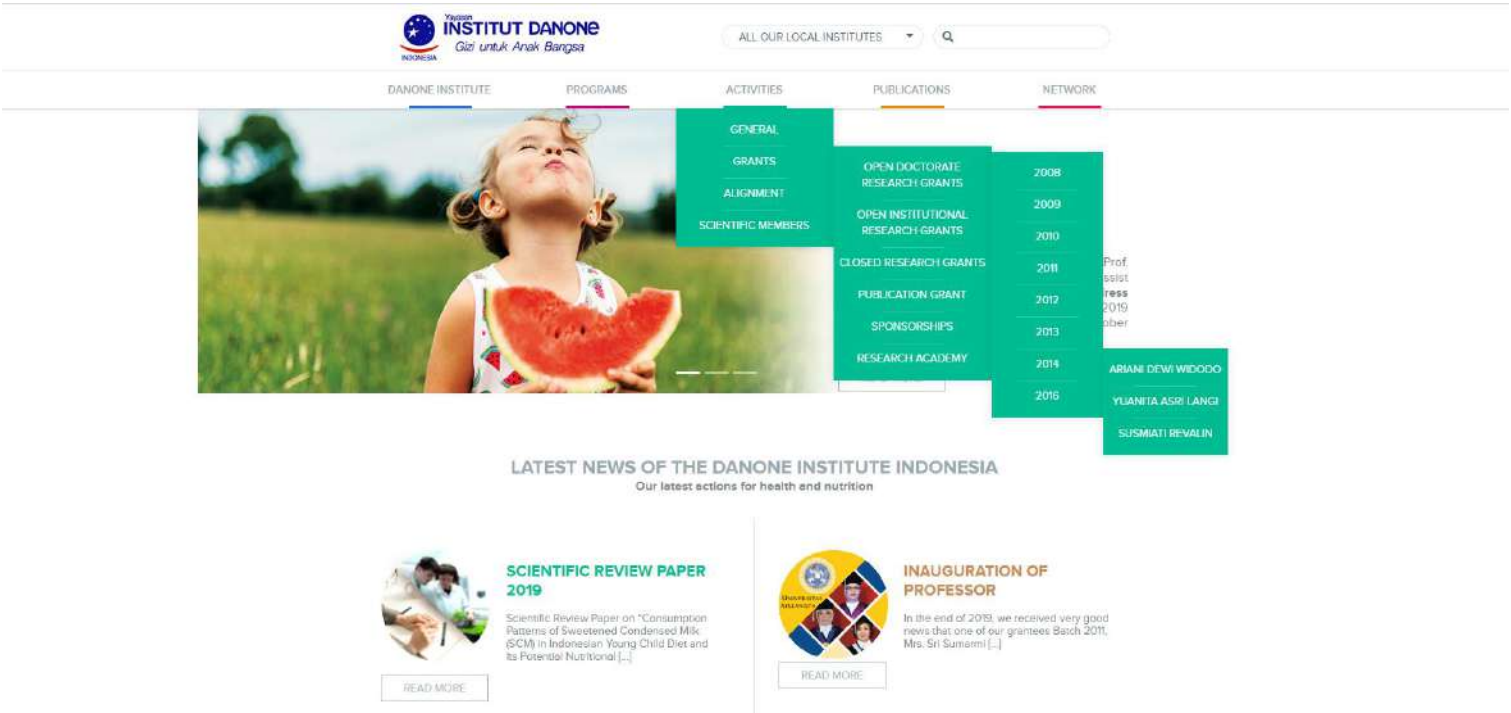
Chart 6 shows that 57.07% users reached the site via mobile device, and 42.29% users used desktop to access the website.

Conclusion

In conclusion, site visits had been decreasing since 2016 to 2019. However, in 2020 it was increased by 16.49%. This increase might have correlation to covid-19 pandemic, where people were searching information in their effort to stay healthy to prevent covid-19 by. This assumption was strengthened by the increase number of visitors who visited the web pages which relate to the topic of Gizi Seimbang.

The website has been ranked number 9 in Google, and number 21 in Yahoo with a keyword of “gizi seimbang”. The website also has been ranked number 2 in Google and, number 1 in Yahoo with a keyword of “real-time manuscript writing”.

VIEW MENU ON DESKTOP/LAPTOP



VIEW MENU ON PHONE/TABLET

VIEW ON DESKTOP/LAPTOP

Yayasan INSTITUT DANONE Gizi untuk Anak Bangsa INDONESIA

ALL OUR LOCAL INSTITUTES

DANONE INSTITUTE | PROGRAMS | ACTIVITIES | PUBLICATIONS | NETWORK

HEADLINE

CAN YOGURT ADDRESS MALNUTRITION

Danone Institute International (DII) has invited Prof. Mohammad Juffrie as IDIF representative to assist the **YINI Symposium** entitled **"Can Yogurt address malnutrition?"** which taken place at FENS 2019 Congress in Dublin (Ireland), on the 16th October 2019.

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LATEST NEWS OF THE DANONE INSTITUTE INDONESIA

Our latest actions for health and nutrition

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Scientific Review Paper on "Consumption Patterns of Sweetened Condensed Milk (SCM) in Indonesian Young Child Diet and Its Potential Nutritional [...]

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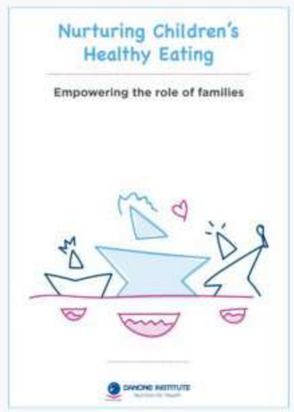
NURTURING CHILDREN'S HEALTHY EATING: EMPOWERING THE ROLE OF FAMILIES



This new document, edited by DII in March 2018, aims to set out the current evidence and lay the foundations for empowering families to nurture healthy eating habits among the children of the world.

Yayasan INSTITUT DANONE Gizi untuk Anak Bangsa INDONESIA

WHAT IS THE DANONE INSTITUTE INDONESIA?

Indonesian Danone Institute Foundation (IDIF) is one of 18 Danone Institutes worldwide. Danone Institutes are not-for-profit organizations, with mission to develop and disseminate scientific knowledge on diet and nutrition to benefit public health.

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ASIAN CONGRESS OF NUTRITION

Widjaja Lukito as Moderator at the **Hydration for Health (H4H) Academy** at Bali International Convention Center in Bali, Indonesia, on August 6th, 2019.

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13TH EUROPEAN NUTRITION CONFERENCE

The Nutrition Society in cooperation with The Nutrition Society Irish Section as hosts conducted the **13th European Nutrition Conference**, Federation of European Nutrition Societies (FENS) 2019 in Dublin, Ireland.

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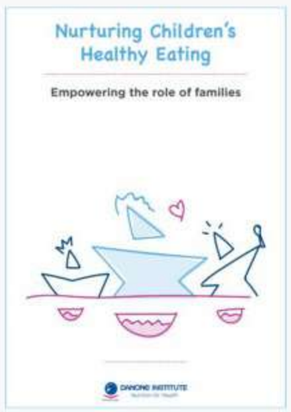

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VIEW ON PHONE/TABLET

Message from the President

The Foundation has gone through another challenging year in 2019. For the last 2 years, with limited budget, the Foundation has paused to support research grants for doctorate candidates. As a replacement of this program, we are now focusing more on specific programs and activities, aligned with the scientific missions of Danone Group. In other words, the Foundation may reoffer research grants to potential doctorate candidates with specific topics.

New initiatives have been taken up by the Foundation, in form of scientific review on specific topic and issue, which have become growing concerns of policy makers, scientific communities and the mainstream Indonesian people. This topic and issue should be discussed and addressed by relevant experts in a transparant way, and results of the review should be socialized to relevant stakeholders for appropriate action plans.

Amongst others, the Foundation has selected specific topics on sweetened condensed milk (SCM), sugar-sweetened beverages (SSBs) and nutritional anemia, to be reviewed and discussed by independent experts. The publication of "Maternal contributors to intergenerational nutrition, health, and well-being: revisiting the Tanjungsari Cohort Study for effective policy and action in Indonesia" in the Asia Pacific Journal of Clinical Nutrition (APJCN) has been well received and acknowledged by the nutritional science communities.

We highly hope that many stakeholders are able to reach out the scientific products of the Foundation, which, we believe, are useful for the improvement of Indonesian health and nutrition policies, aiming at achieving Health for All of Indonesians.

Jakarta, January 2020
Dr. Widjaja Lukito
President, Indonesian Danone Institute Foundation

VIEW ON PHONE/TABLET

Yayasan INSTITUT DANONE Indonesia
Gizi untuk Anak Bangsa

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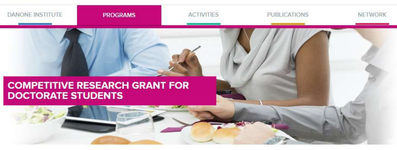


Competitive Research Grant For Doctorate Students

ELIGIBILITY OF RESEARCH PROPOSAL

1. New research proposal or on-going research activity as part of a research umbrella and/or stand alone study
2. Meet the objectives and criteria of Indonesian Danone Institute Foundation (IDIF)
3. Commit to produce a publishable manuscript for International journal within 6 months post final report
4. Grantees must obtain ethical clearance from credible institution

CONDITION OF THE GRANT

1. The awarded length of research is up to one year. Multi-year research can be considered
2. The grantee must sign contract
3. Commit to release data to become public domain three years after last financial disbursement
4. The grantees must add the following sentence in the Acknowledgment section of any publication: "This study is fully/partly funded by the Indonesian Danone Institute Foundation".
5. The use of legal software is a must

PRE-REQUISITE

1. The applicant must be Indonesian citizen
2. The applicant should be a registered doctorate student at universities in Indonesia
3. The applicant should be the Principal Investigator (PI) for the research work
4. The team should consist of PI, and at least one Advisor and research assistants (preferably student)

WHAT TO SUBMIT

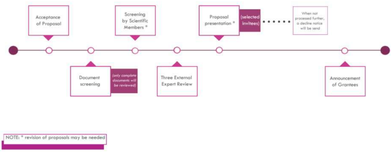
1. Application form [please use the downloadable format only]
2. Curriculum Vitae of PI (doctorate student), Advisor (Promoter) and other research team members, including list of publications within the last five years
3. Recommendation Letter from the First Advisor (Promoter)
4. Copy of Ethical clearance or proof of submission to the Ethical Committee. Please fill-out the downloadable form. Ethical clearance is mandatory before signing of agreement. In case the clearance is not approved, the award will be cancelled.
5. Letter of the student's status from the Dean
6. For on-going research, a Statement Letter from the PI of the Umbrella research (stating that the proposed research is part of the Umbrella research and is not funded)
7. Statement letter agreeing to submit at least one publishable manuscript (general format is AJCN-American Journal of Clinical Nutrition, otherwise should be in accordance to the requirement of the journal).
   Note: Grantee will be automatically eligible to get publication grant in international journal. However, a separate application is required. Please read on the section of PUBLICATION GRANT FOR IN INTERNATIONAL JOURNALS for more information.
8. Research proposal in English [please refer to section PROPOSAL FORMAT and use the downloadable form only].

✉ **Send HARDCOPY of your proposal to:**
Indonesian Danone Institute Foundation
Cyber 2 Tower, 9th Floor
Jl. HR. Rasuna Said Blok X-5 No. 13
Jakarta 12950 - Tel. 021 29961000 ext 5019
or
Send SOFTCOPY of your proposal to:
denone.institute.indonesia@danonenutrindo.org

For independent review purposes, please BLIND all names, including logos & names of institutions Proposals that are not BLINDED will be returned!

SELECTION MECHANISM

The proposal will undergo several evaluation processes, which may take up to six months. Selected candidates will be invited to present their proposals in front of Scientific Members and External Reviewers.



NOTE: * revision of proposals may be needed

PROPOSAL FORMAT

The proposal must contain the following:

1. Executive summary (limit to 1 page)
2. Introduction
   - Rationale and originality
   - research questions
   - causal model (if necessary)
   - hypothesis
   - objectives
   - expected output
   - implications of the research (for researcher, institution, policy, scientific development)
3. Literature review
   - research position to previous research and future scientific development,
   - critical reviews to support the research questions,
   - research roadmap,
   - conceptual framework
4. Research design and method
   - research design
   - population, sample size and sampling procedure
   - variables and indicators
   - type of data and data collection method, including materials and instruments required, data management, quality control, data processing, data management, operational definitions. For an experimental study, explain how the intervention is to be delivered
   - data analysis (including laboratory and statistical analysis)
   - statement on ethical clearance (approved or in-process)
   - mechanism in complying to the ethical conduct (e.g. informed consent)
5. Operational planning
   - Plan of actions and for time schedule use the following table.

No.	Activities	Research Schedule		Others Note
		Start Date	End Date	
1	Preparation			
	a.			
	b.			
	c.			
	etc.			
2	Data collection			
	a.			
	b.			
	c.			
	etc.			
3	Data entry			
4	Data analysis			
5	Report writing			
6	Report submission			
7	Manuscript Preparation			
8	Publication			

   - Human resources (including the research team): Please mention the person in-charge (e.g. PI, Co-PI, Promoter) – NO NAME PLEASE! - for each activity and their time allocation; using the following table.

Role and responsibility

No.	Role in the research study *	Time Allocation (hour/week)	Responsibility in the research

* PI, Co-PI, Promoter, others (please specify)

   - Budget. If not requesting full budget support, please disclose the existing research funding and the gap
   - Dissemination and utilization of the results
6. References
7. Appendices to the proposal
   - Detail Budget
   - Draft of Informed Consent (Please blind all names and institutions)

Please use standard margin, font 11, Times new roman, 1.5 space and limit your proposal to maximum of 20 pages (without the Appendices) and put page numbers on the left hand side of the proposal.

BUDGET FORMAT

Components that could be funded include:

1. Materials and supplies
2. Equipment
3. Data collection and analysis
4. Salary and honorarium (not more than 30% of total budget)
5. Travel cost
6. Other expenditures (not more than 10% of the total budget)

Please provide details of all components, including volume, unit cost, and time of disbursement (i.e. during preparation, data collection/field work, analysis/report writing). Research budget could be multi-sources. Please identify the type of materials/supplies/equipments that are already available at your university/institution and those funded by other organization. No double funding will be allowed for the same activities or the same equipments. Please provide detail target/expected output of each budget sources.

If awarded, Grantee will have to make a new bank account and the money will be disbursed in several disbursement, depending on the type of research project, e.g. upon:

1. Signing of the contract
2. Approval of progress report, which include design, sampling, protocol, instrument; and budget report of the first disbursement, and
3. Approval of final and budget reports, as well as submission of manuscript to international journal.
4. Acceptance of the manuscript in international peer-review journal

The Grantee should keep a log book of daily activities as well as expenses. Original receipts from the vendor must be attached to the financial report.

Components that could not be funded are:

1. Purchasing electronic equipment, such as but not limited to computer, printer, scanner, camera, soft ware, laboratory instruments
2. Dissemination of research results (support from your institution is expected for this matter)
3. Institutional fee

Detail explanation of the items in the budget:

1. Material and supplies. It can be divided into sub component: office supplies, chemicals, and other materials
2. Equipment. Describe investment needed (including name of equipment and its uses) and/or budget required for equipment rental (e.g. computer, printer, and camera). Please provide reference from competence institutions on unit cost for rental.
3. Data collection. This may include: local travel, reward for respondent, specimen collection fee, transportation of the sampled materials, house rental, daily allowance, and health and accident insurance coverage for team members during data collection period. Please provide reference from competence institutions on unit cost for data collection (e.g. taking blood samples, nutrient analysis) and insurance price
4. Salary and honorarium should be not more than 30% of total budget. Salary allocation should be provided only for the advisor and research assistant (if any). State the name of the person who will receive the salary, volume (man month, man days, etc), unit cost and total salary. English translation and editing can also be funded. Please provide reference from competence institution regarding salary and language purposes.
5. Travel cost excluding local travel cost. This includes per diem rate and transportation for supervisor. The current government (Kementerian Keuangan) standard will be used.
6. Other expenditures cannot be more than 10% of the total budget. Eligible expenses include: administration (e.g. study permit fee), communication (correspondence, including internet, voucher, telephone, and fax), maintenance/reparation of equipment, literature review.

MONITORING ACTIVITY

IDIF will monitor the conduct of the research by field visit. An expert will be appointed as Evaluator.

REPORTING

During the period that you are supported by IDIF, you have to submit several reports, depending on the agreement (please use the downloadable format only for progress and financial report). The report must be written in English and acknowledged by the advisor (for Doctorate research). The submission and acceptance of the reports will influence the next financial disbursement. The financial report shall consist of tables showing comparison of planned vs. actual expenses. Original receipts from vendors should be attached and systematically numbered.

VIEW ON PHONE/TABLET


COMPETITIVE RESEARCH GRANT FOR DOCTORATE STUDENTS

ELIGIBILITY OF RESEARCH PROPOSAL

CONDITION OF THE GRANT

PRE-REQUISITE

WHAT TO SUBMIT

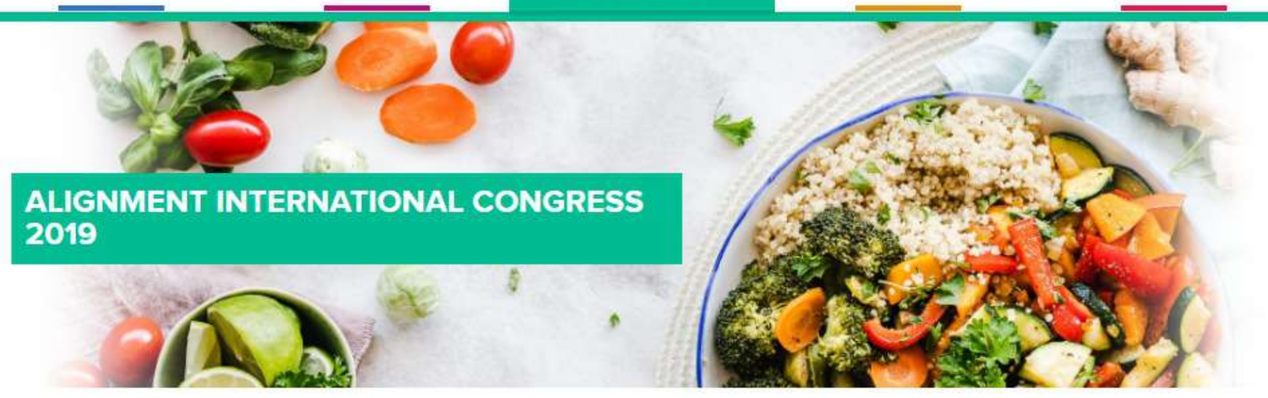
SELECTION MECHANISM

PROPOSAL FORMAT

SUBMIT FORMAT

MONITORING ACTIVITY

REPORTING



Alignment International Congress 2019

13th European Nutrition Conference

Attendee: Prof. Mohammad Juffrie as IDIF representative in Dublin, Ireland, on October 15th – 18th, 2019.

The Nutrition Society in cooperation with The Nutrition Society Irish Section as hosts conducted the 13th European Nutrition Conference, Federation of European Nutrition Societies (FENS) 2019 in Dublin, Ireland.

The conference is held once every four years, and is the premier European meeting within nutritional science for nutrition scientists and researchers, bringing together nutrition and health professionals from across Europe.

In year 2019, the conference has presented European perspectives on 'malnutrition in an obese world'. With increasing rates of non-communicable diseases globally alongside the persistent presence of nutritional deficiencies and undernu trition, the conference has taken a wide-ranging approach to the topic.

The conference has focused on five themes:

- The determinants and drivers of malnutrition across the life-course,
- Novel technologies for dietary assessment,
- An exploration of current metabolic perspectives,
- The food environment, and
- Other emerging issues.

A range of leading researchers, organizations and institutions from across the world has presented cutting-edge research on topics as diverse as the microbiome, chrononutrition, nutritional reductionism, and nutrigenetics. Different perspectives have covered the genetic, molecular and cellular aspects of malnutrition, metabolism and physiology, and the epidemiological evidence, in addition to explore the policies, practices and behaviours implicated in designing successful interventions.

Over 2,500 delegates from across the UK, Europe and further afield attended along with representation from European nutrition societies.

11th Hydration for Health

Attendee: Widjaja Lukito as IDIF representative at the Hydration for Health Annual Scientific Conference in Evian, France, on June 25th, 2019.

CONNECTING THE EXPERTS OF HYDRATION SCIENCE

HYDRATION FOR HEALTH.

Over the past ten years, the Hydration for Health Scientific Conference has become the unique international scientific event dedicated to hydration science and health benefits of water for health. It attracts, experts, scientists, researchers from a wide variety of disciplines from nutrition to nephrology and offers a world-class scientific program. It supports new investigators and encourages them to foster emerging science.

The Annual Hydration for Health conference aims at gathering opinion leaders and scientists across disciplines to share the latest scientific evidence on hydration and health.

The objective of this conference is to communicate the findings of recent studies on hydration and its role in public health.

NEXT CONFERENCE IN 2020

VIEW ON PHONE/TABLET

INSTITUT DANONE
Gizi untuk Anak Bangsa

ALIGNMENT INTERNATIONAL CONGRESS 2019

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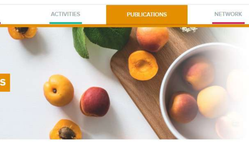
NEXT CONFERENCE IN 2020



INTERNATIONAL JOURNALS

International Journals

YEAR : 2020

1. Aji AS; Erwinda E; Rasyid R; Yusrawati Y; Malik SG; Alathari B; Lovegrove JA; Lipoeto NI; Vimaleswaran KS. 2020. A genetic approach to study the relationship between maternal Vitamin D status and newborn anthropometry measurements: the Vitamin D pregnant mother (VDPM) cohort study. J Diabetes Metab Disord. View full article.

YEAR : 2019

1. Lukito W; Wibowo L; Wahlqvist ML. 2019. Maternal contributors to intergenerational nutrition, health, and well-being: revisiting the Tanjungsari Cohort Study for effective policy and action in Indonesia. Asia Pac J Clin Nutr. 2019;28(Suppl 1):S1-S16. doi: 10.6133/apjcn.201901_28(S1).0001.

2. Alisjahbana B; Rivami D; Octavia L; Susilowati N; Diana A; Pangaribuan M; Alisjahbana A. 2019. Intrauterine growth retardation (IUGR) as determinantand environment as modulator of infant mortality and morbidity: the Tanjungsari Cohort Study in Indonesia. Asia Pac J Clin Nutr. 2019;28(Suppl 1):S17-S31. doi: 10.6133/apjcn.201901_28(S1).0002.

3. Sofiatin Y; Puspardi A; Judistiani TD; Rahmalia A; Diana A; Alisjahbana A. 2019. Maternal and environmental risk for faltered growth in the first 5 years for Tanjungsari children in West Java, Indonesia. Asia Pac J Clin Nutr. 2019; 28(Suppl 1):S32-S42. doi: 10.6133/apjcn.201901_28(S1).0003.

4. Sasongko EPS; Ariyanto EF; Indraswari N; Rachmi CN; Alisjahbana A. 2019. Determinants of adolescent shortness in Tanjungsari, West Java, Indonesia. Asia Pac J Clin Nutr. 2019;28(Suppl 1):S43-S50. doi: 10.6133/apjcn.201901_28(S1).0004.

5. Nugraha GI; Ong PA; Rachmi CN; Karyadi SHKS; Alisjahbana A. 2019. Optimization of birth weight and growth in the first 2 years favors an adult body composition which supports more physiological resting metabolic rates and cognitive function: Tanjungsari Cohort Study. Asia Pac J Clin Nutr. 2019;28(Suppl 1):S51-S62. doi: 10.6133/apjcn.201901_28(S1).0005.

6. Aji AS; Erwinda E; Yusrawati Y; Malik SG; Lipoeto NI. 2019. Vitamin D deficiency status and its related risk factors during early pregnancy: a crosssectional study of pregnant Minangkabau women, Indonesia. BMC Pregnancy and Childbirth (2019) 19:183. doi.

7. Priliani L; Prado EL; Restuadi R; Waturangi DE; Shankar AH; Malik SG. 2019. Maternal Multiple Micronutrient Supplementation Stabilizes Mitochondrial DNA Copy Number in Pregnant Women in Lombok, Indonesia J Nutr. 2019. 001–8. doi.

8. Lee SE; Fenech MF; West KP. 2019. Antenatal Micronutrients and the Mitochondrial Genome: A Glimpse of Future Nutritional Investigation. J Nutr; First published online 0, 2019. doi.

9. Aji AS; Yerizel E; Desmawati D; Lipoeto NI. 2019. Low Maternal Vitamin D and Calcium Food Intake during Pregnancy Associated with Place of Residence: A Cross Sectional Study in West Sumatran Women, Indonesia. Maced J Med Sci. doi.

YEAR : 2018

1. Susmiati; Lipoeto NI; Surono IS; Jamsari J. 2018. Association of Fat Mass and Obesity associated rs9939609 Polymorphisms and Eating Behaviour and Food Preferences in Adolescent Minangkabau Girls. Pak. J. Nutr., 17 (10): 471-479. doi: 10.3923/pjn.2018.471.479.

2. Ahmad A; Madanijah S; Dwinani CM; Kolopaking R. 2018. Complementary feeding practices and nutritional status of children 6-23 months old: formative study in Aceh, Indonesia. Nutrition Research and Practice 2018;12(6):512-520.

3. Aji AS; Yerizel E; Desmawati; Lipoeto NI. 2018. The association between lifestyle and maternal vitamin D during pregnancy in West Sumatra, Indonesia. Asia Pac J Clin Nutr 2018;27(6):1286-1293. doi: 10.6133/apjcn.201811_27(6).0016.

YEAR : 2017

1. Helmizar, H; Jalal, F; Lipoeto, NI; Achadi, EL. 2017. Local food supplementation and psychosocial stimulation improve linear growth and cognitive development among Indonesian infants aged 6 to 9 months. Asia Pac J Clin Nutr. 2017 Jan, 26(1):97-103. doi: 10.6133/apjcn.102015.10. View full article.

2. Lukito, W; Wibowo, L; Wahlqvist, M. L; and The Scientific Advisory Group. 2017. The Clinical Nutrition Research Agenda in Indonesia and beyond: ecological strategy for food in health care delivery. Asia Pac J Clin Nutr. 2017;26(Suppl 1):S1-S8. doi: 10.6133/apjcn.062017.s12. View full article.

3. Angkasa, D; Tambunan, V; Khusun, H; Witjaksono, F; Agustina, R. 2017. Inadequate dietary α-linolenic acid intake among Indonesian pregnant women is associated with lower newborn weights in urban Jakarta. Asia Pac J Clin Nutr. 2017;26(Suppl 1):S9-S18. doi: 10.6133/apjcn.062017.s1. View full article.

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5. Mulyani, E Y; Hardinsyah; Briawan, D; Santoso, B I. 2017. Hydration status of pregnant women in West Jakarta. Asia Pac J Clin Nutr. 2017;26(Suppl 1):S26-S30. doi: 10.6133/apjcn.062017.s14. View full article.

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8. Nirmala, I R; Trees; Suwarni; Pramono, M S. 2017. Sago worms as a nutritious traditional and alternative food for rural children in Southeast Sulawesi, Indonesia. Asia Pac J Clin Nutr. 2017;26(Suppl 1):S40-S49. doi: 10.6133/ apjcn.062017.s4. View full article.

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10. Widodo, A D; Soeleaman, E J; Dwinanda, N; Narendraswari, P P; Purnomo, B. 2017. Chronic liver disease is a risk factor for malnutrition and growth retardation in children. Asia Pac J Clin Nutr. 2017;26(Suppl 1):S57-S60. doi: 10.6133/apjcn.062017.s10. View full article.

11. Palupi, K C; Shih, C-K; Chang, J-S. 2017. Cooking methods and depressive symptoms are joint risk factors for fatigue among migrant Indonesian women working domestically in Taiwan. Asia Pac J Clin Nutr. 2017;26(Suppl 1):S61-S67. doi: 10.6133/apjcn.062017.s3. View full article.

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YEAR : 2016

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2. Lukito, W; Wibowo, L; Wahlqvist, M. 2016. Developments in clinical food and nutrition science in Indonesia. Asia Pac J Clin Nutr. 2016; 25(Suppl 1):S1-S7. doi: 10.6133/apjcn.122016.s14. View full article.

3. Murni, I K; Sulistyoningrum, D C; Oktaria, V. 2016. Association of vitamin D deficiency with cardiovascular disease risk in children: implications for the Asia-Pacific Region. Asia Pac J Clin Nutr. 2016;25(Suppl 1):S8-S19. doi: 10.6133/apjcn.122016.s1. View full article.

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6. Muslihah, N; Khomsan, A; Briawan, D; Riyadi, H. 2016. Complementary food supplementation with a small-quantity of lipid-based nutrient supplements prevents stunting in 6—12-month-old infants in rural West Madura Island, Indonesia. Asia Pac J Clin Nutr. 2016;25(Suppl 1):S36-S42. doi: 10.6133/apjcn.122016.s9. View full article.

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13. Susilowati, R; Sulistyoningrum, D C; Witari, N P D; Huriyati, E; Luglio, H F; Julia, M. 2016. Sexual dimorphism in interleukin 17A and adipocytokines and their association with insulin resistance among obese adolescents in Yogyakarta, Indonesia. Asia Pac J Clin Nutr. 2016;25(Suppl 1):S93-S101. doi: 10.6133/apjcn.122016.s13 . View full article.

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2. Vandenplas, Y. 2015. Lactose intolerance. Asia Pac J Clin Nutr 2015;24(Suppl 1):S9-S13. View full article.

3. Lukito, W; Malik, S G; Surono, I S; Wahlqvist, M L. 2015. From 'lactose intolerance' to 'lactose nutrition'. Asia Pac J Clin Nutr 2015;24(Suppl 1):S1-S8. View full article.

4. Wahlqvist, M L. 2015. Lactose nutrition in lactase nonpersisters. Asia Pac J Clin Nutr 2015;24(Suppl 1):S21-S25. View full article.

5. Surono, I S. 2015. Traditional Indonesian dairy foods. Asia Pac J Clin Nutr 2015;24(Suppl 1):S26-S30. View full article.

6. Hegar, B; Widodo, A. 2015. Lactose intolerance in Indonesian children. Asia Pac J Clin Nutr 2015;24(Suppl 1):S31-S40. View full article.

7. Lee, M S; Wahlqvist, M L; Peng, C J. 2015. Dairy foods and health in Asians: Taiwanese considerations. Asia Pac J Clin Nutr 2015;24(Suppl 1):S14-S20. View full article.

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9. Winarsi, H; Sasongko, N. D; Purwanto, A. 2015. Germinated-soy milk in suppressing inflammation and oxidative stress in blood plasma and breast milk of lactating mothers. International Food Research Journal 23(2): 646-652. View full article.

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YEAR : 2014

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YEAR : 2013

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YEAR : 2012

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YEAR : 2011

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2. Usfar A, Iswarawanti D, Davelyna D, Dillon D. 2010. Personal Hygene Perceptions and Practices among Caregivers whose Children Have Diarrhea: A Qualitative Study of Urban Mothers in Tangerang, Indonesia. J of Nutr and Education Behavior, vol. 42 (1): 33-40 . View full abstract

YEAR: 2009

1. Damanik R. 2009. Torbangun (*Coleus amboinicus Lour*) A Bataknese Traditional Cuisine Perceived as Lactogogue by Bataknese lactating Women in Simalungun, North Sumatera, Indonesia. J Hum Lact; 25: 64-72. View full article

2. Madarina, J. 2009. Adoption of the WHO Child Growth Standards to Classify Indonesian Children under 2 Years of Age According to Nutrition Status: Stronger Indication for Nutritional Intervention. Food and Nutr Bull; 30; 3; 254-259. View full article

3. Usfar A, Achadi E, Martorell R, Hadi H, Thaha R, Jus'at I, Atmarita, Martianto D, Ridwan H, Soekirman. 2009. Expert Meeting on Child Growth and Micronutrient Deficiencies - New Initiatives for Developing Countries to Achieve Millennium Development Goals: Executive Summary report. Asia Pac J Clin Nutr; 18 (3); 462-469. View full article

VIEW ON PHONE/TABLET

ATTACHMENT 7a

Internal Meeting Minutes

- Minute of Meeting: Alignment Meeting with SN (28 January 2020)
- Minute of Meeting: Summary of Advisory Meeting (10 March 2020)
- Minute of Meeting: Advisory Meeting (13 March 2020)
- Minute of Meeting: Meeting with CBU (27 May 2020)
- Minute of Meeting: Meeting with CBU (10 July 2020)
- Minute of Meeting: Audit Checklist for Annual Supervisory Visit of IDI (19 August 2020)
- Minute of Meeting: Alignment Meeting between IDIF and CBU (3 December 2020)

Anemia
Ex-Codi 3, 9th Floor 2020
28 January 2020

Attendance list :
1. Dr. Widjaja Lukito
2. Dr. Tonny Sundjaya
3. Nadhila Renaldi
4. Dewi Maryani Kusumastuti
5. Hilda Banser
6. Dr. Rey

NO	ISSUES / ITEMS	DISCUSSIONS	NEXT STEP	PIC	DUE DATE	Status
1	buat stuctural baru	karena dr. Rey jadi atasan dr. Tonny di health Brief dengn beneace mengenai sircular mau pegang danone institute lagi atau engga	Komunikasi dengan Dr. Tonny	DII team		
2	budget	Dana dari SN Penelitian dari data yang ada	Komuniasi antara DII team dengan SN team	Dewi		
3	project	SN dari Nutritional Anemia hanya sampai literature review	untuk meeting berikutnya ELN sudah dapat dari database			
4	fokus populasi	awalnya maternal, jadi 2 ibu dan anak 3 tahun roadmap 2020 - 2021 - 2022	outcome akan berbeda antara female adolescent, pregnant tidak bisa buat baseline, karena harus memasukkan database apa saja kalau dari paper apakah dimungkinkan jika digabungkan female dan under 5 years old			
5	Outcome	research and policy review				

NO	ISSUES / ITEMS	DISCUSSIONS	NEXT STEP	PIC	DUE DATE	Status
6	Request dari SN apa	prioritasnya apa yang akan di published dibuat 1 paper ada 2 penelitian female - adolescent and under 5 tapi tergantung capacity suatu journal maksimum berapa pages				
7	additional resources	semakin lama penelitian, review paper akan semakin panjang kalau mau di review 1 paper akan panjang		Dr. Widjaja and SM team		
8	Publikasi	the first three semester 2020 bisa untuk submission				
9	Impact	budget akan berbeda	refereing the budget			
10	raw data	untuk re- analysist				
11	next		meeting lagi untuk membahas anemia			
12	publikasi	masuk Plos One tidak perlu APJCN				
13	Forum	forum yang dibentuk scientific member	Hubungi sscientific Member team	DII team		
14	time frame	lebih sukar di kontrol, untuk anemia pak Widjaja yamg kontrol				
15	Scientific Member	Ibu Safarina bagus kenapa nutritional anemic membentuk dr SM atas permintaan by law SN	Membentuk Expert team untuk review anemia paper			
16	next meeeting	small paper - paper awal harus dari pak Widjaja perlu ketemu lagi dengann SM mau di press seperti yang ada di PPT				
17	expected outcomes	dari SM : kalau jadi supplement 4 / 5				

NO	ISSUES / ITEMS	DISCUSSIONS	NEXT STEP	PIC	DUE DATE	Status
		sebelum sampai ke Conny bisa dibuat brief				
18	SM	Dana masih ada, pakai dana contribution dan diseminasi SM	akan di adakan di Februari 2020	DII team	Feb-20	

Summary Minutes

The Advisory Meeting of Indonesian Danone Institute Foundation (IDIF) was Convened at Creates Room, 9th Floor, Cyber 2 Tower, on Tuesday, March 10th , 2020.

The meeting was attended by :

1. Vera Galuh Sugijanto
2. Widianto Juwono
3. Widjaja Lukito
4. Tria Rosemiarti
5. Nadhila Renaldi
6. Beneace Steffens
7. Ray Basrowi
8. Sarah Angelique MS
9. Tonny Sundjaya
10. Dewi Maryani
11. Hilda Banser

The Meeting was opened by the Chair Dr. Widjaja Lukito, and followed with the presentation on IDIF's Roadmap, 2019 Activity updates, work plan of Year 2020 and Proposed Budget for 2020.

Meeting objective :

1. To align and report 2019 activities to the management board
2. To obtain approval for 2020 plan

The following points were raised and consensus have been made:

1. In Year 2020, IDIF will be focused on Alignment Programs and Activities :
   a. Update organizational structure Danone Institute Indonesia 2020
   b. Key Activities update : Scientific review for SN and water
      - Sweetened condensed milk literature review "Consumption patterns of sweetened condensed milk in Indonesian young child diet and its potential nutritional health consequences"
      - Sugar in beverages literature review "Consumption of Sugar Sweetened Beverages (SSB) and its Implications on Health Outcomes in Indonesia"
      - Update pprogres Anemia and stunting project
      - Update infographic Tanjungsari cohort study
   c. Proposed budget 2020 :

Proposed budget to CBU 1,100,000,000 and partnership with R&I 400,000,000 Total : 1,500,000,000

The Advisory Meeting was closed by the Chair at 02:00 pm.

Advisory Meeting

13 March 2020

NO	ISSUES / ITEMS	DISCUSSIONS	NEXT STEP	PIC	STATUS
A	**Organization**	dr. Widjaja explain Organizationall structure before and current advisory, management board and SM member		IDIF team	
B	**what we've done**	Research Grant Real time manuscript Scientific review for SN and waters		IDIF team	
C	**Alignmment Activity**	Prof. Juffrie as board member in YINI Board member he is pediatric and very relevant Dr. Widjaja attend event hydration for health in Evian France 2019		IDIF team	
D	**Plan activity**	Anemia project with scientific member Submmited journal Sweetened sugar beverages Create infographic Tanjungsari Cohort Study Create infographic Lactose intolerence	3rd scientific member meeting discuss about anemia will be held on 11-12 march 2020 will be done on April	IDIF team	Done
E	**1. Question from pak Widi**	**1. Who are the main key stakeholder. when the job done and already published something? who are whose understand when jobs**	dr. Widjaja answer : Policy : Tanjungsasri cohort study actually government understand the problem this they should have been able formulated		

NO	ISSUES / ITEMS	DISCUSSIONS	NEXT STEP	PIC	STATUS
			because at the present time the policy is very weight they take wrong message about stunting, by one year reduce 1% and 2 year 10% its wrong the new born can be normal and be stunted new born its almost 50:50 at the age of 2 they catch up and they become normal and then some of them become stunted some of them can catch up growth they become normal and some of them become still stunted and then at the age of five those who normal some of them become stunted again its continue. Stunting Is lesson learn from the develope country each the continous program intervention program Japan after the first and the second war world a lot of stunted children under five and a lot of children and then a lot of stunted soldier only with intervention because stunted is only chronic mal nutrition when we talk stunted what they do they use dairy product and promote fish for consumption and they have nato from the plan protein they just focus on intervention `		

NO	ISSUES / ITEMS	DISCUSSIONS	NEXT STEP	PIC	STATUS
	2. Question from pak Widi	**Is there any specific action plan be able to engage this all stakeholder until the benefit**	Dr. Tria answer : stakeholder depend on the target market so this is type SOS orther stake holder 1. Advocacy, other stakeholder like government 2. dissemination so with this publication as content to disseminate or to educated the proffesional as well as the general population on consumer Dr. Widjaja answer : 1. Multiple approach, educated media, need to socialized media 2. Advocate what should do best practise if you really want reducec stunted 3. Inform BPOM about labelling warning from the water : the strategy we concern about currently level sugar so team aqua proposed to Danone Institute to make assesment in all beverages and paper is our reference water big issue in Indonesia is about hydration is very important, the problem with Indonesia people is doing a lot of intervention	Dr. Widjaja Dr. Tria	
F	Input from Ibu Vera		input from pak Widi is very balance, so plan that we want to do is disseminating the journal of the literatur review so I think on FGD of International forum we can see how we can help with our connection and entertaing the study and result	Ibu Vera	

NO	ISSUES / ITEMS	DISCUSSIONS	NEXT STEP	PIC	STATUS
			Go back after sharing with corine and Connie not only just about the funding but the direction that we has in several years about trying to make sure that Danone institute can become much more indiependent and credible	Ibu Vera Ibu Vera	
G	Share Data	if Danone have data please share with Danone Institute		Dr. Widjaja / IDIF team	

Meeting with CBU
May, 27 - 2020

1. Dr. Widjaja lukito
2. Nadhila Renaldi
3. Dr. Tonny
4. Dr. Ray Basrowi
5. Dewi Maryani
6. Hilda

NO	ISSUES / ITEMS	DISCUSSIONS	NEXT STEP	PIC	DUE DATE	Status
A	Budget	Funds from SN 800 million for anemia overall the budget can already be directly processed by Dewi	Budget Approval	SN and IDIF team Dewi	Jun-20	Not yet
B	Content	Continues with the draft content and there will be a special chapter nutritional anemia and risk covid disease		dr. Widjaja	Jun-20	
C	Time Frame	Draft : End of September 2020 online publication : 31 Dec 2020	Will be discussed with scientific members	Dr. Widjaja	End of September 2020	Not Yet
D	Publication	The first priority : Frontier nutrion journal / APJCN the second priority : International journal the third priority : National journal >> choice : nutritional or medical journal		Dr. Widjaja	31-Dec-20	Not yet

NO	ISSUES / ITEMS	DISCUSSIONS	NEXT STEP	PIC	DUE DATE	Status
E	Skype Meeting	Skype meeting with scientific member Danone Institute skype with other groups about the dairy product view approach	Contact and create schedule for scientific member	IDIF team / Hilda	Jun-20	Not yet

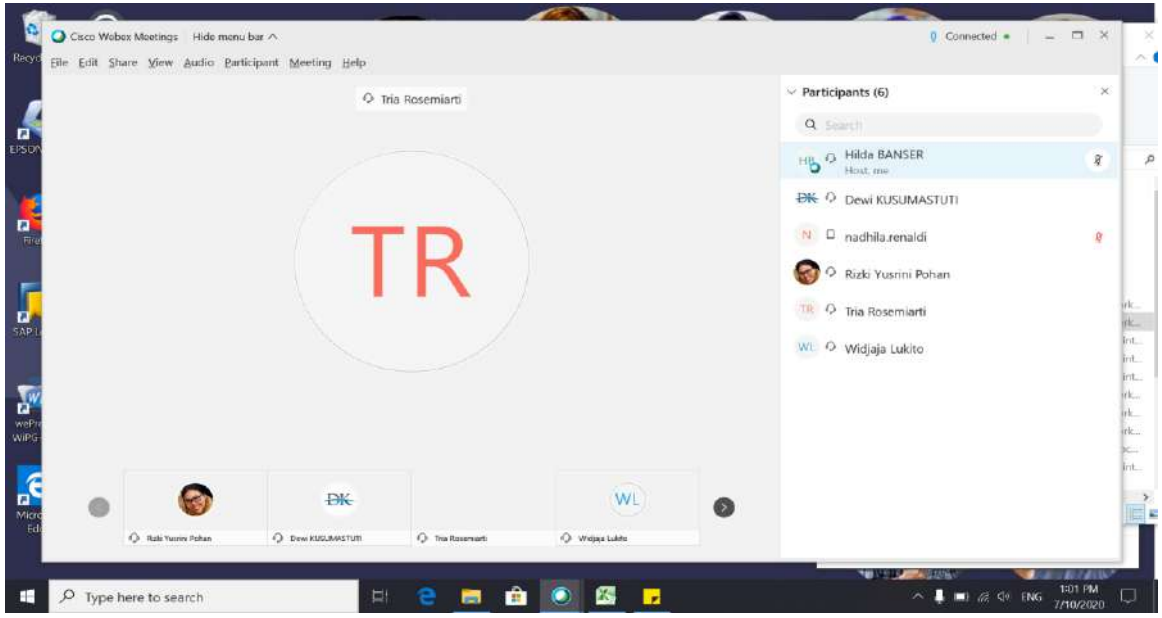
Meeting with CBU 10 Juli 2020

1. Nadhila Renaldi
2. Dewi Maryani
3. Hilda Banser

NO	ISSUES / ITEMS	DISCUSSIONS	NEXT STEP	PIC	DUE DATE	Status
A	**Jadwal meeting**	hari Sabtu dr. Widjaja sudah meeting dengan mba Linda	ada beberapa permintaan data ttg organoleksik, apakah boleh memasukkan data pain ball	Dhea & Rizki		Selesai
B	**Dr. Widjaja**	SSB dalam proses finalisas, yang repot dapurnya linda dan dr. Widjaja Linda sudah dengan kelompok pak Maruf Amin, linda berhasil dengan kepentingan lain, linda dapat data lain dan datanya bagus sekali dan untuk paper SSB bisa di masukkan, kepentingan untuk variabel stunting kita tidak bisaa terlalu lamam menunggu data dan harus tarik deadline, jangan beyond july , ada isu2 yang bagus, other wise review paper ini menjadi kurang 1. aspek organoleptik kenapa orang Indonesia	permintaan2 data dr. Widjaja tidak sebagus dengan apa yang kita mau dan memang tidak mudah dan mereka tidak mau melepas raw data bisanya di analisiskan dan belum tentu sesuai submission			

NO	ISSUES / ITEMS	DISCUSSIONS	NEXT STEP	PIC	DUE DATE	Status
C		pinball sangat berguna banget mungkin nanti akan di modifikasi, sugar content dan dyang lainnya bisa kita presentasikan dr. Widjaja minta organoleptik, kenapa orang indonesia suka yang manis hal ke 5 ide dari Dhea , dhea yang mengusulkan mengenai sugar tax karena dari dhea keluar ide bagaimana dengan intensif, kita lihat dari negara maju mengenai success story intensif dari negara maju	Minta data pinball ke mba rizki			
D		jangan2 edngan intensif menjadi stimulus untk lebih berkembang, kalau bisa dinyatakan karena semua orang bicara tentang sugar tax, karena semua bicara mengenai tax kalau proses bisa dimasukkan menjadi paper yang sangat bagus				
E		catatan kenapa di masukkan bu sapta karena terlibat linq in7, tp karena tidak dapet raw data dari linq in 7, dan bisa menjadi referensi				
F	**Data**	scm sedikit sekali untuk referensi tp ada keuntungan karena prof ayu masih punya raw data dari riskesdas yang lama chalenge ssb kebalikan, saking banyaknya Data tambahan yang dikumpulkan hilda sangat membantu Prof Ayu tidak punya data riskesdas	minta linq in 7 share data Data organoleptic organoleptik milik danone melihat dari kebiasaan konsumen untuk memformulated ke produk tertentu	Linda Dr. Widjaja		

NO	ISSUES / ITEMS	DISCUSSIONS	NEXT STEP	PIC	DUE DATE	Status
		mba linda sudah ada per kelompok umur dan di break down berdasarkan untuk permintaan terkait pola makan mba linda bisa dapet tp ketika ttg ncd tidak dapet				
G	**sosio culture**	paper indonesia tidak kelihatan karena dari Indonesia paper ttg ssb kurang dari 10				
H	**paint ball**	penelitian berangkat dari paint ball 2017 yang dibuat hitungan secara voluime kecendungan 1 x minum tidak setengah untuk memperkuat narasi data dari nilson, dan nilson punya data, kalo data gula dari R&I danone	Follow up mbak Rizki			Selesai
I	**Masukkan dari Dr. Tria**	karena danone masih memproduksi				



DAFTAR AUDIT UNTUK RAPAT PENGAWAS TAHUNAN
YAYASAN INSTITUT DANONE INDONESIA ("YAYASAN") YANG DILAKSANAKAN PADA TANGGAL 1 JANUARI 2020
UNTUK PERIODE 1 JANUARI 2019 SAMPAI DENGAN 31 DECEMBER 2019

Status per tanggal 19 Agustus 2020

No.	Nama Dokumen	Keterangan
I. KEABSAHAN PENDIRIAN YAYASAN, ANGGARAN DASAR DAN PERUBAHANNYA		
1.	Seluruh akta-akta perubahan terhadap Anggaran Dasar Yayasan, beserta bukti: (i) Pemberitahuan/pelaporan kepada Menteri Hukum dan Hak Asasi Manusia Republik Indonesia (ii) Pengumuman dalam Tambahan Berita Negara Republik Indonesia	Tahun 2019: Akta No. 12, tertanggal 30 Januari 2019 Tahun 2020: Akta No. 8, tertanggal 14 Pebruari 2020
2.	Seluruh Berita Acara Rapat Pembina Yayasan (e.g Tahunan)	Rapat Pembina Yayasan telah dilaksanakan pada tanggal 10 Maret 2020
3.	Seluruh Berita Acara Rapat Pengurus Yayasan (wajib diadakan minimal 1 (satu) kali dalam 1 (satu) tahun)	Rapat Pengurus belum dilaksanakan di tahun 2020. Rapat pengurus akan dilaksanakan setelah budget disetujui oleh Pembina, untuk membicarakan tentang program yang dilaksanakan tahun 2020 serta planning untuk program 2021.
4.	Seluruh Berita Acara Rapat Pengawas Yayasan (wajib diadakan minimal 1 (satu) kali dalam 1 (satu) tahun)	Rapat Pengawas telah dilaksanakan pada tanggal 1 Juli 2020 melalui aplikasi video konferensi Webex.
5.	Laporan Keuangan terakhir Yayasan (baik audited, maupun unaudited)	Laporan Keuangan Yayasan tahun 2019 telah diaudit – terlampir laporan audit per tanggal 30 Januari 2020
II. RIWAYAT KEPENGURUSAN YAYASAN		
1.	Keputusan Sirkuler Pembina sehubungan dengan pengangkatan/penggantian/pemberhentian Pengurus Yayasan	1. Keputusan Sirkuler Pembina Yayasan Institut Danone Indonesia tertanggal 16 Januari 2019 terkait pengunduran diri Dr. Fiastuti Dewanti (Wakil Ketua I) dan Rizki Yusrini Pohan (Sekretaris); pengangkatan Nadhila Renaldi sebagai Sekretaris Yayasan.

No.	Nama Dokumen	Keterangan
		2. Keputusan Sirkuler Pembina Yayasan Institut Danone Indonesia tertanggal 29 Januari 2019 terkait pengangkatan kembali Pengurus dan Pengawas Yayasan periode 30 Januari 2019 sampai dengan 30 Januari 2024. 3. Keputusan Sirkuler Pembina Yayasan Institut Danone Indonesia tertanggal 26 Juni 2019 terkait Tugas dan Tanggungjawab Pengurus Yayasan. 4. Keputusan Sirkuler Pembina Yayasan Institut Danone Indonesia tertanggal 13 Desember 2019 terkait Perubahan Susunan Pembina dan Pengurus Yayasan untuk periode 16 Desember 2019 sampai dengan 30 Januari 2024 **Note**: Copy Keputusan Sirkuler Pembina Yayasan sebagaimana disebutkan diatas dikirimkan melalui email tertanggal 15 Juni 2020.
2.	Riwayat hidup ringkas para Pengurus Yayasan	**Note:** Yayasan telah mengirimkan seluruh CV dari Pengurus Yayasan, namun hingga Daftar Audit Untuk Rapat Pengawas Tahunan Yayasan ini ditandatangani, Yayasan masih belum menerima CV dari Ibu Viviani Sutjiadi selaku Bendahara III. Tim Yayasan telah mengirimkan beberapa kali permintaan melalui email, namun belum dikirimkan dari yang bersangkutan hingga saat ini.
3.	Fotokopi KTP para Pengurus Yayasan	Pembina 1. Vera Galuh Sugijanto (KTP, CV, NPWP terlampir dalam email) 2. Widianto Juwono (KTP, CV, NPWP) Supervisory 1. Theresia Lianawaty Setionegoro (KTP, NPWP, CV) Pengurus 1. Widjaja Lukito (KTP, CV, NPWP, Paspor) 2. Ade Umiyama (KTP, CV, NPWP) 3. Rosalina Privita (KTP, CV, NPWP) 4. Tria Rosemiarti (KTP, CV, NPWP) 5. Nadhila Renaldi (KTP, CV, NPWP, Paspor)

No.	Nama Dokumen	Keterangan
		6. Dedi Suwartono (KTP, CV, NPWP terlampir dalam email, Pak Dedi tidak memberikan copy NPWP, hanya memberikan nomor NPWP) 7. Ronny Suwarto (KTP, CV, NPWP) 8. Viviani Sutjiadi (KTP, NPWP)
III. PERJANJIAN		
1.	Seluruh perjanjian material beserta segala perubahannya, dimana Yayasan merupakan pihak dalam perjanjian tersebut.	Tahun 2019 External Consultant 1. IT Consultant (1 April – 31 December 2019) 2. Nutrition Expert (1 April 2019 – 31 March 2020) 3. Consultant for Sugar Sweetened Beverage Project (15 July 2019 – 31 March 2020) Tahun 2020 External Consultant 1. Addendum contract tim expert SSB (4 orang) – (1 Jan – 31 Dec 2020) 2. Consultant for Infographic Tanjung sari Cohort Study (17 Feb – 30 June 2020)
2.	Seluruh dokumen-dokumen yang berkaitan dengan perjanjian material Yayasan (e.g Pengakhiran Perjanjian)	Tidak ada
IV. PERPAJAKAN		
1.	Surat Setoran Pajak Yayasan untuk 2 (dua) bulan terakhir	Lengkap
2.	NPWP (Nomor Pokok Wajib Pajak)	Lengkap
V. ASURANSI		
1.	Seluruh polis asuransi beserta dokumen pendukungnya (e.g. asuransi Yayasan)	Health Insurance (polis berlaku smp 31 Desember 2020)- asli hard copy Pension Program (polis berlaku seterusnya kecuali ada perubahan)-asli hard copy Life Insurance (Polis ikut Tirta Investama – hanya ada kartu aja)

No.	Nama Dokumen	Keterangan
VI. KETENAGAKERJAAN		
1.	Daftar seluruh karyawan Yayasan (karyawan tetap maupun kontrak)	Lengkap
2.	Perjanjian Kerja antara Yayasan dengan karyawan yang telah ditandatangani	Lengkap
3.	Sertifikat Kepersertaan BPJS Ketenagakerjaan dan BPJS Kesehatan	Sertifikat asli hard copy
4.	Wajib Lapor Ketenagakerjaan Yayasan yang terakhir	Bukti bayar terlampir
VII. DOKUMEN-DOKUMEN TERKAIT LAINNYA Semua dokumen, baik asli, maupun fotokopi atau salinan lainnya atau pernyataan tertulis Yayasan dan lampiran serta dokumen lain yang terkait dengan pendirian, tindakan dan kegiatan Yayasan untuk tahun buku yang bersangkutan		
1.	Laporan Tahunan Yayasan (wajib disahkan oleh Pembina dalam rapat tahunan paling lambat 5 (lima) bulan setelah tahun buku Yayasan ditutup atau bulan Mei)	Tim Legal telah menerima Laporan Tahunan Yayasan untuk tahun buku yang berakhir 31 Desember 2019 lengkap dengan dokumen lampiran Laporan Tahunan.
2.	Program kerja dan rancangan anggaran tahunan Yayasan (wajib disahkan oleh Pembina dalam rapat tahunan paling lambat 5 (lima) bulan setelah tahun buku Yayasan ditutup atau bulan Mei)	<u>Program Kerja & Budget 2020</u> • Sudah diajukan dalam Rapat Advisor tanggal 13 March 2020 • Program kerja sudah disetujui tetapi budget masih dalam proses persetujuan
3.	Laporan Pengurus lainnya yang berkaitan dengan kegiatan Yayasan (e.g laporan bulanan, laporan triwulan)	Terlampir Q1 – 2019 Q2 – 2019 Q3 – 2019 Q4 – 2019 Q1 – 2020

No.	Nama Dokumen	Keterangan
4.	Tanda Daftar Yayasan	Diganti dengan NIB (Nomor Induk Berusaha) per tanggal 25 April 2019 – berlaku selama Yayasan berdiri.
5.	Surat Keterangan Domisili Yayasan	Surat Keterangan Domisili berlaku sampai dengan 16 Oktober 2022
6.	Laporan penggunaan *petty cash* 3 bulan terakhir (Oktober 2019 s/d Desember 2019)	Summary Petty Cash Oct – Dec 2019 (terlampir) Payment Voucher No. 147/DII/PV/X/2019 - Petty Cash Sept - Oct 2019 Payment Voucher No. 156/DII/PV/XI/2019 - Petty Cash Oct 2019 Payment Voucher No. 176/DII/PV/XII/2019 - Petty Cash Nov-Dec 2019 Payment Voucher No. 005/DII/PV/I/2020 - Petty Cash Dec 2019 Asli – hard copy
7.	Seluruh SOP yang dikeluarkan oleh Yayasan Tahun 2019	Tidak ada SOP baru.

YAYASAN INSTITUT DANONE INDONESIA

Theresia L. Setionegoro
Pengawas

Dr. Widjaja Lukito
Ketua Pengurus

Alignment Meeting Danone Institute with CBU 03 December 2020

Attendance List :

1. Dr. Widjaja Lukito
2. Anindita Saraswati
3. Dr. Sarah Angelique
4. Dr. Tria Rosemiarti
5. Dr. Tonny Sundjaya
6. Dewi Maryani
7. Hilda Banser

NO	ISSUES / ITEMS	DISCUSSIONS	NEXT STEP	PIC	STATUS
A	SSB	dr. Widjaja discussed with Prof. Mark: SSB becomes a review paper not short communication and it has been approved by Prof. Mark	Today or tomorrow there will be an online submission	Dr. Widjaja	Not yet
B	Nutritional Anemia	already communicated with Prof. Mark 4 x for five hours each session there are 2 papers that have been confirmed 3 more papers will be entered	This afternoon Dr. Widjaja will communicate with Prof. Mark, Keisha Dr. Sarah propose for further discussion on the publication timeline	Dr. Widjaja DII team & CBU	Not yet Not yet
C	Lactose Nutrition	Ongoing project : infographic lactose nutrition dr. Widjaja offer to Danone	dr. Widjaja will discuss this topic further with CBU	DII team & CBU	Not yet
D	SCM	Infographic have done	dr. Sarah communication further for dissemination	DII team & CBU	Not yet
E	Program water collaboration with DIII	Propose dr. Tria to DII: How can you use tanjungsari data but specifically on the topic of water? dr. Widjaja suggested that if you focus on water, it's better to use research from Erry Yudha	Hilda sent final report Erry Yudha to Dr. Tria	Hilda	Done
F	Program SN collaboration with DII	Wenndybell & Fortifit			

NO	ISSUES / ITEMS	DISCUSSIONS	NEXT STEP	PIC	STATUS
		dr. Widjaja: create operational research when the product is launched	Dr. Tonny will discuss further with Dr. Ray for suggestions from dr. Widjaja & Ibu Vera	CBU	Not yet
G	Next Meeting CBU with DII		2 weeks letter	DII team & CBU	

ATTACHMENT 7b

Equipment Purchase

- License Renewal of Office 365 (Subscription Activation Confirmation)
- Quotation Form of Microsoft Office 364 2020 License Renewal
- Invoice of Logitech Webcam C930e Purchase
- Purchase Order of Logitech Webcam C930e

Subscriptions Activation Confirmation

Thank you for selecting the Microsoft Cloud Solution Provider for your organization

Subscription Detail

Microsoft ID	618830f4-7c7c-44fc-820a-aec0f26e92f1
Domain name	danoneinstituteindonesia.org
Company	Indonesian Danone Institute Foundation
Program	Cloud Solution Provider
Primary Contact	deddyand1366@yahoo.com 021-29961000 - ext 5061
Address	Cyber 2 Tower 9th Floor Jakarta DKI 12950
Reseller Name	PT Mitra Integrasi Informatika
Subscriptions Activation Date	26 August 2020
Subscription End Date	26 August 2021
Auto Renewal Date	27 August 2021

Subscriptions

PN	Description	Qty
C00628AA-935C-4891-8F13-72FF803ABD6A	Office 365 Business Essentials	1

PT. MITRA INTEGRASI INFORMATIKA
APL Tower 37th Fl | Jl. Letjen S. Parman Kav 28, Jakarta Barat - 11470
Telp. (62-21) 29345 777 | Fax. (62-21) 29345 700

Quotation Form

Quotation For

Customer name	:	Danone Institute Indonesia	From	:	Fenita R. Elina Tampubolon
Attn.	:	Dewi Maryani	Subject	:	Quotation Renewal License Microsoft O365 2020
Position	:		Quote No.	:	0226/MII/06/2020
Address	:	Cyber 2 Tower 9th Fl, Jl. HR Rasuna Said Blok X5 No.13, Jakarta 12950	Date	:	17 June 2020
Fax No	:		Ref #	:	
Phone No	:	021-29961000	No of Pages	:	2

FACSIMILE TRANSMITTAL - If You Do Not Receive Completely, Please Contact Us

Dear Ibu Dewi,

As per your request, we are pleased to quote our solution. For the complete solution, please see the tables below:

NO	PN/ CSI	Description	Month	QTY	Curr	Price /unit / Month	Price Total / Year
1	AAA-10624	Microsoft 365 Business Basics	12	1	IDR	65,000.000	780,000.00
						Total Price	**780,000.00**
						VAT	**78,000.00**
						Grand Total	**858,000.00**

Price / Payment Term & Conditions

- Price is quoted in IDR and exclude PPN 10% and any other tax
- Price is FOB Jakarta
- Delivery Time: 2-4 weeks after PO received by MII
- Price valid until July 20th, 20120
- No cancellation after PO released
- Payment should be made 100% within 45 days after date of invoice receipt
- Price and stock are subject to be change without any notice before PO Receive by MII
- Any item not stated in this quotation will be consider as additional

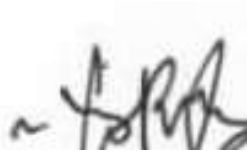
Closing

We do hope this quotation could meet your favorable response. If you have any queries, please feel free to contact us.
If you agree with this Quotation, for the next process please sign this Quotation and follow with your Purchase Order (PO) and send back to us.
This Quotation shall be deemed and binding force as a Purchase Order (PO) upon its signing by the Customer

The person who sign this Quotation has a full Legal Right, Power, and Authority to represent Customer to perform its obligation under this Quotation

In no event that the Customer may cancel this Quotation without prior written approval from and PT Mitra Integrasi Informatika

Sincerely Yours,



(Signature)

Fenita Elina
Account Manager
PT. Mitra Integrasi Informatika - (Metrodata-Group)
Mobile-Phone: 0811 1545 449
Email: Fenita.Tampubolon@mii.co.id

Name
Position
Company

P.T. MITRA INTEGRASI INFORMATIKA
APL Tower, 37th Floor, Jl. Letjen S. Parman kav. 28
Jakarta. 11470 - Indonesia.
Telephone : (62-21) 29345777, Fax : (62-21) 29345700
Email: treasury@metrodata.co.id
Website: www.mii.co.id

INVOICE

YAY. INSTITUT DANONE INDONESIA
CYBER 2 TOWER LT. 16
JL. H.R. RASUNA SAID BLOK X-5 NO.13
KUNINGAN TIMUR - SETIABUDI JAKARTA SELATAN, DKI
JAKARTA RAYA 12950

Invoice Number	:	5883013261
Date	:	01.10.2020
Customer No	:	112709
Payment Terms	:	Payment within 45 days
Order No	:	2883007681
PO Number	:	005/PO/IX/DII/2020

MODEL	QTY	DESCRIPTION	UNIT PRICE IDR	TOTAL PRICE
960-000976	1	Logitech Webcam C930e	1,949,000	1,949,000

Sub Total	1,949,000
VAT 10%	194,900
TOTAL	2,143,900

(TWO MILLION ONE HUNDRED FORTY-THREE THOUSAND NINE HUNDRED IDR)

METERAI TEMPEL
6D2E4AHF675508408
6000
ENAM RIBU RUPIAH
MITRA INTEGRASI INFORMATIKA

Pembayaran dapat dilakukan melalui
rekening Virtual Account sbb :
Bank Mandiri : 89441112709
Bank BCA : 11826112709

Silahkan contact email berikut untuk konfirmasi pelunasan atau masalah pada tagihan / invoice ini :
treasury@metrodata.co.id

Authorized Signatory

Pembayaran dengan transfer / KU atas nama P.T. MITRA INTEGRASI INFORMATIKA. Pembayaran dengan cara lain adalah tanggung jawab pembeli. Pembayaran adalah sah/lunas setelah dana diterima dengan baik pada bank kami.

Payment should always mada by transfer to P.T. MITRA INTEGRASI INFORMATIKA. Any other form of payment will be at the sole responsibility of the payers. Payments are only valid after the fund received by our bank.

BANKERS:
USD : - **Bank HSBC Indonesia**, Cab. World Trade Center
Jl. Jend. Sudirman Kav. 29-31 Jakarta 12920
A/C No. : 001-229-533-007 Swift Code: **HSBCIDJA**
- **Bank Danamon**, Cab. Menara Bank Danamon
Jl. H.R. Rasuna Said Blok C No.10 Jakarta 12920 Indonesia
A/C No. : 417-7127 Swift Code: **BDINIDJA**

BANKERS:
IDR : - **Bank Mandiri**, Cab. Wisma Metropolitan
Jl. Jend. Sudirman Kav. 29-31 Jakarta 12920
A/C No. : 122-00-96008456

P.T. MITRA INTEGRASI INFORMATIKA
APL Tower, 37th Floor, Jl. Letjen S. Parman kav. 28
Jakarta. 11470 - Indonesia.
Telephone : (62-21) 29345777, Fax : (62-21) 29345700
Email: treasury@metrodata.co.id
Website: www.mii.co.id

INVOICE

YAY. INSTITUT DANONE INDONESIA
CYBER 2 TOWER LT. 16
JL. H.R. RASUNA SAID BLOK X-5 NO.13
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VAT 10%	194,900
TOTAL	2,143,900

(TWO MILLION ONE HUNDRED FORTY-THREE THOUSAND NINE HUNDRED IDR)

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rekening Virtual Account sbb :
Bank Mandiri : 89441112709
Bank BCA : 11826112709

Silahkan contact email berikut untuk konfirmasi pelunasan atau masalah pada tagihan / invoice ini :
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Jl. H.R. Rasuna Said Blok C No.10 Jakarta 12920 Indonesia
A/C No. : 417-7127 Swift Code: **BDINIDJA**

BANKERS:
IDR : - **Bank Mandiri**, Cab. Wisma Metropolitan
Jl. Jend. Sudirman Kav. 29-31 Jakarta 12920
A/C No. : 122-00-96008456

Faktur Pajak

Kode dan Nomor Seri Faktur Pajak : 010.007-20.40629565

Pengusaha Kena Pajak

Nama : PT MITRA INTEGRASI INFORMATIKA
Alamat : GEDUNG APL TOWER LT.37 SUITE 1-8 JL LETJEN S. PARMAN KAV 28 RT 012 RW 006 , JAKARTA BARAT
NPWP : 01.764.589.6-062.000

Pembeli Barang Kena Pajak / Penerima Jasa Kena Pajak

Nama : YAY. INSTITUT DANONE INDONESIA
Alamat : CYBER 2 TOWER LT. 16 JL. H.R. RASUNA SAID BLOK X-5 NO.13 KUNINGAN TIMUR - SETIABUDI JAKARTA SELATAN, DKI JAKARTA RAYA 12950
NPWP : 02.312.996.8-063.000

No.	Nama Barang Kena Pajak / Jasa Kena Pajak	Harga Jual/Penggantian/Uang Muka/Termin
1	Logitech Webcam C930e Rp 1.949.000 x 1	1.949.000,00
Harga Jual / Penggantian		1.949.000,00
Dikurangi Potongan Harga		0,00
Dikurangi Uang Muka		0,00
Dasar Pengenaan Pajak		1.949.000,00
PPN = 10% x Dasar Pengenaan Pajak		194.900,00
Total PPnBM (Pajak Penjualan Barang Mewah)		0,00

Sesuai dengan ketentuan yang berlaku, Direktorat Jenderal Pajak mengatur bahwa Faktur Pajak ini telah ditandatangani secara elektronik sehingga tidak diperlukan tanda tangan basah pada Faktur Pajak ini.

JAKARTA BARAT, 01 Oktober 2020

Rismet Gumilar

Inv. 5883013261

PT. MITRA INTEGRASI INFORMATIKA
GEDUNG APL TOWER LT.37 SUITE 1-8 JL. LETJEN S.PARMAN KAV. 28
RT. 012 RW. 006
JAKARTA BARAT
TELP: 021-29345777, FAX: 021-29345700

4366440

DELIVERY NOTE

Sales Group : 86F Fenita R. Elina
Delivery Note : 4883016186
Date : 18.09.2020
Purchase Order : 005/PO/IX/DII/2020
Reference no : 2883007681
Strg. Location : CS 2

Sold to:
112709-YAY. INSTITUT DANONE INDONESIA
CYBER 2 TOWER LT. 16
JL. H.R. RASUNA SAID BLOK X-5 NO.13
KUNINGAN TIMUR - SETIABUDI
JAKARTA SELATAN, DKI JAKARTA RAYA 12950
Telp. 29961234

Attn. ANNE TUPAN

Ship to:
112709-YAY. INSTITUT DANONE INDONESIA
Modernland
Jl. Taman Golf XVIII Blok EG 3/26, Poris Indah, Cipondoh
Tangerang 12950
Telp. 29961234

Attn. Dr Widjaja Lukito

SHIPPING TYPE REGULAR

No	Material	Description	Qty/EA	Vol
1	960-000976	Logitech Webcam C930e	1 EA	2128
	Serial no.: (2027LZ58PG39)			

18/09/20

Customer & Signature Date

MITRA INTEGRASI INFORMATIKA

Approved

Dear Customer, Please take only 1(one) page

Suhartosu 19/09/2020

Yayasan INSTITUT DANONE
Gizi untuk Anak Bangsa

Invoicing Address :
Indonesian Danone Institute Foundation
Cyber 2 Tower 9th Floor
Jl. HR Rasuna Said Blok X-5 No. 13
Jakarta 12950

Vendor Address:
PT. Mitra Integrasi Informatika
Attn . Fenita R. Elina T

Telp : 021-29345 777
Email: Fenita.Tampubolon@mii.co.id

PAYMENT TERMS : Payment 45 days after invoi

Location/ Date : Jakarta 8-Sep-20

Purchase Order No: 005/PO/IX/ DII/2020

Delivery Address :

Indonesian Danone Institute Foundation

Cyber 2 Tower 9th Floor

Jl. HR Rasuna Said Blok X-5 No. 13

Jakarta 12950

Tax ID : 02.312.996.8-063.00

Indonesian Danone Institute Foundation Cont

Payment :

Phone : 021 2996 1000 ext.5019

email: dewi.kusumastuti@danone.com

Requester :

Dewi Maryani

email: dewi.kusumastuti@danone.com

In line with office needed for operation, it is proposed that DII purchase renewal licence to support routine activities as follow:

No	Material Code	Quantity	Description	Unit Price	Value w/o VAT	Delivery Date
01	Logitec C930E HD Webcam 1080p H.264 Video Compression Camera	1	unit	1,949,000	1,949,000	

TOTAL w/o VAT	:	**1,949,000**
VAT 10%	:	**194,900**
TOTAL: IDR	:	**2,143,900**

1. Please acknowledge acceptance of this order by signing/email on the PO form and re-send via fax, email or other means not later than 2 working days from receipt hereof.

2. Indicate the PO# on all billings and documents.

Prepared by :	Approved by:		Acknowledged by:
Dewi Maryani	**Widjaja Lukito**	**Francisca Cicilia**	**Eka Prasetia**
Finance DII	Chairman DII	Danone Group	Danone Group

PT. MITRA INTEGRASI INFORMATIKA
APL Tower 37th Fl | Jl. Letjen S. Parman Kav 28, Jakarta Barat - 11470
Telp. (62-21) 29345 777 | Fax. (62-21) 29345 700

Quotation Form

Quotation For

Customer name	: Yay. Institut Danone Indonesia	From	: Fenita R. Elina Tampubolon
Attn.	: Ibu Dewi Kusumastuti	Subject	: Quotation Logitech HD WebCam
Position	:	Quote No.	: 095/MII/09/2020
Address	: Cyber 2 Tower 9th Fl, Jl. HR Rasuna Said Blok X5 No.13, Jakarta 12950	Date	: 07 Sept 2020
Fax No	:	Ref #	:
Phone No	: 021-29961000	No of Pages	: 2

FACSIMILE TRANSMITTAL - If You Do Not Receive Completely, Please Contact Us

Dear Bu Dewi,

As per your request, we are pleased to quote our solution. For the complete solution, please see the tables below:

NO	Part Number	Description	QTY	Curr	Price /unit	Price Total
		Logitech Webcam				
1	960-000972	**Logitech C930E HD Webcam 1080p H.264 Video Compression Camera**	1	IDR	1,949,000.00	1,949,000.00
					Total Price	**1,949,000.00**
					VAT 10%	**194,900.00**
					Total After VAT	**2,143,900.00**

Price / Payment Term & Conditions

- Price is quoted in IDR and exclude PPN 10% and any other tax
- Price is FOB Jakarta
- Delivery Time: 2 weeks after PO received by MII (ready but limited)
- Price valid until Sept 18th, 2020
- No cancellation after PO release
- Payment should be made 100% within 45 days after date of Invoice receipt
- Price and stock are subject to be change without any notice before PO Receive by MII
- Any item not stated in this quotation will be consider as additional

Closing

We do hope this quotation could meet your favorable response. If you have any queries, please feel free to contact us.
If you agree with this Quotation, for the next process please sign this Quotation and follow with your Purchase Order (PO) and send back to us.
This Quotation shall be deemed and binding force as a Purchase Order (PO) upon its signing by the Customer

The person who sign this Quotation has a full Legal Right, Power, and Authority to represent Customer to perform its obligation under this Quotation

In no event that the Customer may cancel this Quotation without prior written approval from and PT Mitra Integrasi Informatika

Sincerely Yours,

Fenita Elina
Account Manager
PT. Mitra Integrasi Informatika - (Metrodata-Group)
Mobile-Phone: 0811 1545 449
Email: Fenita.Tampubolon@mii.co.id

(Signature)

Name Dr. Widjaja Lukito
Position
Company

ATTACHMENT 7c

Audited Financial Report

- Independent Auditor's Report and Financial Statements of Indonesian Danone Institute Foundation for Period Ended December 31, 2020

LAPORAN AUDITOR INDEPENDEN
DAN
LAPORAN KEUANGAN
YAYASAN INSTITUT DANONE INDONESIA
UNTUK PERIODE YANG BERAKHIR PADA
TANGGAL 31 DESEMBER 2020

INDEPENDENT AUDITOR'S REPORT
AND
FINANCIAL STATEMENTS
INDONESIAN DANONE INSTITUTE FOUNDATION
FOR PERIOD ENDED DECEMBER 31, 2020

Yayasan
INSTITUT DANONE
Gizi untuk Anak Bangsa
INDONESIA

SURAT PERNYATAAN PENGURUS TENTANG TANGGUNG JAWAB ATAS LAPORAN KEUANGAN 31 DESEMBER 2020 DAN UNTUK TAHUN YANG BERAKHIR PADA TANGGAL TERSEBUT

No. 005/IDIF/OUT-FE/I/2021

BOARD OF MANAGEMENT'S STATEMENT LETTER RELATING TO THE RESPONSIBILITY ON THE FINANCIAL STATEMENTS AS OF DECEMBER 31, 2020 AND FOR THE YEAR THEN ENDED

No. 005/IDIF/OUT-FE/I/2021

Kami yang bertanda tangan di bawah ini/ *We, the undersigned:*

1. Nama/ *Name* **Widjaja Lukito**
   Alamat Kantor/ *Office Address* Gedung Cyber 2 Lt 9 Jl HR Rasuna Said Blok X5 No 13 Jakarta, 12950 Indonesia
   Alamat Domisili/ *Domicile* Jl. Taman Golf XVIII Blok EG 3/26 RT 004/RW 014, Poris Plawad Indah, Cipondoh, Tangerang
   Nomor Telepon/ *Phone Number* (6221) 29961000
   Jabatan/ *Position* Ketua / *Chairman*

2. Nama/ *Name* **Dedy**
   Alamat Kantor/ *Office Address* Gedung Cyber 2 Lt 10 Jl HR Rasuna Said Blok X5 No 13 Jakarta, 12950 Indonesia
   Alamat Domisili/ *Domicile* Jl. Kucica 2 Blok JG 6/2 Bintaro Jaya Sek IX, RT 03/RW 011, Pondok Pucung, Pondok Aren, Tangerang Selatan
   Nomor Telepon/ *Phone Number* (6221) 29961000
   Jabatan/ *Position* Bendahara I / *Treasury I*

Menyatakan bahwa:

1. Bertanggungjawab atas penyusunan dan penyajian laporan keuangan Yayasan Institut Danone Indonesia.
2. Laporan keuangan Yayasan Institut Danone Indonesia telah disusun dan disajikan sesuai dengan Standar Akuntansi Keuangan di Indonesia;
3. a. Semua informasi dalam laporan keuangan Perusahaan telah dimuat secara lengkap dan benar;
   b. Laporan keuangan Perusahaan tidak mengandung informasi atau fakta material yang tidak benar, dan tidak menghilangkan informasi atau fakta material.
4. Bertanggungjawab atas sistem pengendalian internal Yayasan .

Demikian pernyataan ini dibuat dengan sebenarnya.

State that:

1. *We are responsible for the preparation and presentation of Indonesian Danone Institute Foundation financial statements;*
2. *Indonesian Danone Institute Foundation financial financial statements have been prepared and presented in accordance with Indonesian Financial Accounting Standards.*
3. *a. All information in the Company's consolidated financial statements is complete and correct;*
   b. The Company's consolidated financial statements do not contain misleading material information or facts, and do not omit material information or facts.
4. *We are responsible for the Foundation's internal control system.*

This statement letter is made truthfully.

Jakarta, 29 Januari 2021

METERAI TEMPEL 6000 ENAM RIBU RUPIAH

WIDJAJA LUKITO	**DEDY**
Ketua / Chairman	Bendahara I / *Treasury I*

KANTOR AKUNTAN PUBLIK
TJAHJO, MACHDJUD MODOPURO & REKAN
Keputusan Menteri Keuangan RI Nomor : KEP-1021/KM.17/1998

Gedung Yayasan Purna Bhakti, Lantai III Ruang 307
Jl. Proklamasi No. 44 Jakarta 10320; Telp.: 3151534, 42882576; Facs.: 42882577; E-mail : kaptim@rad.net.id

LAPORAN AUDITOR INDEPENDEN | ***INDEPENDENT AUDITORS' REPORT***

No. : 00010/2.0225/AU.11/06/0710-2/1/I/2021

Yth,
Dewan Pengurus
Yayasan Institut Danone Indonesia

Kami telah mengaudit laporan keuangan Yayasan Institut Danone Indonesia ("Yayasan"), yang terdiri dari laporan posisi keuangan tanggal 31 Desember 2020, serta laporan penghasilan komprehensif serta perubahan aset neto dan laporan arus kas untuk tahun yang berakhir pada tanggal tersebut, dan suatu ikhtisar kebijakan akuntansi signifikan dan informasi penjelasan lainnya.

Tanggung jawab manajemen atas laporan keuangan

Manajemen bertanggung jawab atas penyusunan dan penyajian wajar laporan keuangan ini sesuai dengan Standar Akuntansi Keuangan di Indonesia, dan atas pengendalian internal yang dianggap perlu oleh manajemen untuk memungkinkan penyusunan laporan keuangan yang bebas dari kesalahan penyajian material, baik yang disebabkan oleh kecurangan maupun kesalahan.

Tanggung jawab auditor
Tanggung jawab kami adalah untuk menyatakan suatu opini atas laporan keuangan tersebut berdasarkan audit kami. Kami melaksanakan audit kami berdasarkan Standar Audit yang ditetapkan oleh Institut Akuntan Publik Indonesia. Standar tersebut mengharuskan kami untuk mematuhi ketentuan etika serta merencanakan dan melaksanakan audit untuk memperoleh keyakinan memadai tentang apakah laporan keuangan tersebut bebas dari kesalahan penyajian material.

To,
Board of Management
Indonesian Danone Institute Foundation

We have audited the accompanying financial statements of Indonesian Danone Institute Foundation which comprise the statement of financial position as of December 31, 2020, and the statements comprehensive income and changes of net assets, and statement of cash flows for the year then ended, and a summary of significant accounting policies and other explanatory information.

Management's responsibility for the financial statements
Management is responsible for the preparation and fair presentation of such financial statements in accordance with Indonesian Financial Accounting Standards, and for such internal control as management determines is necessary to enable the preparation of financial statements that are free from material misstatement, whether due to fraud or error.

Auditors' responsibility
Our responsibility is to express an opinion on such financial statements based on our audit. We conducted our audit in accordance with Standards on Auditing established by the Indonesian Institute of Certified Public Accountants. Those standards require that we comply with ethical requirements and plan and perform the audit to obtain reasonable assurance about whether such financial statements are free from material misstatement.

Cabang:
Bandar Lampung : Jl. Pumawirawan Raya No. 128, Bandar Lampung 35152, Telp.: (0721) 5609431; Facs.: (0721) 5609431
Denpasar : Jl. Drupadi XIV No. 3, Denpasar 80235, Telp.: (0361) 4745880; Facs.: (0361) 4745880
Bogor : Jl. Raya Karanggan No. 234. Gunung Putri, Bogor 16960, Telp.: (021) 83724156; Facs.: (021) 83724155

Suatu audit melibatkan pelaksanaan prosedur untuk memperoleh bukti audit tentang angka-angka dan pengungkapan dalam laporan keuangan. Prosedur yang dipilih bergantung pada pertimbangan auditor, termasuk penilaian atas risiko kesalahan penyajian material dalam laporan keuangan, baik yang disebabkan oleh kecurangan maupun kesalahan. Dalam melakukan penilaian risiko tersebut, auditor mempertimbangkan pengendalian internal yang relevan dengan penyusunan dan penyajian wajar laporan keuangan entitas untuk merancang prosedur audit yang tepat sesuai dengan kondisinya, tetapi bukan untuk tujuan menyatakan opini atas keefektivitasan pengendalian internal entitas. Suatu audit juga mencakup pengevaluasian atas ketepatan kebijakan akuntansi yang digunakan dan kewajaran estimasi akuntansi yang dibuat oleh manajemen, serta pengevaluasian atas penyajian laporan keuangan secara keseluruhan.

An audit involves performing procedures to obtain audit evidence about the amounts and disclosures in the financial statements. The procedures selected depend on the auditors' judgment, including the assessment of the risks of material misstatement of the financial statements, whether due to fraud or error. In making those risk assessments, the auditors consider internal control relevant to the entity's preparation and fair presentation of the financial statements in order to design audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the entity's internal control. An audit also includes evaluating the appropriateness of accounting policies used and the reasonableness of accounting estimates made by management, as well as evaluating the overall presentation of the financial statements.

Kami yakin bahwa bukti audit yang telah kami peroleh adalah cukup dan tepat untuk menyediakan suatu basis bagi opini wajar dengan pengecualian kami.

We believe that the audit evidence we have obtained is sufficient and appropriate to provide a basis for our qualified audit opinion.

Opini

Menurut opini kami, laporan keuangan terlampir menyajikan secara wajar dalam semua hal yang material, posisi keuangan Yayasan Institut Danone Indonesia tanggal 31 Desember 2020, serta kinerja keuangan dan arus kasnya untuk tahun yang berakhir pada tanggal tersebut, sesuai dengan Standar Akuntansi Keuangan di Indonesia.

Opinion

In our opinion, the accompanying financial statements present fairly, in all material respects, the financial position of Indonesian Danone Institute Foundation as of December 31, 2020, and its financial performance and cash flows for the year then ended, in accordance with Indonesian Accounting Standards.

Kantor Akuntan Publik/*Registered Public Accountants*
Tjahjo, Machdjud Modopuro & Rekan

TJAHJO MACHDJUD MODOPURO & REKAN
KANTOR AKUNTAN PUBLIK
JAKARTA

Drs. Tjahjo Nurwantoro, CPA., CA.
NIAP/*License No. 0710*
29 Januari 2021/*January 29, 2021*

Daftar Isi/*Table of Contents*

YAYASAN INSTITUT DANONE INDONESIA
LAPORAN POSISI KEUANGAN
Tanggal 31 Desember 2020
(Disajikan dalam Rupiah, kecuali dinyatakan lain)

INDONESIAN DANONE INSTITUTE FOUNDATION
STATEMENTS OF FINANCIAL POSITION
As of December 31, 2020
(Expressed in Rupiah, unless otherwise stated)

	Catatan/ *Notes*	31 Desember 2020/ *December, 31 2020*	Disajikan Kembali (Catatan 3)/ *As Restated (Note 3)* 31 Desember 2019/ *December, 31 2019*	1 Januari 2019/ 31 Desember 2018/ *January 1, 2019/ December, 31 2018*	
ASET					***ASSETS***
ASET LANCAR					***CURRENT ASSETS***
Kas dan Setara Kas	4	721.480.756	918.040.137	1.005.844.584	*Cash and cash equivalent*
Piutang	5	400.000.000	-	-	*Accounts receivable*
Pajak dibayar dimuka	6	-	-	8.474.561	*Prepaid Tax*
Biaya dibayar dimuka	7	3.076.169	-	-	*Prepaid expense*
Jumlah Aset Lancar		**1.124.556.925**	**918.040.137**	**1.014.319.145**	***Total Current Assets***
ASET TIDAK LANCAR					***NON-CURRENT ASSETS***
Aset tetap	8	28.402.925	39.189.205	37.249.887	*Fixed assets*
Jumlah Aset Tidak Lancar		**28.402.925**	**39.189.205**	**37.249.887**	***Total Non Current Assets***
JUMLAH ASET		**1.152.959.850**	**957.229.342**	**1.051.569.032**	***TOTAL ASSETS***
LIABILITAS DAN ASET NETO					***LIABILITIES AND NET ASSETS***
Liabilitas Jangka Pendek					***Short-term Liabilities***
Hutang usaha	10	160.829.500	187.627.654	411.155.514	*Accounts payable*
Hutang pajak	9a	30.589.399	4.478.714	4.201.329	*Taxes payable*
Hutang akrual	11	246.339.744	185.302.085	202.849.870	*Accrued liabilities*
Jumlah Liabilitas Jangka Pendek		**437.758.643**	**377.408.453**	**618.206.713**	***Total Short-term Liabilities***
Liabilitas Jangka Panjang					***Long-term Liabilities***
Liabilitas imbalan kerja	12	149.515.300	140.991.500	134.974.700	*Employee benefit liabilities*
JUMLAH LIABILITAS		**587.273.943**	**518.399.953**	**753.181.413**	***TOTAL LIABILITIES***

Catatan atas laporan keuangan terlampir merupakan bagian yang tidak terpisahkan dari laporan keuangan secara keseluruhan.

The accompanying notes to the financial statements form an integral part of these financial statements taken as a whole.

(Disajikan dalam Rupiah, kecuali dinyatakan lain) | (Expressed in Rupiah, unless otherwise stated)

	Catatan/ *Notes*	31 Desember 2020/ *December, 31 2020*	Disajikan Kembali (Catatan 3)/ *As Restated (Note 3)* 31 Desember 2019/ *December, 31 2019*	1 Januari 2019/ 31 Desember 2018/ *January 1, 2019/ December, 31 2018*	
ASET NETO					***NET ASSETS***
Tanpa pembatasan dari pemberi kontribusi		565.685.907	438.829.389	298.387.619	*Without restriction from contribution*
Dengan pembatasan dari pemberi kontribusi		-	-	-	*With restriction from contribution*
Jumlah Aset Neto		**565.685.907**	**438.829.389**	**298.387.619**	***Total Net Assets***
JUMLAH LIABILITIAS DAN ASET BERSIH		**1.152.959.850**	**957.229.342**	**1.051.569.032**	***TOTAL LIABILITIES AND NET ASSETS***

Catatan atas laporan keuangan terlampir merupakan bagian yang tidak terpisahkan dari laporan keuangan secara keseluruhan.

The accompanying notes to the financial statements form an integral part of these financial statements taken as a whole.

YAYASAN INSTITUT DANONE INDONESIA
LAPORAN PENGHASILAN KOMPREHENSIF SERTA PERUBAHAN ASET NETO
Untuk tahun berakhir pada tanggal 31 Desember 2020
(Disajikan dalam Rupiah, kecuali dinyatakan lain)

INDONESIAN DANONE INSTITUTE FOUNDATION
STATEMENTS OF COMPREHENSIVE INCOME AND CHANGES OF NET ASSETS
For the Year Ended 31 December 2020
(Expressed in Rupiah, unless otherwise stated)

	Catatan/ *Notes*	31 Desember 2020/ *December, 31 2020*	Disajikan Kembali (Catatan 3)/ *As Restated (Note 3)* 31 Desember 2019/ *December, 31 2019*	1 Januari 2019/ 31 Desember 2018/ *January 1, 2019/ December, 31 2018*	
PENDAPATAN					***REVENUES***
Kontribusi	13	1.900.000.000	1.435.000.000	2.000.000.000	*Contribution*
Pendapatan Lain-lain	13	2.569.187	3.921.845	5.321.376	*Other Income*
Jumlah		**1.902.569.187**	**1.438.921.845**	**2.005.321.376**	***Total***
BEBAN					***EXPENSE***
Beban Operasi	14	932.038.668	485.431.122	2.348.580.389	*Operating Expenses*
Beban Umum dan Administrasi	15	798.701.701	754.326.953	990.061.593	*General and Administration Expense*
Beban lain-lain	16	44.972.300	58.722.000	83.014.275	*Other Expenses*
Jumlah		**1.775.712.669**	**1.298.480.075**	**3.421.656.257**	***Total***
KENAIKAN (PENURUNAN) ASET NETO SEBELUM PAJAK PENGHASILAN		**126.856.518**	**140.441.770**	**(1.416.334.881)**	***INCREASE (DECREASE) NET ASSETS BEFORE INCOME TAX***
Pajak Penghasilan		-	-	-	*Income Tax*
KENAIKAN (PENURUNAN) ASET NETO		**126.856.518**	**140.441.770**	**(1.416.334.881)**	***INCREASE (DECREASE) IN NET ASSET***
Aset Bersih Awal Tahun		438.829.389	298.387.619	1.714.722.500	***Net Assets at the beginning of the year***
Aset Bersih Akhir Tahun		**565.685.907**	**438.829.389**	**298.387.619**	***Net Assets at the end of this year***

Catatan atas laporan keuangan terlampir merupakan bagian yang tidak terpisahkan dari laporan keuangan secara keseluruhan.

The accompanying notes to the financial statements form an integral part of these financial statements taken as a whole.

YAYASAN INSTITUT DANONE INDONESIA
LAPORAN ARUS KAS
Untuk tahun yang berakhir pada tanggal 31 Desember 2020
(Dinyatakan dalam Rupiah, kecuali dinyatakan lain)

INDONESIAN DANONE INSTITUTE FOUNDATION
STATEMENTS OF CASH FLOW
For the Year Ended 31 Desember 2020
(Expressed in Rupiah, unless otherwise stated)

	2020	2019	
Perubahan dalam aset bersih	126.856.518	140.441.770	*Change in net assets*
Penyesuain untuk:			*Adjusment for:*
Penyusutan	13.788.180	27.820.808	*Depreciation*
Imbalan kerja	8.523.800	6.016.800	*Employee benefit*
Perubahan untuk :			*Changes in working capital :*
- Piutang kontribusi	(400.000.000)	-	*Receivables contributions* -
- Piutang	-	-	*Receivables* -
- Pajak dibayar dimuka	-	8.474.561	*Prepaid tax* -
- Biaya dibayar dimuka	(3.076.169)	-	*Prepaid expenses* -
- Hutang usaha	(26.798.154)	(223.527.860)	*Account payable* -
- Hutang pajak	26.110.685	277.385	*Taxes payable* -
- Biaya yang masih harus dibayar	61.037.659	(17.547.785)	*Accrued payable* -
- Utang lain-lain	-	-	*Other payable* -
Jumlah arus kas aktivitas operasi	(193.557.480)	(58.044.321)	*Total cashflow operation activity*
Arus kas dari aktivitas investasi			*Cashflow from investment activity*
Perolehan aset tetap	(3.001.900)	(29.760.126)	*Addition of fixed asset*
Jumlah arus kas dari aktivitas investasi	(196.559.380)	(87.804.447)	*Total cashflow investment activity*
Arus kas dari aktivitas pendanaan	-	-	*Cashflow from capital activity*
Jumlah arus kas aktivitas pendanaan	-	-	*Total cashflow capital activity*
Penurunan Bersih kas dan setara kas	(196.559.380)	(87.804.447)	***Decrease netto cash and cash equivalent***
Kas dan setara kas saldo awal	918.040.137	1.005.844.584	***Cash and cash equivalent beginning***
Kas dan setara kas saldo akhir	721.480.756	918.040.137	***Ending balance cash and cash equivalent***

Catatan atas laporan keuangan terlampir merupakan bagian yang tidak terpisahkan dari laporan keuangan secara keseluruhan

The accompanying notes to the financial statements form an integral part of these financial statements taken as a whole

(Expressed in Rupiah, unless otherwise stated)

1. UMUM

a. Pendirian dan Informasi Umum

Yayasan Institut Danone Indonesia ("Yayasan") didirikan dengan Akta Notaris No.23 dari Notaris Linda Herawati, S.H., notaris di Jakarta tanggal 4 Mei 2007. Akta pendirian yayasan telah mendapat pengesahan dari Menteri hukum dan Hak Asasi Manusia Republik Indonesia dengan Surat Keputusan No.C-3394.HT.01.02.TH 2007 tanggal 10 Oktober 2007.

Anggaran Dasar Pendirian tersebut telah mengalami beberapa kali perubahan, terakhir dengan Akta No.01 dari Notaris Bertha S.Ihalauw H., S.H. notaris di Jakarta Pusat tanggal 04 September 2020 tentang Penyataan Keputusan Pembina Yayasan Institut Danone Indonesia.

Berdasarkan anggaran dasar Pasal 2, maksud dan tujuan di dirikannya Yayasan adalah di bidang sosial.

Untuk mencapai maksud dari tujuan tersebut, Yayasan memiliki kegiatan antara lain:

1. Mendirikan dan/atau mengelola lembaga formal dan non-formal.
2. Penelitian di bidang ilmu pengetahuan terutama di bidang gizi.
3. Studi banding.

b. Susunan Pengurus dan Informasi lain

Susunan Pembina dan Pengurus Yayasan pada tanggal 31 Desember 2020 dan 2019 adalah sebagai berikut:

1. GENERAL

a. Establishment and General Information

Indonesia Danone Institute Foundation ("The Foundation") was established by notary deed No.23 of Linda herawati, S.H., notary in Jakarta on May 4, 2007. Article of Incorporation has been approved by Minister of Law and Human Right of Indonesia Republic with Desicion Letter No.C-3394.HT.01.02.TH 2007 dated October 10,2007.

The Articels of Incoporation have been amended several times, most recently by Deed No.01 of Bertha S. Ihalauw H., S.H., notary in Central Jakarta on dated September 04, 2020 regarding supervisor's decision statement of Indonesian Danone Institute Foundation.

According to article 2 of Article of Association, the purposes and objective of the Foundation is in social affairs.

To achieve that purpose and objective, the Foundation has activities among of which are:

1. *Create and/or manage of formal and non formal organization.*
2. *Scientific research, especially in nutrition.*
3. *Comparetive study.*

b. Management and Other Information

The composition of the Foundation's Advisory and Supervisory as of December 31, 2020 and 2019 are as follows:

	2020	**2019**	
Pembina			*Advisory*
Ketua	Vera Galuh Sugijanto	Corine Danielle Tap	*Chairman*
Anggota	Widianto Juwono	Connie Ang	*Member*
Pengawas			*Supervisory*
Ketua	Theresia Lianawaty Setionegoro	Theresia Lianawaty Setionegoro	*Chairman*

1. UMUM (lanjutan)

b. Susunan Pengurus dan Informasi lain (lanjutan)

1. GENERAL (continued)

b. Management and Other Information (continued)

	2020	2019	
Pengurus			*Management*
Ketua	Widjaja Lukito	Widjaja Lukito	*Chairman*
Wakil Ketua I	Ade Umiyana	Julie Wendy Jones	*Vice chairman I*
Wakil Ketua II	Rosalina Privita	Rosalina Privita	*Vice chairman II*
Wakil Ketua III	Tria Rosemiarti	Tria Rosemiarti	*Vice chairman III*
Sekretaris	Anindita Saraswati	Nadhila Renaldi	*Secretary*
Bendahara I	Dedi Suwartono	Sebastianus Comelis Verweij	*Treasury I*
Bendahara II	Ronny Suwarto	Rizki Raksanugraha	*Treasury II*
Bendahara III	Viviani Sutjiadi	Chen Chui Yng	*Treasury III*
Bendahara IV	-	Lim Chin Chew	*Treasury IV*

2. IKHTISAR KEBIJAKAN AKUNTANSI PENTING YANG DITERAPKAN

a. Dasar Penyajian Laporan Keuangan

Laporan keuangan ini telah disajikan sesuai dengan prinsip akuntansi yang berlaku umum di Indonesia yang mencakup Pernyataan Standar Akuntansi Keuangan (PSAK). Kebijakan akuntansi yang penting yang diterapkan secara konsisten dalam penyusunan laporan keuangan untuk tahun yang berakhir pada tanggal 31 Desember 2020 sebagai berikut:

Dasar yang dikenakan dalam penyusunan laporan keuangan adalah biaya historis, kecuali beberapa akun tertentu yang diukur dengan dasar lain yang dijelaskan dalam kebijakan akuntansi terkait. Laporan keuangan disusun dengan metode akrual kecuali laporan arus kas.

Laporan arus kas disusun dengan metode tidak langsung (*indirect method*) dengan mengelompokan arus kas dalam aktivitas operasi, investasi dan pendanaan.

Mata uang fungsional dan presentasi yang digunakan dalam penyusunan laporan keuangan adalah Rupiah Indonesia.

b. Transaksi dengan Pihak Berelasi

Suatu pihak dianggap berelasi dengan Yayasan jika:

1. Langsung atau tidak langsung yang melalui satu atau lebih perantara. Suatu pihak (i) mengendalikan, atau dikendalikan oleh, atau berada di bawah pengendalian bersama dengan Yayasan; (ii) memiliki kepentingan dalam Yayasan yang memberikan pengaruh signifikan atas Yayasan, atau (iii) memiliki pengendalian bersama atas Yayasan;

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES IMPLEMENTED

a. Basis of financial statements preparation

The financial statements have been prepared in accordance with generally accepted accounting principles in Indonesia comprising of the Statement of Financial Accounting Standards (SFAS). Significant accounting policies applied consistently in the preparation of The financial statement for the years ended December 31, 2020 are as follows:

The basic used in preparing the financial statement is historical cost except for certain accounts which are measured on another basis describeb in the related accounting policy. The financial position are prepared under accrual basis of accounting except for the statements of cash flows.

The statements of cash flows have been prepared using the indirect method and classifying cash flows into operating, investing, and financing activities.

The functional and presentation currency used in preparation of the financial statement is Indonesian Rupiah.

b. Transaction with Related Parties

A party is considered to be related to the Foundation if:

1. *Directly or indirectly through one or more intermediaries. The party (i) controls, or is controlled by or is under common control with the Foundation; (ii) has an interest in the Foundation that gives significant influence over the Foundation, or (iii) has joint control over the Foundation;*

2. IKHTISAR KEBIJAKAN AKUNTANSI PENTING YANG DITERAPKAN (lanjutan)

b. Transaksi dengan Pihak Berelasi (lanjutan)

2. Suatu pihak yang berelasi dengan Yayasan.
3. Suatu pihak adalah ventura bersama di mana Yayasan sebagai *venturer;*
4. Suatu pihak adalah anggota dari personil manajemen kunci Yayasan atau induk;
5. Suatu pihak adalah anggota keluarga dekat dari individu yang diuraikan dalam butir (1) atau (4);
6. Suatu pihak adalah entitas yang dikendalikan, dikendalikan bersama atau dipengaruhi signifikan oleh atau untuk di mana hak suara signifikan pada beberapa entitas, langsung maupun tidak langsung individu seperti diuraikan dalam butir (4) atau (5); atau
7. Suatu pihak adalah suatu program imbalan paska kerja untuk imbalan kerja dari Yayasan atau entitas yang terkait dengan Yayasan.

Transaksi ini dilakukan berdasarkan persyaratan yang disetujui oleh kedua belah pihak. Dimana persyaratan tersebut mungkin tidak sama dengan transaksi lain yang dilakukan dengan pihak-pihak yang tidak berelasi. Saldo dan transaksi yang material antara Yayasan dengan pihak berelasi diungkapkan dalam catatan 5.

c. Kas dan Setara Kas

Kas dan setara kas terdiri dari saldo kas dan bank, serta deposito berjangka pendek yang jatuh tempo dalam waktu tiga bulan atau kurang dari tanggal perolehannya dan yang tidak dijaminkan serta tidak dibatasi penggunaannya.

d. Aset Tetap

Aset tetap dinyatakan sebesar biaya perolehan dikurangi akumulasi penyusutan dan rugi penurunan nilai. Biaya perolehan termasuk biaya penggantian bagian aset tetap saat biaya tersebut terjadi, jika memenuhi kriteria pengakuan.

Selanjutnya, pada saat inspeksi yang signifikan dilakukan, biaya inspeksi itu diakui ke dalam jumlah tercatat aset tetap sebagai suatu penggantian jika memenuhi kriteria pengakuan. Semua biaya pemeliharaan dan perbaikan yang tidak memenuhi kriteria pengakuan diakui dalam laporan penghasilan komprehensif pada saat terjadinya.

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES IMPLEMENTED (continued)

b. Transaction with Related Parties (continued)

2. The party is an associate of the Foundation;
3. The party is a joint venture in which the Foundation is a venturer;
4. The party is a member of the key management personnel of the Foundation or its parent;
5. The party is a close member of the family of any individual referred to (1) or (4);
6. The party is an entity that is controlled, jointly controlled or significant voting power in such entity resides with directly or indirectly any individual referred to (4) or (5); or

7. The party is a post employment benefit plan for the benefit of employees of the Foundation or any entity that is a related party of the Foundation.

The transaction to related parties are made based on agreed terms. Whereas such terms may not be the same as those with the transactions to third parties. All significant transactions and balances with related parties are disclosed in note 5.

c. Cash and Cash Equivalents

Cash and cash equivalents consist of cash on hand and bank, and short term deposit with maturities of three months or less from the dates of placement and not pledge as collateral or restricted in use.

d. Fixed Assets

Fixed assets are stated at cost less accumulated depreciation and impairment losses. Such cost includes the cost of replacing part of fixed assets when that cost is incurred, if the recognition criteria are met.

Likewise, when a major inspection is perfomed, its cost is recognized in the carring amount of fixed assets as a replacement if the recognition criteria are satisfied. All repairs and maintenance costs that do not meet the recognition criteria are recognized in the statements of comprehensive income as incurred.

2. IKHTISAR KEBIJAKAN AKUNTANSI PENTING YANG DITERAPKAN (lanjutan)

d. Aset Tetap (continued)

Penyusutan dihitung dengan menggunakan metode garis lurus selama umur manfaat aset tetap yang diestimasi sebagai berikut:

	Tahun/Years	
Peralatan kantor	4	*Office Equipment*

Akumulasi biaya perolehan yang akan dipindahkan ke masing-masing pos aset tetap yang sesuai pada saat aset tersebut selesai dikerjakan atau siap digunakan dan disusutkan sejak beroperasi.

Nilai tercatat dari suatu aset tetap dihentikan pengakuannya pada saat pelepasan atau ketika tidak terdapat lagi manfaat ekonomis masa depan yang diharapkan dari penggunaan atau pelepasannya.

Keuntungan atau kerugian yang timbul dari penghentian pengakuan tersebut (yang ditentukan sebesar selisih antara jumlah hasil pelepasan neto, jika ada dan jumlah tercatatnya) dimasukan dalam penghasilan komprehensif pada saat penghentian pengakuan tersebut dilakukan.

Pada akhir periode pelaporan, Yayasan melakukan penelaahan berkala atas masa manfaat, nilai residu, metode penyusutan, dan sisa umur pemakaian berdasarkan kondisi teknis.

e. Perpajakan

Beban pajak adalah jumlah gabungan pajak kini dan pajak tangguhan yang diperhitungkan dalam menentukan penghasilan komprehensif pada suatu periode. Pajak kini dan pajak tangguhan diakui dalam penghasilan komprehensif, kecuali pajak penghasilan yang timbul dari transaksi atau peristiwa yang diakui dalam penghasilan komprehensif lain atau secara langsung di ekuitas. Dalam hal ini, pajak tersebut masing-masing diakui dalam penghasilan komprehensif lain atau ekuitas.

Jumlah pajak kini untuk periode berjalan dan periode sebelumnya yang belum dibayar diakui sebagai liabilitas.

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES IMPLEMENTED (continued)

d. Fixed Assets (continued)

Depreciation is computed using the straight-line method over the estimated useful lives of the assets as follows:

The accumulated costs will be transferred to the respective fixed assets item at the time the the asset is completed or ready for use and are depreciate since the operation.

The carrying amount of an item of fixed asset is derecognized on disposal or when no future economic benefits are expected from its use or disposal.

Any gain or loss arising from derecognition (that determined as the difference between the net disposal proceeds, if any, and the carrying amount of the item) is included in comprehensive income when item is derecognized.

At the end of each reporting period, the Foundation made regular review of the useful lives, residual values, depreciation method and residual life based on the technical conditions.

e. Taxation

Tax expense is the aggregate amount included in the determination of comprehensive income for the period in respect of current tax and deferred tax. Current tax and deferred tax is recognized in comprehensive income, except for income tax arising from transaction or event that are recognized in other comprehensive income or directly in equity, in this case, the tax is recognized in other comprehensive income or equity, respectively.

Curtrent tax for current and prior periodes shall, to the extent unpaid, be recognized as a liability.

2. IKHTISAR KEBIJAKAN AKUNTANSI PENTING YANG DITERAPKAN (lanjutan)

f. Estimasi liabilitas Imbalan Kerja

Imbalan paska kerja diakui sebesar jumlah diskonto ketika pekerja telah memberikan jasanya kepada Yayasan dalam suatu periode akuntansi. Kewajiban dan beban diukur dengan menggunakan teknik tertentu yang mencakup kewajiban konstruksi yang timbul dari praktik kebiasaan Yayasan. Dalam perhitungan kewajiban, imbalan harus didiskontokan dengan menggunakan metode *projected unit credit.* Yayasan mengakui imbalan kerja karyawan berdasar undang-undang ketenagakerjaan. Yayasan memutuskan untuk tidak menggunakan jasa aktuaris dalam menghitung imbalan kerja karena jumlah karyawan yang tidak signifikan, dimana pada 31 Desember 2020 hanya terdiri dari 1 (satu) orang.

g. Pengakuan Pendapatan dan Beban

Pendapatan diakui pada saat anggaran disetujui oleh *Contribution Business Unit (CBU)* yang terdiri dari PT Sari Husada, PT Nutricia Indonesia Sejahtera dan PT Tirta Investama. Beban diakui pada saat terjadinya (metode akrual).

h. Instrumen Keuangan

Pengakuan dan Pengukuran Awal

Yayasan mengakui aset keuangan atau liabilitas keuangan dalam laporan posisi keuangan, jika dan hanya jika, Yayasan menjadi salah satu pihak dalam ketentuan pada kontrak instrument tersebut. Pada saat pengakuan awal aset keuangan atau liabilitas keuangan, Yayasan mengukur pada nilai wajarnya.

Dalam hal aset keuangan atau liabilitas keuangan tidak diukur pada nilai wajar melalui penghasilan komprehensif, nilai wajar tersebut ditambah atau dikurang dengan biaya transaksi biaya transaksi yang dapat diatribusikan secara langsung dengan perolehan atau penerbitan aset keuangan atau liabilitas keuangan tersebut. Biaya transaksi yang dikeluarkan sehubungan dengan perolehan. aset keuangan dan penerbitan liabiltas keuangan yang diklasifikasikan pada nilai wajar melalui penghasilan komprehensif dibebankan segera.

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES IMPLEMENTED (continued)

f. Estimated Liability for Employee Benefit

Post employement benefits are recognized at a discounted amount when an employee has rendered service to the foundation during an accounting period. Liabilities and expense are measured using certain techniques which include constructive obligation that arises from the Foundation informal pratices. In calculating the liabilities, benefits should be discounted by using projected unit credit method. The foundation recognized its employee benefits liabilities based on existing labor law. The Foundation estimated it was not material to the balance, thereforcer the Foundation decided not to compute using the independent actuary due to calculate employee benefit the total permanent employee of the Foundation is not significant, which in December 31, 2020 only consist of 1 (one) person.

g. Revenue and Expense Recognition

Revenue are generally recognized when the budget being approved by the Contribution Business Unit (CBU) which consist of PT Sari Husada, PT Nutricia Indonesia Sejahtera and PT Tirta Investama. Expense are recognized when incurred (accrual method).

h. Financial Instruments

Initial Recognition and Measurement

Foundation recognized a financial assets or a financial liabilities in the statement of financial position when, and only when, it becomes a party to the contractual provisions of the instruments. At initial recognition, the Foundation measure all financial assets and financial liabilities at its fair value.

In the case of financial assets or financial liability not at fair value though comprehensive income, fair value is added or deducted with the transaction cost that are directly attributable to the acquisition or issue of the financial assets or financial liability. Transaction cost incurred on acqusition of a financial assets and issue of a financial liabilities classified at fair value through comprehensive income are expenses immediately.

2. IKHTISAR KEBIJAKAN AKUNTANSI PENTING YANG DITERAPKAN (lanjutan)

h. Instrumen Keuangan (continued)

Pengukuran Aset Keuangan Setelah Tanggal Neraca
Pengukuran selanjutnya aset keuangan tergantung pada klasifikasinya ada saat pengakuan awal. Yayasan mengklasifikasikan aset keuangan dalam salah satu dari empat kategori berikut:

(i) Aset keuangan yang Diukur pada Nilai Wajar Melalui Penghasilan Komprehensif (FVTCI)

Aset keuangan yang diukur pada FVTCI adalah aset keuangan yang dimiliki untuk diperdagangkan atau yang pada saat pengakuan awal telah ditetapkan untuk diukur pada nilai wajar melalui penghasilan komprehensif.

Aset keuangan diklasifikasikan dalam kelompok diperdagangkan jika diperoleh atau dimiliki terutama untuk tujuan dijual atau dibeli kembali dalam waktu dekat, atau bagian dari portofolio instrument keuangan tertentu yang dikelola bersama dan terdapat bukti mengenai pola ambil untuk dalam jangka pendek aktual saat ini, atau merupakan derivatif, kecuali derivatif yang ditetapkan dan efektif sebagai instrument lindung nilai.

Pada tanggal 31 Desember 2020, tidak ada aset keuangan yang diukur menggunakan metode ini.

(ii) Pinjaman dan Piutang
Pinjaman yang diberikan dan piutang adalah aset keuangan non-derivatif dengan pembayaran tetap atau telah ditentukan dan tidak mempunyai kuotasi di pasar aktif, kecuali:

a. Pinjaman yang diberikan dan piutang yang dimaksudkan untuk dijual dalam waktu dekat dan yang pada saat pengakuan awal ditetapkan sebagai asei aset keuangan yang diukur pada nilai wajar melalui penghasilan komprehensif;
b. Pinjaman yang diberikan dan piutang yang pada saat pengakuan awal ditetapkan sebagai tersedia untuk dijual; atau
c. Pinjaman yang diberikan dan piutang dalam hal pemilik mungkin tidak akan memperoleh kembali investasi awal secara substansial kecuali yang disebabkan oleh penurunan kualitas pinjaman.

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES IMPLEMENTED (continued)

h. Financial Instruments (continued)

Subsequent Measurement of Financial Assets
Subsequent measurement of financial assets depends on their classification on initial recognition. The foundation classifies financial assets in one of the following four categories:

(i) *Financial Assets at Fair Value Through Comprehensive Income (FVTCI)*

Financial assets at FVTCI are financial assets held for trading or upon initial recognition are designated as at fair value through comprehensive income.

Financial asset classified as held for trading if it is acquired or incurred principally for the purpose of selling and repurchasing it in the near term, or it is a part of a portofolio of identified financial instrument that are managed together and for which there which evidence of a recent actual pattern of short-term profit taking, or it is derivative, except for a derivative that is a designated and effective hedging istrument.

As of December 31, 2020, there is no financial asset that measured with this method.

(ii) Loans and Receivables
Loans dan receivables are non-derivative financial assets with fixed or determinable payment that are not quoted in an active market, other than:

a Those that intends to be sold immediately or in the near term and upon initial recognition designated as at fair value through comprehensive income;

b Those that upon initial recognition designated as available for sale; or

c. Thoses for which the holder may not recover substantially all of its initial investment, other than those cause by credit deterioration.

2. IKHTISAR KEBIJAKAN AKUNTANSI PENTING YANG DITERAPKAN (lanjutan)

h. Instrumen Keuangan (continued)

(ii) Pinjaman dan Piutang (lanjutan)
Pada tanggal 31 Desember 2020, aset keuangan yang diukur menggunakan metode ini adalah kas dan setara kas dan piutang.

(iii) Investasi dimiliki hingga jatuh tempo (HTM)
Investasi HTM adalah aset keuangan non-derivatif dengan pembayaran tetap atau telah ditentukan dan jatuh temponya telah ditetapkan, serta Yayasan mempunyai intensi positif dan kemampuan untuk memiliki aset keuangan tersebut hingga jatuh tempo.

(iv) Aset keuangan tersedia untuk dijual (AFS)
Aset keuangan AFS adalah aset keuangan non-derivatif yang ditetapkan sebagai tersedia untuk dijual atau yang tidak diklasifikasikan sebagai (a) pinjaman yang diberikan dan piutang, (b) investasi yang diklasifikasikan dalam kelompok dimiliki hingga jatuh tempo, atau (c) aset keuangan yang diukur pada nilai wajar melalui penghasilan komprehensif.

Setelah pengakuan awal, aset keuangan AFS diukur pada nilai wajarnya. Keuntungan atau kerugian yang timbul dari perubahan nilai wajar diakui dalam penghasilan komprehensif lain, kecuali untuk kerugian penurunan nilai dan keuntungan atau kerugian akibat perubahan kurs, sampai aset keuangan tersebut dihentikan pengakuannya. Pada saat itu, keuntungan atau kerugian kumulatif yang sebelumnya diakui dalam penghasilan komprehensif lain direklasifikasi dari ekuitas ke penghasilan komprehensif sebagai penyesuaian reklasifikasi.

Pada tanggal 31 Desember 2020, tidak ada aset keuangan yang diukur menggunakan metode ini.

Pengukuran Liabilitas Keuangan Setelah Tanggal Neraca
Pengukuran selanjutnya liabilitas keuangan tergantung pada klasifikasinya pada saat pengakuan awal. Yayasan mengklasifikasikan liabilitas keuangan dalam salah satu dari kategori berikut:

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES IMPLEMENTED (continued)

h. Financial Instruments (continued)

(ii) Loans and Receivables (continued)
As of December 31, 2020, financial asset that measured with this method are cash and cash equivalent and account receivable.

(iii). Held-to-Maturity
HTM investments are non-derivative financial asset with determinable payment and fixed maturity that the Foundation has the positive intention and ability to hold to maturity.

(iv). Avaible-for-Sale (AFS) Financial Assets
AFS financial assets are non-derivative financial assets that are designated as available for sale or initial recognition or are not classified as (a) loans and receivable, (b) held-to-maturity investment, or (c) financial assets at fair value through comprehensive income.

After initial recognition, AFS financial assets are measured at its fair value. Gains or losses arising from a change in the fair value is recognized on other comprehensive income, except for impairment losses and foreign exchange gains and losses, until the financial assets is derecognized. At the time, the cumulative gains or losses previously recognized in other comprehensive income shall be reclassified from equity to comprehensive income as reclassification adjustment.

As of December 31, 2020, there is no financial asset that measured with this method.

Subsequent Measurement of Financial Liabilities.
Subsequent measurement of financial liabilities depends on their classification on initial recognition. The Foundation classifies financial liabilities into one of the following categories:

2. IKHTISAR KEBIJAKAN AKUNTANSI PENTING YANG DITERAPKAN (lanjutan)

h. Instrumen Keuangan (continued)

(i). Liabilitas Keuangan yang Diukur pada Nilai Wajar Melalui Penghasilan Komprehensif (FVTCI)
Liabilitas keuangan yang diukur FVTCI adalah liabilitas keuangan yang dimiliki untuk diperdagangkan atau yang pada saat pengakuan awal telah ditetapkan untuk diukur pada nilai wajar melalui penghasilan komprehensif. Liabilitas keuangan diklasifikasikan dalam kelompok diperdagangkan jika diperoleh atau dimiliki terutama untuk tujuan dijual atau dibeli kembali dalam waktu dekat, atau bagian dari portofolio instrument keuangan tertentu yang dikelola bersama dan terdapat bukti mengenai pola ambil untung dalam jangka pendek aktual saat ini, atau merupakan derivatif, kecuali derivatif yang ditetapkan dan efektif sebagai instrument lindung nilai.

Setelah pengakuan awal, liabilitas keuangan yang diukur pada FVTCI diukur pada nilai wajarnya. Keuntungan atau kerugian yang timbul dari perubahan nilai wajar diakui dalam penghasilan komprehensif.

(ii). Liabilitas Keuangan Lainnya
Liabilitas keuangan yang tidak diklasifikasikan sebagai liabilitas keuangan yang diukur pada FVTCI dikelompokan dalam kategori ini dan diukur pada biaya perolehan diamortisasi dengan menggunakan metode suku bunga efektif.

Penghentian Pengakuan Aset dan Liabilitas keuangan
Penghentian pengakuan aset keuangan dilakukan ketika hak kontraktual atas arus kas yang berasal dari aset keuangan tersebut berakhir, atau ketika aset keuangan tersebut telah ditransfer dan secara substansial seluruh risiko dan manfaat atas kepemilikan aset tersebut telah ditransfer (jika, secara substansial seluruh risiko dan manfaat tidak ditransfer, maka Yayasan melakukan evaluasi untuk memastikan keterlibatan berkelanjutan atas kendali yang masih dimiliki tidak mencegah penghentian pengakuan). Liabilitas keuangan dihentikan pengakuannya ketika liabilitas telah dilepaskan atau dibatalkan atau kadaluarsa.

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES IMPLEMENTED (continued)

h. Financial Instruments (continued)

(i). Financial Liabilities at Fair Value Through Comprehensive Income (FVTCI)
Financial liabilities at FVTCI are financial liabilities held for trading or upon initial recognition it is designated as at fair value through comprehensive income. Financial liabilities classified as held for trading if it is acquired or incurred principally for the purpose of selling and repurchasing it in the near term, or it is a part of a portfolio of identified financial instrument that are managed together and for which there is evidence of a recent actual pattern of short-term profit taking, or it is a derivative, except for a derivative that is a designated and effective hedging instrument.

After initial recognition, financial liabilities at FVTCI are measured at its fair value. Gains or losses arising from a change in the fair value are recognized in comprehensive income.

(ii). Other Financial Liabilities
Financial liabilities that are not classified as financial liabilities at FVTCI are classified in this category and are measured at amortized cost using the effective interest method.

Derecognition of Financial Assets and Liabilities
Financial assets are direcognized when the contractual rights to receive the cash flows from these assets have ceased to exist or the assets have been transferred and all the risks and benefits have been transferred substantially (if, substantially all the risk and benefits have not been transferred, the Foundation conducts the evaluation to ensure that continuing involvement on the basis of any retained powers of control does not prevent derecognized). Financial liabilities are derecognized when the liabilities has dischanged or cancelled or otherwise expires.

2. IKHTISAR KEBIJAKAN AKUNTANSI PENTING YANG DITERAPKAN (lanjutan)

h. Instrumen Keuangan (continued)

Pada setiap tanggal pelaporan, Yayasan melakukan penilaian apakah terdapat bukti yang objektif bahwa aset keuangan atau kelompok aset keuangan mengalami penurunan nilai. Sebuah aset keuangan mengalami penurunan nilai dan kerugian penurunan nilai terjadi, jika dan hanya jika, terdapat bukti objektif penurunan nilai sebagai akibat dari satu atau lebih peristiwa yang terjadi setelah pengakuan awal aset (peristiwa rugi) dan peristiwa yang merugikan tersebut berdampak pada estimasi arus kas masa depan atas aset keuangan atau kelompok aset keuangan yang dapat diestimasi secara handal.

Berikut ini adalah bukti yang objektif bahwa aset keuangan atau kelompok aset keuangan atau kelompok aset keuangan mengalami penurnan nilai:

a. Kesulitan keuangan signifikan yang dialami penerbit atau pihak peminjam;
b. Sebuah pelanggaran kontrak, seperti wanprestasi atau tunggakan pembayaran pokok atau bunga;
c. Terdapat kemungkinan bahwa pihak peminjam akan dinyatakan pailit atau melakukan reorgarnisasi keuangan lainnya.

Data di observasi mengindikasikan adanya penurunan yang dapat diukur pada taksiran arus uang tunai masa datang dari aset keuangan Yayasan sejak pengakuan awal, seperti memburuknya status pembayaran debitur atau kondisi ekonomi yang berkolerasi dengan wanprestasi.

Untuk investasi di instrumen ekuitas, penurunan yang signifikan dan berkepanjangan dalam nilai wajar instrumen ekuitas dibawah biaya perolehannya merupakan bukti objektif penurunan nilai.

Jika terdapat bukti objektif bahwa kerugian penurunan nilai telah terjadi atas pinjaman dan piutang atau dimiliki hingga jatuh tempo dicatat pada biaya perolehan diamortisasi, jumlah kerugian penurunan nilai diukur sebagai selisih antara nilai tercatat aset keuangan dengan nilai kini estimasi arus kas masa depan yang didiskontokan pada suku bunga efektif awal dari aset keuangan tersebut dan diakui dalam laporan aktivitas dan perubahan aset bersih tidak terikat.

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES IMPLEMENTED (continued)

h. Financial Instruments (continued)

At each reporting period, the Foundation assets whether there is objective evidence that financial assets or group of financial assets is impaired. A financial assets or group of financial assets is impaired and impairment losses are incurred, if only if, there is objective evidence of impairment as a result of one or more events that occurred after the initial recognition of the asset (loss event), and that loss event has an impact on the estimated future cash flows of the financial asset or group of financial assets that can be reliabily estimated.

The following are objective evidence that a financial asset or group of financial asset is impaired:

a. Significant financial difficult of the issuer or obligator;
b. A breach of contract, such as default or delinquency in interest or principal payments;
c. It becoming probable that the borrower will enter bankruptcy or other financial reorganization.

Observable data indicating that there is a measurable decrease in the estimated future cash flows from a Foundation of financial assets of the Foundation since the initial recognition, such as adverse changes in the payment status of borrowers or economic condition that correlate with defaults.

For investment in equity instrument, a significant and prolonged decline in the fair value of the equity instrument below its cost is an objective evidence of impairment.

If there is objective evidence that an impairment loss has been incurred on loans and receivable or hield-to-maturity investments carried at amortized cost, the amount of impairment loss is measured as the difference between the carrying amount of the financial asset and the present value of estimated future cash flows discounted at the financial assets original effective interest rate and recognized in the statement of activities and changes in unrestricted net assets.

2. IKHTISAR KEBIJAKAN AKUNTANSI PENTING YANG DITERAPKAN (lanjutan)

h. Instrumen Keuangan (continued)

Ketika penurunan nilai wajar aset keuangan tersedia untuk dijual telah diakui dalam pendapatan komprehensif lain dan terdapat bukti objektif bahwa aset tersebut mengalami penurunan nilai, kerugian kumulatif yang telah diakui, dalam pendapatan komprehensif lain harus direklasifikasi dari ekuitas kenaikan atau penurunan sebagai penyesuaian reklasifikasi meskipun aset keuangan belum dihentikan pengakuannya.

Jumlah kerugian kumulatif yang direklasifikasi adalah selisih antara biaya perolehan (dikurangi pembayaran pokok dan amortisasi) dan nilai wajar kini, dikurangi kerugian penurunan nilai aset keuangan yang sebelumnya telah diakui dalam laporan penghasilan komprehensif serta perubahan aset neto dan perubahan aset bersih tidak terikat.

Metode Bunga Efektif

Metode suku bunga efektif adalah metode menghitung biaya perolehan diamortisasi dari aset keuangan atau kewajiban keuangan (atau aset keuangan atau kewajiban keuangan Yayasan) dan metode untuk mengalokasikan pendapatan bunga atau beban bunga selama periode yang relevan. Suku bunga efektif adalah suku bunga yang secara tepat mendiskontokan estimasi pembayaran atau penerimaan kas selama perkiraan umur dari instrumen keuangan, atau lebih tepatnya digunakan periode yang lebih singkat untuk memperoleh nilai tercatat bersih dari aset keuangan atau kewajiban keuangan.

Pada saat menghitung suku bunga efektif, Yayasan mengestimasi arus kas dengan mempertimbangkan seluruh persyaratan kontraktual dalam instrumen keuangan misalnya pembayaran di muka, opsi panggilan dan sejenisnya tetapi tidak akan mempertimbangkan kerugian kredit di masa mendatang. Perhitungan ini mencakup seluruh komisi dan dibayarkan atau diterima oleh para pihak dalam kontrak yang merupakan bagian tak terpisahkan dari suku bunga efektif, biaya transaksi dan seluruh premi dan diskon.

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES IMPLEMENTED (continued)

h. Financial Instruments (continued)

When a decline in the fair value of an avaible for-sale financial asset has been recognized in other comprehensive income and there is objective evidence that the asset is impaired, the cumulative loss that had been recognized in other comprehensive income shall be reclassified from equity to increase or decrease as a reclassification adjustment even though the financial assets has not been derecognized.

The amount of the cumulative loss that is reclassified are the difference between the acquisition cost (net of an principal repayment and amortisation) and current fair value, less any impairment loss on that financial asset previously recognized in the statement of comprehensive income and changes of net assets and changes in unrestricted net assets.

The Effective interest Method

The effective interest method is a method of calculating the amortized cost of a financial asset or a financial liability (or Foundation's financial assets or financial liabilities) and of allocating the interest income or interest expense over that relevant period. The effective interest rate is the the rate that exactly discount estimated future cash payment or receipts through the expected life of the financial instrument or, when appropriate, a shorter period to the net carrying amount of the financial asset or financial liability.

When calculating the effective interest rate, the Foundation estimates cash flows considering all contractual terms of the financial instrument, for example, prepayment, call and similar option, but shall not consider, future credit losses. The calculating includes all fees and points paid or received between parties to the contract that are an integral part of the effective interest rate, transaction costs, and all other premiums or discounts.

2. IKHTISAR KEBIJAKAN AKUNTANSI PENTING YANG DITERAPKAN (lanjutan)

h. Instrumen Keuangan (continued)

Reklasifikasi

Yayasan tidak akan mereklasifikasi derivatif dari kategori nilai wajar melalui kategori laporan aktivitas dan perubahan aset bersih tidak terikat ketika sedang dimiliki atau diterbitkan dan tidak mereklasifikasi instrumen keuangan dari kategori nilai wajar melalui kategori nilai wajar melalui kategori aktivitas dan perubahan aset bersih tidak terikat jika pada saat pengakuan awal itu ditunjuk oleh Yayasan sebagai pada nilai wajar melalui laporan penghasilan komprehensif. Yayasan mungkin *reclassify* bahwa aset keuangan dari kategori nilai wajar melalui kategori laporan aktivitas dan perubahan aset bersih tidak terikat jika aset keuangan tidak lagi dimiliki untuk tujuan dijual atau dibeli kembali dalam waktu dekat. Yayasan tidak diperkenankan untuk mereklasifikasi instrumen keuangan ke dalam kategori nilai wajar melalui penghasilan komprehensif setelah pengakuan awal.

Jika sebagai akibat dari perubahan niat atau kemampuan Yayasan, tidak lagi tepat untuk mengklasifikasikan investasi dimiliki hingga jatuh tempo, maka harus diklasifikasi benar pada nilai wajar.

Setiap kali penjualan atau reklasifikasi dari investasi dimiliki hingga jatuh tempo dengan jumlah yang lebih tidak signifikan, investasi jatuh tempo selebihnya harus diklasifikasikan sebagai tersedia untuk dijual, selain penjualan atau reklasifikasi yang begitu dekat dengan jatuh tempo atau semua pokok awal dari aset keuangan tersebut telah dikumpulkan secara susbtansial melalui pembayaran di muka, atau disebabkan peristiwa yang terisolasi yang berada di luar kendali, tidak berutang dan tidak diantisipasi dengan layak.

Saling Hapus Aset keuangan dan Liabilitas Keuangan

Sebuah aset keuangan dan kewajiban keuangan akan saling hapus jika dan hanya jika, yayasan saat ini memiliki hak yang berkekuatan hukum untuk melakukan saling hapus dalm jumlah yang diakui; dan berniat baik untuk menyelesaikan secara neto atau untuk merealisasikan aset dan menyelesaikan liabilitasnya secara bersamaan.

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES IMPLEMENTED (continued)

h. Financial Instruments (continued)

Reclassification

The Foundation shall not reclassify a derivative out of the fair value through statement of activities and changes in unrestricted net assets category while it is held or issued and not reclassify any financial instrument out of the fair value through statement of activities and changes in unrestricted net assets category if upon initial recognition it was designated by the foundation as at fair value through comprehensive income. The foundation may reclassify that financial assets is not longer held for the near term. The Foundation shall no reclassify any financial instrument into the fair value through comprehensive income category after initial recognition.

If, as a result of a change in foundation's intention or ability, it is no longer appropriate to classify an investment as held to maturity, it shall be reclassified as available for sale and remeasured at fair value.

Whenever sales or reclassification of more than an insignificant amount of held-to-maturity investments, any remaining held-to-maturity invesment shall be reclassified as avaible for sale, other than sales or reclassification that are so close to maturity or the financial asset's original principal has been collected substantially through scheduled payment or prepayments, or are attributable to an isolated event that is beyond control, non-recurring, and could not have been reasonably anticipated.

Offsetting a Financial Asset a Financial Liability

A financial asset and financial liability shall be offset if and only when, the Foundation's currently has a legally enforceable right to offset the recognized amount and intends either to settle on a net basis, or to realise the asset and settle the liability simultaneously.

2. IKHTISAR KEBIJAKAN AKUNTANSI PENTING YANG DITERAPKAN (lanjutan)

h. Instrumen Keuangan (continued)

Pengukuran Nilai Wajar

Nilai wajar adalah harga yang akan diterima untuk menjual aset atau dibayar untuk mentransfer kewajiban dalam transaksi yang teratur antara pelaku pasar pada tanggal pengukuran.

Nilai wajar aset keuangan dan kewajiban keuangan harus diperkirakan untuk pangakuan dan pengukuran atau untuk tujuan pengungkapan.

Nilai wajar dikategorikan ke dalam tingkat yang berbeda dalam hirarki nilai wajar didasarkan pada sejauh mana masukan untuk pengukuran yang diamati dan pentingnya masukan ke pengukuran nilai wajar secara keseluruhan:

(i) Harga kuotasian (tanpa penyesuaian) di pasar aktif untuk aset atau liabilitas yang identik yang dapat diakses pada tanggal pengukuran (level 1).
(ii) Input selain harga kuotasian yang termasuk dalam Level 1 yang dapat diobservasi untuk aset atau liabilitas, baik secara langsung maupun tidak langsung (level 2).
(iii) Input yang tidak dapat diobservasi untuk aset atau liabilitas (level 3).

Ketika mengukur nilai wajar aset atau kewajiban, Yayasan menggunakan data pasar yang dapat diobservasi sejauh mungkin. Jika nilai wajar aset atau kewajiban tidak langsung diamati, Yayasan menggunakan teknik penilaian yang sesuai dengan keadaan yang memaksimalkan penggunaan input diamati relevan yang dapat diamati dan meminimalkan penggunaan input yang tidak dapat teramati.

Transfer antara tingkat hirarki nilai wajar diakui oleh Yayasan pada akhir periode pelaporan selama perubahan terjadi.

i. Penurunan Aset Non-Keuangan

Pada setiap akhir periode pelaporan, Yayasan menilai apakah terdapat indikasi bahwa aset mengalami penurunan nilai. Jika terdapat indikasi, Yayasan harus memperkirakan jumlah terpulihkan aset tersebut. Jumlah terpulihkan ditentukan untuk aset individual, jika tidak memungkinkan, Yayasan menentukan jumlah terpulihkan unit penghasil kas aset.

2. SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES IMPLEMENTED (continued)

h. Financial Instruments (continued)

Fair Value Measurement

Fair value is the price that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date.

The fair value of financial assets and financial liabilities must be estimated for recognition and measurement or for disclosure purposes.

Fair values are categorised into different levels in a fair value hierarchy based on the degree to which the inputs to the measurement are observable and the significance of the inputs to the fair value measurement in its entirety:

(i) Quoted prices (unadjusted) in active markets for identical asset or liabilities that can be accesed at the measurement data (level 1).
(ii) Inputs other than quoted prices included in Level 1 that are observable for the assets or liabilities, other directly or indirectly (level 2).
(iii) Unobservable inputs for the assets or liabilities (level 3).

When measuring the fair value of an asset or liability, the Foundation uses market observable data to the extent possible. If the fair value of an asset or a liability is not directly observable, the Foundation uses valuation techniques that appropriate in the circumstances that maximizes the use of unobservable inputs and minimize the use of observable input.

Transfer between levels of the fair value hierarchy are recognized by the Foundation at the end of the reporting period during which the change occurred.

i. Impairment of Non-Financial Assets

At the end of each reporting period, the Foundation assets whether there is any indication that an asset may be impaired, if any such indication exists, the Foundation shall estimate the recoverable amount of the asset. Recoverable amount is determined for an individual asset, if it is not possible, the Foundation determines the recoverable amount of the asset's cash-generating unit.

2. IKHTISAR KEBIJAKAN AKUNTANSI PENTING YANG DITERAPKAN (lanjutan)

i. Penurunan Aset Non-Keuangan (lanjutan)

Jumlah terpulihkan adalah yang lebih tinggi dari nilai wajar dikurangi biaya untuk menjual dan nilai pakai. Nilai yang digunakan adalah nilai sekarang dari estimasi arus kas masa depan atas aset atau unit penghasil kas satuan. Nilai sekarang dihitung dengan menggunakan tingkat diskonto sebelum pajak yang mencerminkan nilai waktu dari uang dan risiko spesifik atas aset atau unit yang sedang diukur penurunan nilainya. Jika jumlah terpulihkan aset kurang dari jumlah tercatatnya, nilai tercatat aset harus dikurangi untuk jumlah terpulihkannya.

Pengurangan adalah penurunan nilai dan diakui bersih tidak terikat. Rugi penurunan nilai diakui dalam periode sebelumnya untuk aset selain *goodwill* dibalik jika, dan hanya jika, telah terjadi perubahan dalam perkiraan yang digunakan untuk menentukan jumlah terpulihkan aset sejak rugi penurunan nilai terakhir diakui.

Jika hal ini terjadi, nilai tercatat aset harus dinaikan ke jumlah terpulihkannya. Kenaikan itu,adalah kebalikan dari penurunan nilai.

j. Sumber Estimasi Ketidakpastian dan Pertimbangan Akuntansi Kritis

Yayasan membuat estimasi dan asumsi mengenai masa depan. Estimasi dan pertimbangan yang digunakan dalam penyusunan laporan keuangan interim terus dievaluasi berdasarkan pengalaman historis dan faktor-faktor lain, termasuk harapan kejadian masa depan yang diyakini wajar. Walaupun estimasi ini dibuat berdasarkan pengetahuan terbaik manajemen atas kejadian dan tindakan saat ini, hasil aktual mungkin berbeda dengan estimasi. Asumsi dan pertimbangan memiliki pengaruh yang signifikan pada jumlah tercatat aset dan kewajiban yang diungkapkan dibawah ini.

Perkiraan Umur Manfaat Aset Tetap

Ulasan tentang masa manfaat aset tetap berdasarkan pada beberapa faktor yaitu kondisi teknis dan pengembangan teknologi di masa depan. Hasil operasi di masa depan akan dipengaruhi oleh perkiraan perubahan faktor tersebut.

2. *SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES IMPLEMENTED (continued)*

i. Impairment of Non-Financial Assets (continued)

The recoverable amount is the higher of fair value less costs disposal and its value in use. Value in use is the present value of the estimated future cash flows of the assets or cash generating unit. Present values are computed using pre-tax discount rate that reflect the time value of money and the risks spesific to the asset or unit whose impairment is being measured. If the recerrable amount of an asset is less than is carrying amount, the carrying amount of the asset shall be reduced to its recoverable amount.

The reduction is an impairment loss and is recognized immediately in statement of activitie and changes in unrestricted net assets. An impairment loss recognized in prior period for an asset other than goodwill is reversed if, and only if, there has been a change in the estimates used to determine the asset's recoverable amount since the last impairment loss and recognized.

If this is the case, the carrying amount of the asset shall be increased to its recoverable amount. That increase is a reversal of an impairment loss.

j. Source of Estimation Uncertainty and Critical Accounting Judgements

The Foundation makes estimates and assumptions concerning the future. Estimates and considerations used in the preparation of item financial statements continue to be evaluated based on historical experience and other factors, including expectations of future events that are believed to be reasonable. Although these estimates are based on management's best knowledge of current events and actions, actual results may different from those estimates. Assumptions effect and considerations have a significant and carrying amount of assets and liabilities disclosed below.

Estimated of Useful Life of fixed Assets

The Foundation reviews on useful lives of property and equipment based on several factors I,e. technical conditions and technology development in the future. Operating results in the future will be affected by the estimated changes on those factors.

2. IKHTISAR KEBIJAKAN AKUNTANSI PENTING YANG DITERAPKAN (lanjutan)

j. Sumber Estimasi Ketidakpastian dan Pertimbangan Akuntansi Kritis (Lanjutan)

Manfaat Pasca Kerja

Nilai imbalan kerja paska kerja tergantung pada beberapa faktor yang ditentukan dengan dasar actuarial berdasarkan beberapa asumsi. Asumsi biaya(manfaat) mencakup tingkat diskonto. Perubahan asumsi dapat mempengaruhi nilai imbalan paska kerja.

Yayasan menentukan tingkat diskonto yang sesuai pada pelaporan akhir, dengan mempertimbangkan tingkat diskonto pada obligasi pemerintah yang dalam mata uang imbalan yang akan dibayarkan dan memiliki persyaratan yang sama dengan ketentuan kewajiban yang bersangkutan.

Klasifikasi Aset Keuangan dan Kewajiban Keuangan

Yayasan menentukan klasifikasi aset dan kewajiban tertentu sebagai aset keuangan dan kewajiban keuangan dengan menilai apakah mereka memenuhi definisi yang ditetapkan dalam PSAK. Dengan demikian, aset keuangan dan kewajiban keuangan yang dicatat sesuai dengan kebijakan akuntasi Yayasan diungkapkan dalam Catatan 2h.

Penyisihan Kerugian Penurunan Nilai atas Piutang

Yayasan mengevaluasi akun tertentu dimana memiliki informasi bahwa pelanggan tertentu tidak dapat memenuhi kewajiban mereka.

Dalam kasus ini, Yayasan menggunakan pertimbangan, berdasarkan fakta dan keadaan terbaik yang tersedia.

Termasuk namun tidak terbatas pada jangka waktu hubungan dengan pelanggan dan status kredit pelanggan saat ini, untuk merekam ketentuan khusus bagi pelanggan terhadap jumlah karena mengurangi jumlah piutang yang diharapkan dapat tertagih.

Ketentuan khusus ini dievaluasi kembali dan disesuaikan sebagai informasi tambahan yang diterima yang mempengaruhi jumlah penyisihan kerugian kerugian penurunan nilai piutang usaha.

2. *SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES IMPLEMENTED (continued)*

j. Source of Estimation Uncertainty and Critical Accounting Judgements (continued)

Post Employment Benefit

The present value of post employment benefit depends on several factors which are determined by actuarial basis based on several assumptions. Assumptions used to determine pension costs (benefit) covered discount rate. The changes of assumption might affect carrying value of post employment benefit.

The Foundation dtermines the appropriate discount rate at the final reporting, by considering the discount rate on government's bond which denominated in benefit's currency that will be paid and have a similar terms with the terms of the related liabilities.

Classification of Financial Assets and Financial

The Foundation determines the classifications of certain assets and liabilities as financial assets and financial laibilities by judging if they meet the definition set forth in SFAS. Accordingly, the financial assets and financial liabilities are accounted for in accordance with the foundation accounting policied diclosed in note 2h.

Allowance for Impairment Losses on Accounts

The Foundation evaluates specific accounts where it has information that certain customers are unable to meet their financial obligations.

In these cases the Foundation uses judgement, based on the best available facts and circumstances.

Including but not limited to the length of its relationship with the customer and the customer's current credit status, to record specific provisions for customers againts amounts due to reduce its receivable amount that the Foundation expects to collect.

These specific provisions are re-evaluated and adjusted as additional information received affects the amounts of allowance for impairment losses on trade receivables.

(Expressed in Rupiah, unless otherwise stated)

3. PENYAJIAN KEMBALI LAPORAN KEUANGAN

Tabel berikut menyajikan dampak perubahan penerapan PSAK No. 45, Pelaporan Keuangan Organisasi Nirlaba terhadap laporan posisi keuangan dan laporan penghasilan komprehensif lain:

3. *RESTATEMENT OF FINANCIAL STATEMENTS*

The following tables summarize the impact application of PSAK No. 45, Financial Reporting For Non Profit Organizations to the financial position and statement of comprehensive income:

	Disajikan Sebelumnya	**Penyajian**	**Disajikan**	
Aset				***Assets***
Aset Lancar	1.124.556.925	1.124.556.925	1.124.556.925	***Current Assets***
Aset Tidak Lancar	28.402.925	28.402.925	28.402.925	***Non Current Assets***
Jumlah Aset	1.152.959.850	1.152.959.850	1.152.959.850	***Total Assets***
Liabilitas dan Aset Neto				***Liabilities and Net Assets***
Pajak Tangguhan	-	-	-	*Deferred tax*
Jumlah Liabilitias	587.273.943	587.273.943	587.273.943	***Total Liabilities***
Aset Bersih				***Net Assets***
Tanpa pembatasan dari pemberi kontribusi	565.685.907	565.685.907	565.685.907	*Without restriction from contribution*
Dengan pembatasan dari pemberi kontribusi	-	-	-	*With restriction from contribution*
Jumlah Aset Neto	565.685.907	565.685.907	565.685.907	*Total Net Assets*
Jumlah Liabilitias dan Aset Bersih	1.152.959.850	1.152.959.850	1.152.959.850	***Total liabilities Assets Netto***
Pendapatan	1.902.569.187	1.902.569.187	1.902.569.187	***Revenues***
Beban	1.775.712.669	1.775.712.669	1.775.712.669	***Expense***
Kenaikan (Penurunan) Aset Neto Sebelum Pajak Penghasilan				***Increase (Decrease) In Net Assets Before Income Tax***
Kenaikan (Penurunan)	126.856.518	126.856.518	126.856.518	**Increase (Decrease) In**
Aset Bersih Awal Tahun	438.829.389	438.829.389	438.829.389	***Net Assets at the beginning of the year***
Aset Bersih Akhir tahun	565.685.907	565.685.907	565.685.907	***Net Assets at the end of this year***

(Expressed in Rupiah, unless otherwise stated)

4. KAS DAN SETARA KAS / *4. CASH AND CASH EQUIVALENT*

Terdiri atas: / *Consist of:*

	2020	2019	
Kas	5.000.400	5.000.400	*Cash*
Bank			*Bank*
PT Bank Central Asia Tbk	716.480.356	913.039.737	*PT Bank Central Asia Tbk*
Jumlah	721.480.756	918.040.137	*Total*

5. PIUTANG USAHA / *5. ACCOUNTS RECEIVABLE*

Terdiri atas: / Consist of:

	2020	2019	
Kontribusi	400.000.000	-	*Contibution*
Lain-lain	-	-	*Others*
Jumlah	400.000.000	-	*Total*

6. PAJAK DIBAYAR DIMUKA / *6. PREPAID TAX*

Terdiri atas: / Consist of:

	2020	2019	
PPh Pasal 21	-	8.474.561	*Income tax article 21*
Jumlah	**-**	8.474.561	*Total*

7. BIAYA DIBAYAR DIMUKA / *7. PREPAID EXPENSE*

Terdiri atas: / Consist of:

	2020	2019	
Biaya komunikasi	1.279.669	-	*Communication expense*
Tunjangan staff	1.796.500	-	*Staff Allowance*
Jumlah	3.076.169	**-**	Total

(Expressed in Rupiah, unless otherwise stated)

8. ASET TETAP / 8. *FIXED ASSETS*

2020 / *2020*

	Saldo Awal / *Begginning Balance*	Penambahan / *Additions*	Pengurangan / *Deductions*	Saldo Akhir / *Ending Balance*	
Harga perolehan					*Acquisition Cost*
Peralatan Kantor	294.595.193	3.001.900	-	297.597.093	*Office equipment*
	294.595.193	3.001.900	-	297.597.093	
Akumulasi Penyusutan					*Accumulated Depreciation*
Peralatan Kantor	255.405.988	13.788.180	-	269.194.168	*Office Equipment*
	255.405.988	13.788.180	-	269.194.168	
Nilai Buku	39.189.205			28.402.925	*Book Value*

2019 / *2019*

	Saldo Awal / *Begginning Balance*	Penambahan / *Additions*	Pengurangan / *Deductions*	Saldo Akhir / *Ending Balance*	
Harga perolehan					*Acquisition Cost*
Peralatan Kantor	264.835.067	29.760.126	-	294.595.193	*Office equipment*
	264.835.067	29.760.126	-	294.595.193	
Akumulasi Penyusutan					*Accumulated Depreciation*
Peralatan Kantor	227.585.180	27.820.808	-	255.405.988	*Office Equipment*
	227.585.180	27.820.808	-	255.405.988	
Nilai Buku	37.249.887			39.189.205	*Book Value*

Beban penyusutan pada 31 Desember 2020 sebesar Rp13.788.180 serta dicatat pada laporan penghasilan komprehensif (catatan 15).

Depreciation expense in December 31, 2020 is Rp13.788.180 and were recorded as statements of comprehensive income (notes 15).

Berdasarkan evaluasi yang dilakukan yayasan, tidak terdapat kejadian atau perubahan atas keadaan yang menununjukkan adanya penurunan nilai aset tetap pada tanggal 31 Desember 2020 dan 2019, sehingga tidak diperlukan adanya penyisihan penurunan nilai aset tetap.

Based on the evaluation carried out by the foundation, there were no events or changes to the circumstances that indicated a decrease in the value of fixed assets as of December 31, 2019 and 2020, so that no impairment in the value of fixed assets is needed.

(Expressed in Rupiah, unless otherwise stated)

9. PERPAJAKAN / 9. *TAXATION*

a. Utang Pajak / a. *Tax Payable*

	2020	2019	
PPh pasal 21	9.494.903	4.465.247	*Income tax article 21*
PPh pasal 23	21.094.496	13.467	*income tax article 23*
Jumlah	30.589.399	4.478.714	***total***

b. Beban Pajak / b. *Tax Expense*

	2020	2019	
Pajak kini	-	-	*Current tax*
Pajak tangguhan	-	-	*Deferred tax*
Jumlah	-	-	***Total***

c. Pajak kini / c. *Current tax*

	2020	2019	
Kenaikan (penurunan) aset bersih tidak terikat sebelum pajak	126.856.518	140.441.770	*Increase (decrease) in Unrestricted net assets income tax*
Perbedaan waktu	126.856.518	140.441.770	*Temporary differences*
Perbedaan tetap			*Permanent differences*
Beban yang tidak dapat diperhitungkan	2.838.113	23.050.800	*Non deductible expense*
Total beda tetap	2.838.113	23.050.800	*Total Permanent differences*
Estimasi laba (rugi) fiskal	129.694.631	163.492.570	*Estimated taxable income (loss)*

	2020	2019	
Rugi fiskal:			*Fiscal loss:*
2019	163.492.570	-	*2019*
2018	(1.394.695.492)	(1.394.695.492)	*2018*
2017	(1.053.490.639)	(1.053.490.639)	*2017*
2016	(2.573.851.465)	(2.573.851.465)	*2016*
Akumulasi rugi fiskal	(4.728.848.375)	(4.858.543.007)	*Accumulated fiscal loss*

d. Pajak Penghasilan / d. *Corporate Income taxes*

Penurunan bersih yang berasal dari sisa hasil aktivitas Yayasan tidak dikenakan pajak.

Decrease in net assets from the remaining result of the Foundation's activity is not taxable.

(Expressed in Rupiah, unless otherwise stated)

10. HUTANG USAHA / 10. *ACCOUNTS PAYABLE*

Terdiri dari: / *Consist of:*

	2020	2019	
Danone Institute Internasional	160.000.000	160.000.000	*Danone Institute Internasional*
PT Smailing Tour & Travel	-	4.828.650	*PT Smailing Tour & Travel*
PT Iron Mountain Indonesia	-	602.085	*PT Iron Mountain Indonesia*
DPLK Astra Aviva	-	2.369.250	*DPLK Astra Aviva*
Perhimpunan Nutrisi Indonesia	-	700.000	*Perhimpunan Nutrisi Indonesia*
Jasa Professional	-	11.000.000	*Professional fee*
PT Damai Abadi Karya Sentosa	-	500.000	*PT Damai Abadi Karya Sentosa*
PT Royal Express Indonesia	-	8.181	*PT Royal Express Indonesia*
Lain-lain	829.500	7.619.488	*Others*
Jumlah	160.829.500	187.627.654	*Total*

11. UTANG AKRUAL / 11 *ACCRUED LIABILITIES*

Terdiri atas : / *Consist of:*

	2020	2019	
Jasa professional	64.939.744	47.300.000	*Professional fee*
Membership fee	181.400.000	137.400.000	*Membership fee*
Lain-lain	-	602.085	*Others*
Jumlah	246.339.744	185.302.085	*Total*

12. LIABILITAS IMBALAN KERJA / 12. *EMPLOYEE BENEFIT LIABILITY*

Terdiri atas: / *Consist of:*

	2020	2019	
Saldo awal	140.991.500	134.974.700	*Beginning balance*
Cadangan tahun berjalan	8.523.800	6.016.800	*Provision for the year*
Jumlah	149.515.300	140.991.500	*Total*

Nilai liabilitas manfaat karyawan per 31 Desember 2020 dan 2019 dihitung berdasarkan asumsi:

Present value of employee benefit liabilities as of December 31, 2020 and 2019 were calculated based on the following assumptions:

	2020	2019	
Umur pensiun	55%	55%	*Retirement age*
Tingkat diskonto	8,25%	8,25%	*Discount rate*
Tingkat kenaikan gaji	8%	8%	*Salary incerment rate*

Pada tahun 2020 dan 2019, imbalan kerja dihitung berdasarkan UU No. 13 tahun 2003.

In 2020 dan 2019, employee benefit was calculated based on UU No. 13 Year 2003.

Biaya terkait dengan imbalan kerja diakui dalam biaya administrasi dan umum di dalam laporan perubahan aktivitas dan perubahan aset neto.

The expense related to employee benefit was presented under general and administration expense in the statement of activities and changes in unrestricted net assets.

(Expressed in Rupiah, unless otherwise stated)

13. PENDAPATAN / 13. *REVENUE*

Terdiri atas: / *Consist of:*

	2020	2019	
PT Tirta Investama	550.000.000	655.500.000	*PT Tirta Investama*
PT Sari Husada	1.075.000.000	511.500.000	*PT Sari Husada*
PT Nutricia Indonesia	275.000.000	268.000.000	*PT Nutricia Indonesia*
Sub total	1.900.000.000	1.435.000.000	*Sub Total*
Lain-lain	-	-	*Others*
Pendapatan bunga	2.569.187	3.921.845	*Interest Income*
Sub total	2.569.187	3.921.845	*Sub total*
Total	1.902.569.187	1.438.921.845	*Total*

Selama tahun 2020 dan 2019 sumber dana dari sumbangan umum dan kontribusi yang diterima merupakan sumbangan tidak terikat.

During the year 2020 and 2019 the source of fund from public and donor contribution represent unrestricted fund.

14. BEBAN OPERASI / 14 *OPERATING EXPENSES*

Terdiri atas: / *Consist of:*

	2020	2019	
Dana Bantuan			***Grant***
Dana penelitian -institusi	-	72.746.410	*Research grant-institution*
Dana penelitian-doktor	-	56.223.000	*Research grant-doctorate*
Hibah Publikasi	24.173.000	42.181.066	*Publication Grants*
Jasa professional	205.332.399	69.897.435	*Professional fee*
Biaya publikasi	303.633.430	7.581.230	*Publication cost*
Honorarium	347.468.939	129.538.461	*Honorarium*
Tunjangan PPh 21	-	-	*Tax art 21 allowance*
Perjalanan	16.794.900	30.286.890	*Traveling*
Material dan dokumentasi	-	13.841.250	*Material and documentation*
Sponsorship	-	6.000.000	*Sponsorship*
Akomodasi & Rapat	34.636.000	57.135.380	*Accomodation & Meeting*
Produksi dan promosi	-	-	*Production and promotion*
Lain-lain	-	-	*Others*
Total	932.038.668	485.431.122	*Total*

(Expressed in Rupiah, unless otherwise stated)

15. BEBAN UMUM DAN ADMINISTRASI / *15 GENERAL AND ADMINISTRATION EXPENSES*

Terdiri atas: / *Consist of:*

	2020	2019	
Gaji staff	314.866.178	253.166.659	*Staff salaries*
Honor ketua dan Wakil ketua	240.000.000	240.000.000	*Chairman & vice chairman honorarium*
Jasa professional dan konsultan	93.500.000	93.500.000	*Professional & consultant fee*
Tunjangan staff	61.365.004	50.521.999	*Staff allowance*
Penyusutan Kantor	13.788.180	27.820.808	*Depreciation office*
Tunjangan PPh 21	27.871.030	26.528.046	*Tax art 21 allowance*
Sewa	7.432.260	10.613.680	*Rent*
Rapat	6.120.929	12.103.146	*Meeting expense*
Perjalanan/transportasi lokal	12.524.935	11.061.960	*Travel/local transport*
Pelatihan karyawan	-	3.500.000	*Staff training*
Perlengkapan	781.500	3.697.500	*Stationary*
Komunikasi	6.056.042	4.835.511	*Communication*
Surat menyurat/pos/fotokopi	2.308.671	6.689.972	*Correspondence/mailing/photocopy*
Pemeliharaan	110.000	705.000	*Maintenance*
Lainnya	11.976.971	9.582.672	*Others*
Jumlah	798.701.701	754.326.953	*Total*

16. BEBAN LAIN-LAIN / *16 OTHER EXPENSE*

Terdiri atas: / Consist of:

	2020	2019	
Membership fee	44.000.000	57.400.000	*Membership fee*
Beban lainnya	972.300	1.322.000	*Other expenses*
Jumlah	44.972.300	58.722.000	*Total*

17. STANDAR AKUNTANSI KEUANGAN (SAK) BARU / *17. NEW FINANCIAL ACCOUNTING STANDARD (FAS)*

Standar akuntansi dan interpretasi yang telah disahkan oleh Dewan Standar Akuntansi Keuangan (DSAK), tetapi belum berlaku efektif untuk laporan keuangan tahun berjalan diungkapkan di bawah ini. Yayasan bermaksud untuk menerapkan standar tersebut, jika dipandang relevan, saat telah menjadi efektif.

The standards and interpretations that are issued by the Indonesian Financial Accounting Standards Board (DSAK), but not yet effective for current financial statements are disclosed below. The Foundation intends to adopt these standards, if applicable, when they become effective.

17. STANDAR AKUNTANSI KEUANGAN (SAK) BARU (Lanjutan)

- Amandemen PSAK 22: Definisi Bisnis, berlaku efektif 1 Januari 2021.

  Amandemen ini dikeluarkan untuk membantu entitas menentukan apakah serangkaian kegiatan dan aset yang diperoleh adalah bisnis atau tidak. Mereka mengklarifikasi persayaratan minimum untuk bisnis, menghapus penilaian apakah pelaku pasar mampu mengganti elemen yang hilang, menambah panduan untuk membantu entitas menilai apakah proses yang diperoleh adalah substantif, mempersempit definisi bisnis dan output, dan memperkenalkan uji konsentrasi nilai wajar opsional. Contoh ilustratif baru diberikan bersama dengan amandemen.

- PSAK No. 71: Instrumen Keuangan, yang diadopsi dari IFRS 9, berlaku efektif 1 Januari 2020 dengan penerapan dini diperkenankan.

  PSAK ini mengatur klasifikasi dan pengukuran instrumen keuangan berdasarkan karakteristik dari arus kas kontraktual dan model bisnis entitas; metode kerugian kredit ekspektasian untuk penurunan nilai yang menghasilkan informasi yang lebih tepat waktu, relevan dan dimengerti oleh pemakai laporan keuangan; akuntansi untuk lindung nilai yang merefleksikan manajemen risiko entitas lebih baik dengan memperkenalkan persyaratan yang lebih umum berdasarkan pertimbangan manajemen.

- PSAK No. 72: Pendapatan dari Kontrak dengan Pelanggan, yang diadopsi dari IFRS 15, berlaku efektif 1 Januari 2020 dengan penerapan dini diperkenankan.

  PSAK ini adalah standar tunggal untuk pengakuan pendapatan yang merupakan hasil dari joint project yang sukses antara International Accounting Standards Board (IASB) dan Financial Accounting Standards Board (FASB), mengatur model pengakuan pendapatan dari kontrak dengan pelanggan, sehingga entitas diharapkan dapat melakukan analisis sebelum mengakui pendapatan.

  Standar akuntansi dan interpretasi yang telah disahkan oleh Dewan Standar Akuntansi Keuangan (DSAK), tetapi belum berlaku efektif untuk laporan keuangan periode berjalan diungkapkan di bawah ini. Grup bermaksud untuk menerapkan standar tersebut, jika dipandang relevan, saat telah menjadi efektif.

17 *NEW FINANCIAL ACCOUNTING STANDARD (FAS) (Continued)*

- *Amendments to PSAK 22: Definition of Business, effective from 1 January 2021.*

  This amendments were issued to help entities determine whether an acquired set of activities and assets is a business or not. They clarify the minimum requirements for a business, remove the assessment of whether market participants are capable of replacing any missing elements, add guidance to help entities assess whether an acquired process is substantive, narrow the definitions of a business and of outputs, and introduce an optional fair value concentration test. New illustrative examples were provided along with the amendments.

- *PSAK No. 71: Financial Instruments, adopted from IFRS 9, effective January 1, 2020 with earlier application is permitted.*

  This PSAK provides for classification and measurement of financial instruments based on the characteristics of contractual cash flows and business model of the entity; expected credit loss impairment model that resulting information more timely, relevant and understandable to users of financial statements; accounting for hedging that reflect the entity's risk management better by introduce a more general requirements based on management's judgment.

- *PSAK No. 72: Revenue from Contracts with Customers, adopted from IFRS 15, effective January 1, 2020 where earlier application is permitted.*

  This PSAK is a single standard that a joint project between the International Accounting Standards Board (IASB) and the Financial Accounting Standards Board (FASB), provides revenue recognition from contracts with customers, and the entity is expected to have analyzed before recognizing the revenue.

  The standards and interpretations that are issued by the Indonesian Financial Accounting Standards Board (DSAK), but not yet effective for current financial statements are disclosed below. The Group intends to adopt these standards, if applicable, when they become effective.

17. STANDAR AKUNTANSI KEUANGAN (SAK) BARU (Lanjutan)

- PSAK No. 73: Sewa, yang diadopsi dari IFRS 16, berlaku efektif 1 Januari 2020 dengan penerapan dini diperkenankan untuk entitas yang juga telah menerapkan PSAK No. 72: Pendapatan dari Kontrak dengan Pelanggan.

  PSAK ini menetapkan prinsip pengakuan pengukuran, penyajian, dan pengungkapan atas sewa dengan memperkenalkan model akuntansi tunggal dengan mensyaratkan untuk mengakui aset hak-guna (right-of-use assets) dan liabilitas sewa. Terdapat dua (2) pengecualian opsional dalam pengakuan aset dan liabilitas sewa, yakni untuk: (i) sewa jangka-pendek dan (ii) sewa yang aset pendasarnya (underlying assets) bernilai-rendah.

- ISAK No. 35: Penyajian laporan keuangan, berlaku efektif 1 Januari 2020 dengan penerapan dini diperkenankan.

  Interpretasi ini mengatur penyajian laporan keuangan untuk entitas yang tidak berorientasi laba.

  Yayasan sedang mengevaluasi dampak dari standar akuntansi tersebut dan belum menentukan dampaknya terhadap laporan keuangan.

17 NEW FINANCIAL ACCOUNTING STANDARD (FAS) (Continued)

- *PSAK No. 73: Leases, adopted from IFRS 16, effective January 1, 2020 with earlier application is permitted, but not before an entity applies PSAK No. 72: Revenue from Contracts with Customers.*

  This PSAK establish the principles of recognition, measurement, presentation, and disclosure of the lease by introducing a single accounting model, with the requirement to recognize the right-of-use assets and liability of the lease; there are two (2) optional exclusions in the recognition of the lease assets and liabilities: (i) short-term lease and (ii) lease with low-value underlying assets.

- *ISAK No. 35: Presentation of financial statements, effective January 1, 2020 with earlier application is permitted.*

  This interpretation regulates the presentation of financial statements for not-for-profit oriented entities.

  The Foundation is presently evaluating and has not yet determined the effects of accounting standards on its financial statements.

18. PERISTIWA SETELAH PERIODE PELAPORAN

Penyebaran virus Covid-19
Operasi Yayasan telah dan mungkin terus dipengaruhi oleh penyebaran virus Covid-19 yang kemudian menyebar ke negara-negara lain termasuk Indonesia. Efek virus Covid-19 terhadap ekonomi global dan Indonesia termasuk efek terhadap pertumbuhan ekonomi, penurunan pasar modal, peningkatan risiko kredit, depresiasi nilai tukar mata uang asing dan gangguan operasi bisnis.

Efek masa depan dari virus Covid-19 terhadap Indonesia dan Yayasan masih belum dapat ditentukan saat ini. Peningkatan jumlah infeksi Covid-19 yang signifikan atau penyebaran yang berkepanjangan dapat mempengaruhi Indonesia.

Sampai dengan tanggal penyelesaian laporan keuangan ini, telah terjadi penurunan nilai tukar mata uang Rupiah terhadap mata uang asing yang sebagian disebabkan oleh dampak virus Covid-19.

18. EVENTS AFTER THE REPORTING PERIOD

The outbreak of Covid-19
The Foundation operation has and may continue to be impacted by the outbreak of Covid-19 virus which subsequently spread to other countries including Indonesia. The effects of Covid-19 virus to the global and Indonesian economy include effect to economic growth, decline in capital markets, increase in credit risk, depreciation of foreign currency exchange rates and disruption of business operation.

The future effects of the outbreak of Covid-19 virus to Indonesia and the Foundation are unclear at this time. A significant rise in the number of Covid-19 virus infections or prolongation of the outbreak may affect Indonesia.

As of the date of completion of these financial statements, there has been decline in the Rupiah foreign currency exchange rates which partially due to impact of Covid-19 virus.

19. PERSETUJUAN LAPORAN KEUANGAN

Pengurus bertanggung jawab sepenuhnya terhadap penyusunan dan penyajian laporan keuangan. Laporan keuangan telah di setujui untuk diterbitkan oleh pengurus pada tanggal 29 Januari 2021.

19. COMPLETION OF FINANCIAL STATEMENTS

The management is responsible for the preparation and presentation of financial statements. The financial statements has been authorized for issuance by the management on January 29, 2021.