Anaemia and its relation to physical and mental health of Indonesian adolescents

Muhammad Asrullah

PROPOSITIONS

1. Mental health is a potential contributing factor to anaemia in adolescents.
   (this thesis)

2. The occurrence of mental health problems among adolescents in households with higher socioeconomic status requires a redesign of preventive interventions.
   (this thesis)

3. Health interventions will benefit from better use of existing data by policy makers.

4. Data tell unexpected stories louder than words.

5. Doing fieldwork during the COVID-19 pandemic deserves extra credits for the TSP.

6. An international marriage during the final PhD year is taking stress relief to the next level.

Propositions belonging to the thesis, entitled

Anaemia and its relation to physical and mental health of Indonesian adolescents

Muhammad Asrullah
Wageningen, 9 May 2023

Anaemia and its relation to physical and mental health of Indonesian adolescents

Muhammad Asrullah

Thesis Committee

Promotor
Prof. Dr Edith JM Feskens
Professor of Global Nutrition
Wageningen University & Research

Co-Promotor
Dr Alida Melse-Boonstra
Associate Professor, Division of Human Nutrition and Health
Wageningen University & Research

Dr Monique L'Hoir
Senior Researcher, Division of Human Nutrition and Health
Wageningen University & Research

Other Members
Dr Robert Sparrow, Wageningen University & Research
Dr Elvina Karyadi, The World Bank, Jakarta, Indonesia
Dr Erik Giltay, Leiden University Medical Centre
Dr Eva Corpeleijn, University Medical Centre Groningen

This research was conducted under the auspices of VLAG Graduate School (Biobased, Biomolecular, Chemical, Food, and Nutrition sciences)

Anaemia and its relation to physical and mental health of Indonesian adolescents

Muhammad Asrullah

Thesis

Submitted in fulfilment of the requirements for the degree of doctor
at Wageningen University,
by the authority of the Rector Magnificus,
Prof. Dr A.P.J. Mol,
in the presence of the
Thesis Committee appointed by the Academic Board
to be defended in public
on Tuesday 9 May 2023
at 1.30 p.m. in the Omnia Auditorium

Muhammad Asrullah
Anaemia and its relation to physical and mental health of Indonesian adolescents
Pages 170
PhD thesis, Wageningen University, Wageningen, NL (2023)
With references, with summary in English

ISBN: 978-94-6447-576-0
DOI: https://doi.org/10.18174/586155

Adolescence is always a comma, not a full stop

TABLE OF CONTENTS

Chapter 1

General Introduction

For long, research and policy on adolescent nutrition has been neglected globally. This thesis is part of the Ten2Twenty project, which started in 2015. The project aims to improve understanding of the interactions and interrelationships between nutritional, psychosocial, and economic trajectories in order to optimize adolescent nutrition for better health, pregnancy, and birth outcomes. Apart from Indonesia, the overall project is conducted in a range of low- and middle-income countries such as Mexico [1], Nepal [2], Ghana [3], Philippines, Malawi, Bangladesh [4], Ethiopia, and Vietnam. Adolescence is viewed as a so-called 'second window of opportunity', a period during the life span that can have great impact on health at later age. However, many knowledge gaps in adolescent nutrition have been identified, and hence the Ten2Twenty project was initiated. This chapter provides an overview of adolescent health and nutrition globally, and then explores the Indonesian context specifically. The chapter ends with the rationale and aims of this thesis.

ADOLESCENCE: PHYSICAL, SOCIAL, AND PSYCHOLOGICAL CHANGES

About 1.3 billion people around the world are adolescents, defined by WHO as persons aged 10 to 19 years old [5]. Adolescence is a period of rapid physical growth, and of cognitive and socio-emotional development, also known as puberty [6]. While the age at which people become socially mature rises, the age at which puberty begins is gradually declining [6,7]. The most noticeable changes during puberty are those that affect the body such as growth in height, muscle mass gain, body fat distribution, and the emergence of secondary sexual traits such as breast development in girls, increase in the size of penis and testicles in boys, and appearance of pubic hair in boys and girls. Another physical change in puberty is continued brain development that affects complex behaviour and social skills, including self-control and decision making.

As a consequence of physical maturation, adolescents may feel social pressure to become acknowledged as well-adjusted adults in their society [8]. Some of the significant psychosocial changes in adolescents are the development of personal and sexual identity, the emergence of abstract thinking, and an increased capacity for social life [9]. With regard to personal identity, for instance, adolescents generally have trouble answering the question "*Who am I?*". This includes inquiries on their physical characteristics, vocations and career goals, relationships, sexuality, social beliefs, personality, and interests [10]. The transitional changes also critically depend on social structure such as norms and culture in the community [7,11]. For example, the physical onset of puberty has been found to occur earlier in some ethnic groups [12], among those with a lower economic status, and those living in urban areas [13]. Circumstances and limited access to resources may expose less privileged adolescents to stressors, and trigger them to take excessive risks, which will have a negative impact on adolescents' life-course trajectories [6]. Furthermore, adolescents in the modern society experience an increasing amount of insecurity related to income disparities, unstable families, loss of social coherence, violence, pressure from social media, conflict, climate change, forced displacement and migration [14].

The developmental stage of puberty, particularly early puberty, has been linked to a wide range of psychopathological symptoms during adolescence for both boys and girls [15]. In boys maturing early, lower self-esteem and higher incidence of tobacco use were found [16], while in girls with early menarche a higher occurrence of depressive disorders and eating disorders was reported [17]. Adolescents are at increased risk for psychological problems due to a variety of social and cultural factors that are greatly influenced by interactions with their peers, connections to their school and other community organizations, and ties with their parents [18].

NUTRITIONAL DEMANDS DURING ADOLESCENCE

Good nutrition during adolescence is essential to meet the demands of physical and cognitive growth and development, provide adequate energy stores during illnesses and pregnancy, and to prevent the development of diseases related to nutrition in adulthood [19]. Moreover, good nutrition during adolescence may support the catch-up from nutritional deficiencies experienced during childhood. Due to physical and nutrition demands, adolescents' metabolism, determined by basal metabolic rate (BMR), energy cost of growth (ECG), and Activity Energy Expenditure (AEE), is directly related to total energy requirements and indirectly to growth spurt [20]. The need of energy requirements for boys is higher than girls, but for requirements of nutrients this is not necessarily so. For instance, there is a difference in the iron requirement for girls compared to boys of the same age. The reason for sex discrepancies in nutrient requirements after the age of 10 are earlier puberty in girls and physiological needs for some specific nutrients [21]. Iron is needed for myoglobin in muscles, and haemoglobin in blood increases due to the rapid growth that occurs during adolescence, including the sharp rise in lean body mass, blood volume, and red cell mass. Especially for girls, overall iron requirements increase from a pre-adolescent level of ~0.7– 0.9 mg Fe/day to as much as 2.2 mg Fe/day and are probably even higher in adolescents with heavy menstruation [22]. Overconsumption of total calories can cause overweight and obesity, but if total calories are dropped to below BMR, ECG and AEE will cause growth retardation, pubertal delay, aberrant menstrual cycles in females, and interference with bone mass accumulation [23].

Recently, adolescent obesity has become more prevalent globally, which is explained by widespread dietary shifts toward energy-rich diets and a decline in physical activity [24]. The tendency to consume higher total fat, saturated fat, cholesterol, sodium, and sugar has become part of adolescents' lifestyle [25]. Furthermore, nutritional studies revealed that many youngsters consumed insufficient amounts of vitamins and minerals, with girls being more likely than boys to fall into this category [26]. A variety of factors, such as peer pressure, parental modelling, food availability, dietary preferences, pricing, convenience, personal and cultural values, mass media, and body image, have an impact on eating patterns and behaviour [27,28]. These factors can be broadly divided into two categories: *personal variables*, such as attitudes, beliefs, food preferences, self-efficacy, and biological changes; and *environmental influences*, such as peer networks, family, and friends [25]. The rapid growth that adolescents undergo in terms of physical changes, combined with increased loss of nutrients (such as loss of iron through menstrual blood among girls), make adolescents susceptible to nutritional deficiencies [21]. Therefore, adequate dietary intake is crucial reach their full growth potential.

ADOLESCENCE IS A VULNERABLE PHASE OF LIFE FOR PHYSICAL AND MENTAL HEALTH

Anaemia

For many years, anaemia has been recognized as a major health problem in low- and middle-income countries (LMICs). WHO (2011) estimated that 27% of adolescents in developing countries were anaemic [29]. A more recent publication showed that the numbers of anaemia cases in 10-24 year old youngsters rose from approximately 202.6 million in 1990 to 243.3 million in 2016 for women, and from 153.9 to 187.3 million for men [30]. Anaemia in adolescents affects their health [31], physical and mental development, and work and study performance [21,32–35]. Adolescent anaemia is associated with and caused by several factors such as sex, age, inadequate intake or absorption of iron and other nutrients, increased iron loss during menstruation, increased iron requirement during pregnancy, infectious diseases (e.g., malaria), and genetics [36–38]. Adolescent boys and girls have a high risk of anaemia because of the increase in blood volume related to their growth spurt, and specifically for girls the onset of menstruation [39]. Depending on when it occurs, how severe it is, and how long it lasts, anaemia can have a variety of effects, from persistent fatigue to a higher chance of mortality due to e.g. infections [40].

Early puberty and the risk of overweight and obesity

Age at menarche is often used to determine a girls' physical maturity level, while for boys' features such as facial hair and voice break are being used. Puberty in girls begins between 8 to 13 years of age, while in boys it starts between 10 to 14 years of age [41,42]. Factors associated with timing of puberty comprise genetics, nutritional status [43–47], ethnicity and environmental factors [48]. A longitudinal study published in 2020 comprising 14,545 U.S youngsters showed that earlier pubertal timing in both girls and boys was associated with a higher body-mass index (BMI), more screen time, and less sleep, while later timing of puberty showed the opposite [49]. Worldwide, the prevalence of overweight and obesity in boys and girls aged 10 to 24 years has increased by 120% from approximately 147.3 million in 1990 to 324 million in 2016, with a higher increase in girls compared to boys [30]. Overweight and obese teenagers are more likely to develop long-term health conditions such as type II diabetes, cardiovascular disease, and certain types of cancer. Specifically in girls, overweight is related to complications in pregnancy, such as gestational diabetes and pre-eclampsia, high birth weight, and features of the metabolic syndrome in later life of their offspring [50]. Data from a large population cohort study in the US indicated that an increase of one BMI unit before 5 years of age was associated with earlier puberty of 0.11 years on average in 7,495 boys and girls [51]. In contrast, a smaller long-term cohort study among 215 German boys, of which the first one was examined at 3 months old and the last one followed until the age of 23 years, did not identify an association between childhood BMI, timing of puberty and later BMI [42].

Early puberty has been shown to cause higher risk for adult diseases such as diabetes, heart diseases, obesity and breast cancer [52–54]. Pubertal timing has also been identified as a risk factor for early initiation of first sexual activity, pregnancy, and having a poor body image [55]. Adolescent girls experiencing early menarche were found to have more frequent intercourse, more sexual partners, and to use contraception less often [56]. As such, timing of onset of puberty can also predict the outcomes of pregnancy, because early maturing girls are more likely to be sexually active, which increases their risk of adolescent pregnancy [57], and adolescent mothers are more likely to have eclampsia, puerperal endometritis, and systemic infections than women in their 20s and 30s [58]. Their offspring is also more likely to have low birth weight, to be delivered preterm, and to have a serious neonatal condition [59]. For boys, health and behavioural consequences of pubertal timing are far less well studied. For a large part, this is due to the lack of a distinct, quantifiable pubertal event (like menarche in girls) that can be accurately and retrospectively documented in epidemiological studies.

Cognitive development

Adolescence is a period of distinctive neurocognitive growth. A previous large longitudinal study showed that a basic reorganization of the brain occurs during adolescence [60]. An imbalance between the more mature subcortical areas and less mature prefrontal areas occurs during adolescent age and may account for typical adolescent behaviour patterns, including risk-taking [61]. Pubertal status was found to be a crucial factor, as the hormonal differences affect the sex-specific restructuring of the adolescent brain. For instance, girls may be more sensitive to stress because of oestrogen, while androgens make boys more resilient to it [62]. Furthermore, the following types of factors can have an impact on cognitive development during childhood and adolescence: biologic factors, for instance maternal and infant nutrition, infectious illnesses, and birth weight [63]; socioeconomic factors, such as parental income and education [64]; contextual factors, including the family environment, the availability of appropriate toys and developmental materials, and access to healthcare [53]; and psychosocial factors including opportunities for learning and parent-child interactions [65]; and, finally, parental mental health [66].

Mental health

Mental health disorders have a high prevalence globally, especially in LMICs [67]. Worldwide, adolescents carry a significant disease burden due to mental health issues, with one out of seven adolescents estimated to be affected in 2019 [68]. During adolescence the prevalence of mental health disorders is generally higher in girls than in boys [69]. Poor mental health during adolescence is a predictor of several risky behaviors, such as self-harm, use of cigarettes, alcohol, and other drugs, risky sexual behavior, and violence [70], of which the repercussions can last over the course of a person's life. Moreover, one of the top three leading causes of death among adolescents is suicide [71]. The COVID-19 pandemic has generally worsened the mental health situation of youngsters globally [72].

As the world community works to achieve the Sustainable Development Goals (SDGs) by 2030, particularly SDG 3: “Ensure healthy lives and promote well-being for all at all ages”, the need to focus on adolescents' mental health is becoming more and more evident [73]. In order to meet the SDG targets, it is essential to address the major determinants of adolescents' health including their mental health.

ZOOMING IN ON ADOLESCENT NUTRITION AND HEALTH IN INDONESIA

Indonesia has a population of 45 million adolescents, which makes up 4% of the global adolescent population [74]. Anaemia is one of the major public health problems among Indonesian adolescents. The prevalence of anaemia was 26.4% and 32% among age groups 5-14 years and 15-24 years respectively, based on the Indonesian National Health Survey (or Riskesdas: *Riset Kesehatan Dasar*) in 2018 [75], which was higher than in 2013, 29.4% among 5-12 years old and 17.9% among 13-18 years [76]. In the same time period, the prevalence of adolescents with obesity increased from 10.8% to 16.0% among 13–15-year-olds, and from 7.3% to 13.5% among 16–18-year-olds [75]. The data showed that the prevalence of obesity was higher in girls (15.9%) than in boys (11.3%) [75]. Gender-specific risks may be involved: obese adolescent boys were found more likely to have a sedentary lifestyle and lower levels of education, whereas obese girls were more likely to have a depression, to be married, and to have high fat intake [77]. Daily meal frequency (3 times or more) was found to be associated with higher odds of developing anaemia compared to fewer eating occasions [78]. Regarding mental health, the prevalence of depression among all age groups in Indonesia was found to be 6.1%, and that of mental health disorders was 9.1% [75]. The percentages of depression and mental health disorders among 15-24 year-olds were higher than the national prevalence among all age groups [75].

A recent publication in Indonesia highlighted the lack of information on drivers and determinants of the triple burden of malnutrition [79]. In addition, a call was made to use national and disaggregated data to investigate associations and time trends in adolescent nutrition and health outcomes, and to conduct in-depth research to identify vulnerable groups in order to support the development and implementation of effective integrated nutrition and health programs for Indonesian adolescents [80].

PROBLEM STATEMENT

Anaemia is a persistent public health problem in Indonesia, that threatens the long-term health status of adolescents. Understanding the context-specific causes of anaemia, such as timing of puberty, will help to identify vulnerable population groups for interventions.

Intra-uterine maternal anaemia to adolescents' cognitive function

Previous studies showed that children and adolescents who were anaemic during prenatal life or infancy tend to have delayed a mental and motor development [81–83]. However, there are only few studies that investigated the consequences of exposure to intrauterine maternal anaemia for cognitive function with long-term follow-up into adolescence and adulthood [84,85]. Knowing the long-term implications of maternal anaemia will help to explain and tackle inequalities between population groups in Indonesia.

Anaemia and mental health

Depression has been identified as a marker of anaemia [86]. Iron, folic acid and vitamin B12 have crucial roles in normal formation of red blood cells resulting in anaemia due to ineffective erythropoiesis when they fall short [87]. The same nutrients are also known to be involved in processes affecting mental disorders [88–90]. A study showed that iron and folic acid supplementation may help to prevent mental disorders by providing proper folate and iron for the brain [88]. In other studies, it has been shown that vitamin B12 deficiency increased depressive symptoms in patients [89,90]. During puberty, requirements for energy, protein, and other nutrients markedly increase, including iron, folic acid, and vitamin B12 [91]. So far, however, there is limited evidence on the role of anaemia in the development of mental health disorders in adolescents, specifically regarding the direction of the association between the two conditions. Research on this topic is important to build the evidence-base for health programming, both targeting anaemia as well as mental health disorders.

Pubertal development and mental health

Previous studies have indicated that a strong association exists between early menarche and increased risk of depression and mental health problems in adolescents worldwide [92–97]. Onset of menstruation can be a shocking event for girls, and may trigger anxiety and negative feelings, both because of the physical manifestation itself as well as by increased sex steroid circulation [98]. Experiencing physical changes earlier than peers can give rise to a negative attitude for both boys and girls [99,100], can make them feel sick and moody, and may also hamper their school performance [101,102]. Girls who mature early were found to be more worried about their periods, and this was correlated with depressive symptoms, lower body satisfaction, lower self-esteem, a more external locus of control, and anxiety [103]. In Indonesia, the prevalence of depression and mental health problems among 15-24 year-olds is higher than in other age groups [75].

Because depressive symptoms are more common in girls with early menarche, and because pubertal development is accelerating worldwide, it is important to better understand the association between Age at Menarche (AAM), depression, and mental health in the Indonesian context. Better understanding of the prevalence of early puberty and how this is perceived by adolescents, as well as its longitudinal effect on mental health, would facilitate better design of interventions for effective prevention, and assessment of whether, when, and on what processes to intervene.

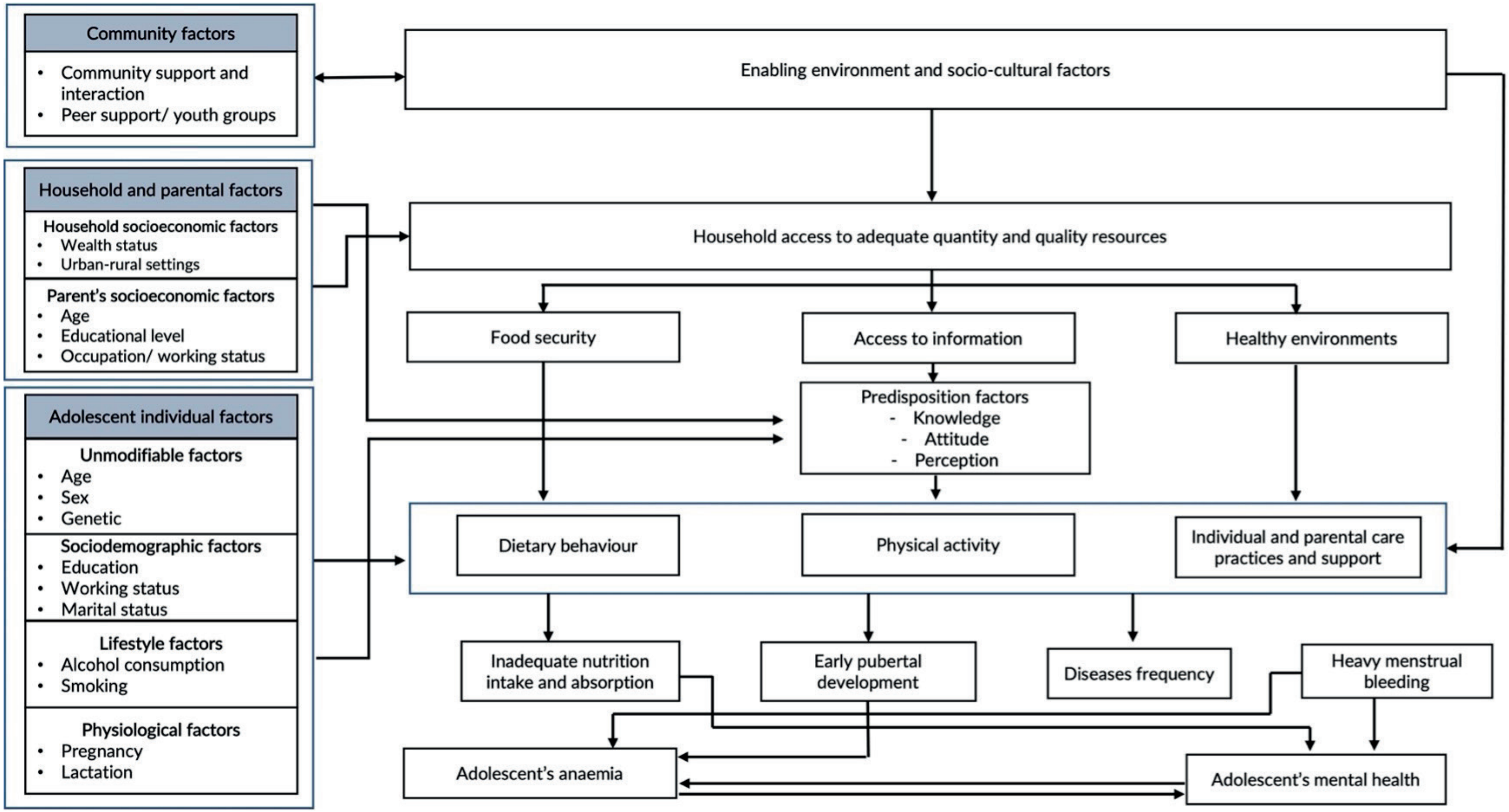


Figure 1.1. Conceptual model of the relationship between pubertal development, anaemia and mental health in adolescents, adapted from frameworks published by Unicef (2017) [104], Madjian *et al*. (2018) [105], and van Zutphen *et al.* (2021) [106]

STUDY AIMS

The aim of the research described in this thesis was to better understand the connections between pubertal development, anaemia, and nutritional status in relation to physical, mental, and cognitive health of Indonesian adolescents. The specific objectives were:

1. To identify the time trend of AAM and its association with obesity and NCD among women from diverse socio-economic groups, living areas, and regions in Indonesia;
2. To evaluate the relationship between intra-uterine maternal Hb concentration and cognitive function of their offspring at adolescent age;
3. To assess associations between pubertal development, anaemia, and mental health outcomes.

THESIS OUTLINE

This thesis consists of two methodological approaches: secondary analysis of nationally representative data (Chapters 2, 3, and 4), and analysis of primary collected data (Chapter 5). After this introductory **chapter 1**, in **chapter 2**, the time trend of AAM and its association with BMI and Non-Communicable Disease (NCD) prevalence at later age was analysed using data of 15,744 women aged 15-65 years from 5 waves of the Indonesian Family Life Survey (IFLS) conducted in the period 1993 to 2015. In **chapter 3**, the association between intra-uterine maternal hemoglobin (Hb) concentration and cognitive function of their adolescent offspring aged 10-14 years old was investigated using longitudinal cohort data of 363 paired pregnant mothers and their offspring at 10-14 years of age from the Indonesian Family Life Survey (IFLS) conducted in 1997-2014. In **chapter 4**, the association between AAM, haemoglobin concentration and other determinants of Common Mental Disorders (CMD) was investigated based on data of 1,052 adolescent girls aged 15-19 years old from the Indonesian Basic Health Survey 2018. For **chapter 5**, baseline (2021) and follow-up (2022) data of 452 adolescents (boys and girls) aged 10 to 19 years old were collected across all subdistricts in Gunungkidul district, Yogyakarta province, Indonesia. These data were analysed to determine the association between haemoglobin concentrations, sleep quality, and depressive symptoms. Lastly, **chapter 6** provides the summary, synthesis, and discussion of all main findings from chapters 2-5.

STUDY SETTING

For the work described in **Chapter 5,** a survey has been conducted in the district of Gunungkidul in Yogyakarta Province, which has a high prevalence of anaemia (23%) and mental health problems (18.4%). The total population in Yogyakarta is 3.6 million, of which 14.5% consists of adolescents aged 10-19 years. The survey was conducted in 9 subdistricts and 18 villages in Gunungkidul district. A structured manual mapping strategy was employed to produce valid data by visiting households with adolescents and listing a total of 9,942 adolescents to select from. Due to the COVID-19 pandemic, the baseline study had to be postponed by about one year from 2020 to 2021. During the pandemic, we successfully conducted the interviews with all participants while respecting and applying all local health protocols. The data collection manual and protocol were developed by Wageningen University and Research (WUR) and the Centre for Health Policy and Management (CHPM) and approved by the Ethical Committee of the Universitas Gadjah Mada, Indonesia. The follow-up study was conducted in 2022, one year after the baseline study. Fourteen data collectors were involved in this study, and the same data collectors were recruited for the follow-up study. Data collectors were hired based on their academic background in health, and their willingness to stay in the study area during the periods of data collection. Data collectors were trained online and off-line before each round of data collection in Yogyakarta for two days. The training manual included explanations of all study questions, data collection protocols, and procedures.

Regarding data quality and data validation, we randomly re-visited several respondents in each village. Questions were asked to respondents and head of villages, to validate both the interview process, listing, and the mapping methods by the data collectors. To minimize interview bias, adolescents were interviewed by the same data collectors during baseline and follow-up. During data collection we used two web-based apps, *LimeSurvey* (LimeSurvey GmbH), for data verification and quality processes. If a problem was encountered either online or offline, the data collectors used a paper-based questionnaire.

We collected, amongst others, the following data from respondents through structured questionnaires: demographics; socioeconomic variables; ethnicity and culture; disease history; mental health and well-being; pubertal development; physical activity; disabilities/ injury; characteristics of menstruation; anthropometry; and haemoglobin concentration.

1

a)

b)

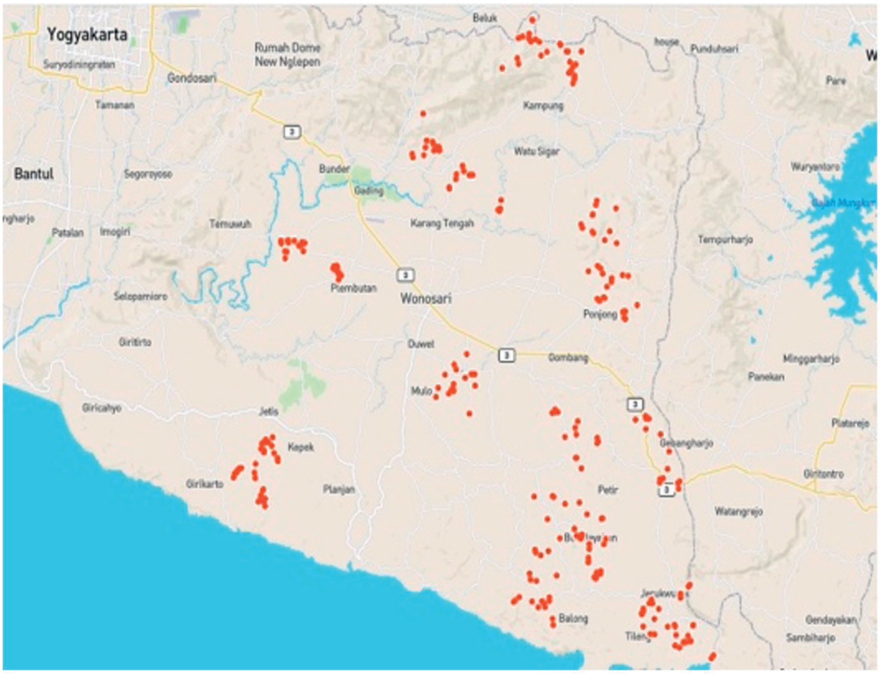


Figure 1.2. a) Map of Gunugkidul district in DI Yogyakarta province; b) Map of the geographic distribution of adolescents across villages selected for the study described in Chapter 5

REFERENCES

[1] Zárate-Ortiz AG, Melse-Boonstra A, Rodríguez-Ramírez S, Hernández-Cordero S, Feskens EJM. Dietary patterns and the double burden of malnutrition in mexican adolescents: Results from ENSANUT-2006. Nutrients 2019;11. https://doi.org/10.3390/nu11112753.

[2] Madjdian DS, Talsma EF, Vaandrager L, Gupta A Sen, van de Geest JMJ, Koelen M, et al. Nourishing Hope? Changes in Malnutrition and Changes in Girls' Aspirations—Evidence From the Suaahara II Adolescent Girls Panel in Nepal. J Adolesc Heal 2022;70:617–24. https://doi.org/10.1016/j.jadohealth.2021.10.029.

[3] Azupogo F, Abizari AR, Aurino E, Gelli A, Osendarp SJM, Bras H, et al. Trends and factors associated with the nutritional status of adolescent girls in Ghana: a secondary analysis of the 2003-2014 Ghana demographic and health survey (GDHS) data. Public Health Nutr 2022;25:1912–27. https://doi.org/10.1017/S1368980021003827.

[4] Akter MS, Talsma EF, Feskens EJM, Thilsted SH, Rasheed S. How did the COVID-19 pandemic affect food environment, food purchase, and fish consumption among low-income urban households in Bangladesh—A path analysis. Front Public Heal 2022;10. https://doi.org/10.3389/fpubh.2022.994236.

[5] World Health Organization (WHO). Global Accelerated Action for the Health of Adolescents (AA-HA!). Geneva World Heal Organ 2017.

[6] National Academies of Sciences, Engineering and M. The Promise of Adolescence: Realizing Opportunity for All Youth. Washington, DC: The National Academies Press; 2019. https://doi.org/10.17226/25388.

[7] Gluckman PD, Hanson MA. Evolution, development and timing of puberty. Trends Endocrinol Metab 2006;17:7–12. https://doi.org/10.1016/j.tem.2005.11.006.

[8] Blakemore SJ. Development of the social brain during adolescence. Q J Exp Psychol 2008;61:40–9. https://doi.org/10.1080/17470210701508715.

[9] Remschmidt H. Psychosocial milestones in normal puberty and adolescence. Horm Res 1994;41 Suppl 2:19–29. https://doi.org/10.1159/000183955.

[10] Marcia JE. Handbook of Stressful Transitions Across the Lifespan. Handb Stress Transitions Across Lifesp 2010:19–34. https://doi.org/10.1007/978-1-4419-0748-6.

[11] Gladwin TE, Figner B, Crone EA, Wiers RW. Addiction, adolescence, and the integration of control and motivation. Dev Cogn Neurosci 2011;1:364–76. https://doi.org/10.1016/j.dcn.2011.06.008.

[12] Euling SY, Selevan SG, Pescovitz OH, Skakkebaek NE. Role of Environmental Factors in the Timing of Puberty. Pediatrics 2008;121:S167–71. https://doi.org/10.1542/peds.2007-1813c.

[13] Hariadi Edi Saputra, Hakimi, Melda Deliana, Siska Mayasari Lubis KSA. Puberty onset in rural and urban children. Paediatr Indones 2011;51:207–12. https://doi.org/10.14238/pi.

[14] Lassi ZS, Salam RA, Bhutta ZA. Recommendations on Arresting Global Health Challenges Facing Adolescents and Young Adults. Ann Glob Heal 2017;83:704–12. https://doi.org/10.1016/j.aogh.2017.10.027.

[15] Negriff S, Susman EJ. Pubertal Timing, Depression, and Externalizing Problems: A Framework, Review, and Examination of Gender Differences. J Res Adolesc 2011;21:717–46. https://doi.org/https://doi.org/10.1111/j.1532-7795.2010.00708.x.

[16] Graber JA, Seeley JR, Brooks-Gunn J, Lewinsohn PM. Is pubertal timing associated with psychopathology in young adulthood? J Am Acad Child Adolesc Psychiatry 2004;43:718–26. https://doi.org/10.1097/01.chi.0000120022.14101.11.

[17] Copeland W, Shanahan L, Miller S, Costello EJ, Angold A, Maughan B. Outcomes of early pubertal timing in young women: A prospective population-based study. Am J Psychiatry 2010;167:1218–25. https://doi.org/10.1176/appi.ajp.2010.09081190.
[18] Oldfield J, Humphrey N, Hebron J. The role of parental and peer attachment relationships and school connectedness in predicting adolescent mental health outcomes. Child Adolesc Ment Health 2016;21:21–9. https://doi.org/10.1111/camh.12108.
[19] Asia WHORO for S-E. Adolescent nutrition: a review of the situation in selected South-East Asian Countries. New Delhi PP - New Delhi: WHO Regional Office for South-East Asia; 2006.
[20] Das JK, Salam RA, Thornburg KL, Prentice AM, Campisi S, Lassi ZS, et al. Nutrition in adolescents: physiology, metabolism, and nutritional needs. Ann N Y Acad Sci 2017;1393:21–33. https://doi.org/10.1111/nyas.13330.
[21] Haider R. Adolescent nutrition: A Review of the Situation in Selected South-East Asian Countries 2006:96. https://doi.org/10.1371/journal.pone.0091738.
[22] Beard JL. Symposium : Improving Adolescent Iron Status before Childbearing Iron Requirements in Adolescent Females. J Nutr 2000;22:440–2.
[23] Spear BA. Adolescent growth and development. J Am Diet Assoc 2002;102. https://doi.org/10.1016/s0002-8223(02)90418-9.
[24] Kansra AR, Lakkunarajah S, Jay MS. Childhood and Adolescent Obesity: A Review. Front Pediatr 2021;8:1–16. https://doi.org/10.3389/fped.2020.581461.
[25] Moreno LA, Rodríguez G, Fleta J, Bueno-Lozano M, Lázaro A, Bueno G. Trends of dietary habits in adolescents. Crit Rev Food Sci Nutr 2010;50:106–12. https://doi.org/10.1080/10408390903467480.
[26] Schneider D. International trends in adolescent nutrition. Soc Sci Med 2000;51:955–67. https://doi.org/10.1016/S0277-9536(00)00074-5.
[27] Liu KSN, Chen JY, Ng MYC, Yeung MHY, Bedford LE, Lam CLK. How does the family influence adolescent eating habits in terms of knowledge, attitudes and practices? A global systematic review of qualitative studies. Nutrients 2021;13. https://doi.org/10.3390/nu13113717.
[28] Scaglioni S, De Cosmi V, Ciappolino V, Parazzini F, Brambilla P, Agostoni C. Factors influencing children’s eating behaviours. Nutrients 2018;10:1–17. https://doi.org/10.3390/nu10060706.
[29] World Health Organization. Prevention of iron deficiency anaemia in adolescents role of weekly iron and folic acid supplementation 2011:50.
[30] Azzopardi P, Hearps S, Francis KL, Kennedy E, Mokdad AH, Kassebaum N, et al. Progress in adolescent health and wellbeing: tracking 12 headline indicators from 1990 to 2016 for 195 countries. Lancet 2018:1101–18. https://doi.org/10.1016/S0140-6736(18)32427-9.
[31] WHO/UNICEF. Clinical Management of Leading Cause of Child 2004:2–4.
[32] Scanlon KS, Yip R, Schieve LA, Cogswell ME. High and Low Hemoglobin Levels During Pregnancy. Obstet Gynecol 2016;96:741–8. https://doi.org/10.1097/00006250-200011000-00018.
[33] Allen LH. Pregnancy and iron deficiency: unresolved issues. Nutr Rev 1997;55:91–101.
[34] Sen A, Kanani SJ. Impact of iron-folic acid supplementation on cognitive abilities of school girls in Vadodara. Indian Pediatr 2008;46:137–43.
[35] Bruce D, B JF. Health for the World’s Adolescents: A second chance in the second decade. J Adolesc Heal 2015;volume 56:3–6.
[36] Nelima D. Prevalence and Determinants of Anaemia among Adolescent Girls in Secondary Schools in Yala Division Siaya District, Kenya. Univers J Food Nutr Sci 2015;3:1–9. https://doi.org/10.13189/ujfns.2015.030101.

1

[37] Ranganath TS, Debata I. Assessment of Diet and Anaemia status among Adolescent girls in Urban Bangalore. J Interdiscip Multidiscip Res 2015;2:36–42.

[38] Sachan B, Idris M, Singh A. Effect of socio-demographic characteristics on the prevalence of anemia among school going adolescent girls in Lucknow district, India. South East Asia J Public Heal 2013;2:8–12. https://doi.org/10.3329/seajph.v2i1.15254.

[39] Meier PR, Nickerson HJ, Olson KA, Berg RL, Meyer JA. Prevention of iron deficiency anemia in adolescent and adult pregnancies. Clin Med Res 2003;1:29–36. https://doi.org/10.3121/cmr.1.1.29.

[40] Chaparro CM, Suchdev PS. Anemia epidemiology, pathophysiology, and etiology in low- and middle-income countries. Ann N Y Acad Sci 2019;1450:15–31. https://doi.org/10.1111/nyas.14092.

[41] Styne DM. The regulation of pubertal growth. Horm Res 2003;60:22–6. https://doi.org/10.1159/000071222.

[42] Bolzenius K, Kroke A, Günther ALB, Karaolis-Danckert N, Buyken AE. Body composition trajectories into adolescence according to age at pubertal growth spurt. Am J Hum Biol 2010;23:216–24. https://doi.org/10.1002/ajhb.21125.

[43] Böttner A, Kratzsch J, Müller G, Kapellen TM, Blüher S, Keller E, et al. Gender differences of adiponectin levels develop during the progression of puberty and are related to serum androgen levels. J Clin Endocrinol Metab 2004;89:4053–61. https://doi.org/10.1210/jc.2004-0303.

[44] He Q, Karlberg J. BMI in childhood and its association with height gain, timing of puberty, and final height. Pediatr Res 2001;49:244–51. https://doi.org/10.1203/00006450-200102000-00019.

[45] Davison KK, Birch LL. Childhood overweight: A contextual model and recommendations for future research. Obes Rev 2001;2:159–71. https://doi.org/10.1046/j.1467-789x.2001.00036.x.

[46] Johnson W, Stovitz SD, Choh AC, Czerwinski SA, Towne B, Demerath EW. Patterns of linear growth and skeletal maturation from birth to 18 years of age in overweight young adults. Int J Obes 2012;36:535–41. https://doi.org/10.1038/ijo.2011.238.

[47] Rasmussen F, Haukka J, Silventoinen K, Dunkel L, Tynelius P. Genetics of Pubertal Timing and Its Associations With Relative Weight in Childhood and Adult Height: The Swedish Young Male Twins Study. Pediatrics 2008;121:e885–91. https://doi.org/10.1542/peds.2007-1615.

[48] Teilmann G, Skakkebaek NE, Parent A-S, Toppari J, Bourguignon J-P, Juul A. The Timing of Normal Puberty and the Age Limits of Sexual Precocity: Variations around the World, Secular Trends, and Changes after Migration. Endocr Rev 2003;24:668–93. https://doi.org/10.1210/er.2002-0019.

[49] Hoyt LT, Niu L, Pachucki MC, Chaku N. Timing of puberty in boys and girls: Implications for population health. SSM - Popul Heal 2020;10:100549. https://doi.org/10.1016/j.ssmph.2020.100549.

[50] Aguayo VM, Paintal K. Nutrition in adolescent girls in South Asia. BMJ 2017;357:1–4. https://doi.org/10.1136/bmj.j1309.

[51] Aris IM, Perng W, Dabelea D, Ganiban JM, Liu C, Marceau K, et al. Analysis of Early-Life Growth and Age at Pubertal Onset in US Children. JAMA Netw Open 2022;5:1–14. https://doi.org/10.1001/jamanetworkopen.2021.46873.

[52] Petersohn I, Zarate-Ortiz A, Cepeda-Lopez A, Melse-Boonstra A, Petersohn I, Zarate-Ortiz AG, et al. Time Trends in Age at Menarche and Related Non-Communicable Disease Risk during the 20th Century in Mexico. Nutrients 2019;11:394. https://doi.org/10.3390/nu11020394.

[53] Freedman DS, Berenson GS, Dietz WH, Serdula MK, Srinivasan SR, Khan LK. Relation of Age at Menarche to Race, Time Period, and Anthropometric Dimensions: The Bogalusa Heart Study. Pediatrics 2004;110:e43–e43. https://doi.org/10.1542/peds.110.4.e43.
[54] Elks CE, Perry JRB, Ong KK, Day FR, Murray A. Puberty timing associated with diabetes, cardiovascular disease and also diverse health outcomes in men and women: the UK Biobank study. Sci Rep 2015;5:1–12. https://doi.org/10.1038/srep11208.
[55] Dick DM, Rose RJ, Pulkkinen L, Kaprio J. Measuring Puberty and Understanding Its Impact: A Longitudinal Study of Adolescent Twins. J Youth Adolesc 2001;30:385–99. https://doi.org/10.1023/A:1010471015102.
[56] The Alan Guttmacher Institute. In Their Own Right. Addressing the Sexual and Reproductive Health Needs of American Men. J Nerv Ment Dis 2003;191:67–8. https://doi.org/10.1097/00005053-200301000-00023.
[57] Deardorff J. Early Puberty and Adolescent Pregnancy: The Influence of Alcohol Use. Pediatrics 2005;116:1451–6. https://doi.org/10.1542/peds.2005-0542.
[58] Cavazos-Rehg PA, Krauss MJ, Spitznagel EL, Bommarito K, Madden T, Olsen MA, et al. Maternal Age and Risk of Labor and Delivery Complications. Matern Child Health J 2015;19:1202–11. https://doi.org/10.1007/s10995-014-1624-7.
[59] Ganchimeg T, Ota E, Morisaki N, Laopaiboon M, Lumbiganon P, Zhang J, et al. Pregnancy and childbirth outcomes among adolescent mothers: a World Health Organization multicountry study. BJOG 2014;121 Suppl:40–8. https://doi.org/10.1111/1471-0528.12630.
[60] Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, et al. Brain development during childhood and adolescence: A longitudinal MRI study [2]. Nat Neurosci 1999;2:861–3. https://doi.org/10.1038/13158.
[61] Konrad K, Firk C, Uhlhaas PJ. Brain development during adolescence. Dtsch Arztebl Int 2013;110:425–31. https://doi.org/10.3238/arztebl.2013.0425.
[62] Naninck EFG, Lucassen PJ, Bakker J. Sex Differences in Adolescent Depression: Do Sex Hormones Determine Vulnerability? J Neuroendocrinol 2011;23:383–92. https://doi.org/10.1111/j.1365-2826.2011.02125.x.
[63] Murray-Kolb LE, Acosta AM, De Burga RR, Chavez CB, Flores JT, Olotegui MP, et al. Early childhood cognitive development is affected by interactions among illness, diet, enteropathogens and the home environment: Findings from the MAL-ED birth cohort study. BMJ Glob Heal 2018;3:1–11. https://doi.org/10.1136/bmjgh-2018-000752.
[64] Drago F, Scharf RJ, Maphula A, Nyathi E, Mahopo TC, Svensen E, et al. Psychosocial and environmental determinants of child cognitive development in rural south africa and tanzania: Findings from the mal-ed cohort. BMC Public Health 2020;20:1–8. https://doi.org/10.1186/s12889-020-08598-5.
[65] Cooper PJ, Tomlinson M, Swartz L, Landman M, Molteno C, Stein A, et al. Improving quality of mother-infant relationship and infant attachment in socioeconomically deprived community in South Africa: Randomised controlled trial. BMJ 2009;338:997. https://doi.org/10.1136/bmj.b974.
[66] Wemakor A, Mensah KA. Association between maternal depression and child stunting in Northern Ghana: A cross-sectional study. BMC Public Health 2016;16:1–7. https://doi.org/10.1186/s12889-016-3558-z.
[67] Holck S, Murray C, Murthy RS, Prentice T, Saraceno B, Yach D, et al. The WHO report 2001; Menthal health: new understanding, new hope 2001.
[68] Abbafati C, Abbas KM, Abbasi-Kangevari M, Abd-Allah F, Abdelalim A, Abdollahi M, et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic

1

analysis for the Global Burden of Disease Study 2019. Lancet 2020;396:1223–49. https://doi.org/10.1016/S0140-6736(20)30752-2.
[69] Ge X, Conger RD, Elder GH. The Relation between Puberty and Psychological Distress in Adolescent Boys. J Res Adolesc 2001;11:49–70. https://doi.org/10.1111/1532-7795.00003.
[70] Richert T, Anderberg M, Dahlberg M. Mental health problems among young people in substance abuse treatment in Sweden. Subst Abus Treat Prev Policy 2020;15:1–10. https://doi.org/10.1186/s13011-020-00282-6.
[71] WHO. Global Accelerated Action for the Health of Adolescents (AA-HA!) Guidance to Support Country Implementation. 2017.
[72] Theberath M, Bauer D, Chen W, Salinas M, Mohabbat AB, Yang J, et al. Effects of COVID-19 pandemic on mental health of children and adolescents: A systematic review of survey studies. SAGE Open Med 2022;10:205031212210867. https://doi.org/10.1177/20503121221086712.
[73] United Nations. Transforming our world: the 2030 Agenda for Sustainable Development. New York: 2015.
[74] Sammon EM, Martinez M, Jagmag M, Wahyudi R. Overview of Promising Practices in Adolescent Programming in Indonesia by UNICEF (and other partners): Document Review 2017:53.
[75] Kementerian Kesehatan Republik Indonesia. Laporan Nasional Riset Kesehatan Dasar 2018 (Report of Indonesian Basic Health Survey 2018). 2018.
[76] Kementerian Kesehatan Republik Indonesia. Riset Kesehatan Dasar Kementerian RI. Proceedings, Annu Meet - Air Pollut Control Assoc 2013;6. https://doi.org/1 Desember 2013.
[77] Agustina R, Meilianawati, Fenny, Atmarita, Suparmi, Susiloretni KA, et al. Psychosocial, Eating Behavior, and Lifestyle Factors Influencing Overweight and Obesity in Adolescents. Food Nutr Bull 2021;42:S72–91. https://doi.org/10.1177/0379572121992750.
[78] Agustina R, Nadiya K, El Andini A, Setianingsih AA, Sadariskar AA, Prafiantini E, et al. Associations of meal patterning, dietary quality and diversity with anemia and overweight-obesity among Indonesian schoolgoing adolescent girls in West Java. PLoS One 2020;15:1–19. https://doi.org/10.1371/journal.pone.0231519.
[79] Rah JH, Melse-Boonstra A, Agustina R, van Zutphen KG, Kraemer K. The Triple Burden of Malnutrition Among Adolescents in Indonesia. Food Nutr Bull 2021;42:S4–8. https://doi.org/10.1177/03795721211007114.
[80] Sparrow R, Agustina R, Bras H, Sheila G, Rieger M, Yumna A, et al. Adolescent Nutrition—Developing a Research Agenda for the Second Window of Opportunity in Indonesia. Food Nutr Bull 2021;42:S9–20. https://doi.org/10.1177/0379572120983668.
[81] Sania A, Sudfeld CR, Danaei G, Fink G, McCoy DC, Zhu Z, et al. Early life risk factors of motor, cognitive and language development: A pooled analysis of studies from low/middle-income countries. BMJ Open 2019;9. https://doi.org/10.1136/bmjopen-2018-026449.
[82] Grantham-McGregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. J Nutr 2001;131:649S-668S.
[83] Tran TD, Tran T, Simpson JA, Tran HT, Nguyen TT, Hanieh S, et al. Infant motor development in rural Vietnam and intrauterine exposures to anaemia, iron deficiency and common mental disorders: A prospective community-based study. BMC Pregnancy Childbirth 2014;14. https://doi.org/10.1186/1471-2393-14-8.
[84] Alwan Hanan NA. H. Maternal Iron Status in Pregnancy and Long-Term Health Outcomes in the Offspring. J Pediatr Genet 2015;04:111–23. https://doi.org/10.1055/s-0035-1556742.

[85] Janbek J, Sarki M, Specht IO, Heitmann BL. A systematic literature review of the relation between iron status/anemia in pregnancy and offspring neurodevelopment. Eur J Clin Nutr 2019;73:1561–78. https://doi.org/10.1038/s41430-019-0400-6.

[86] Ludwig H, Strasser K. Symptomatology of anemia. Semin Oncol 2001;28:7–14.

[87] Koury MJ, Ponka P. New insights into erythropoiesis: The roles of folate, vitamin B 12, and iron. Annu Rev Nutr 2004;24:105–31. https://doi.org/10.1146/annurev.nutr.24.012003.132306.

[88] Ramaekers VT, Sequeira JM, Quadros E V. The basis for folinic acid treatment in neuro-psychiatric disorders. Biochimie 2016;126:79–90. https://doi.org/10.1016/j.biochi.2016.04.005.

[89] Coppen A, Bolander-Gouaille C. Treatment of depression : time to consider folic acid and vitamin B12 . Central articles PubMed Commons. J Psychopharmacol 2005;19:59–65. https://doi.org/10.1177/0269881105048899.

[90] Syed EU. Vitamin B12 Supplementation in Treating Major Depressive Disorder: A Randomized Controlled Trial. Open Neurol J 2013;7:44–8. https://doi.org/10.2174/1874205x01307010044.

[91] Das JK, Salam RA, Mahmood S Bin, Moin A, Kumar R, Mukhtar K, et al. Food fortification with multiple micronutrients: impact on health outcomes in general population. Cochrane Database Syst Rev 2019;12:CD011400. https://doi.org/10.1002/14651858.CD011400.pub2.

[92] Miller S, Shanahan L, Angold A, Maughan B, Copeland W, Costello EJ. Outcomes of Early Pubertal Timing in Young Women: A Prospective Population-Based Study. Am J Psychiatry 2010;167:1218–25. https://doi.org/10.1176/appi.ajp.2010.09081190.

[93] Natsuaki MN, Biehl MC, Ge X. Trajectories of depressed mood from early adolescence to young adulthood: The effects of pubertal timing and adolescent dating. J Res Adolesc 2009;19:47–74. https://doi.org/10.1111/j.1532-7795.2009.00581.x.

[94] Boden JM, Fergusson DM, Horwood LJ. Age of menarche and psychosocial outcomes in a new zealand birth cohort. J Am Acad Child Adolesc Psychiatry 2011;50:132-140.e5. https://doi.org/10.1016/j.jaac.2010.11.007.

[95] Lien L, Haavet OR, Dalgard F. Do mental health and behavioural problems of early menarche persist into late adolescence? A three year follow-up study among adolescent girls in Oslo, Norway. Soc Sci Med 2010;71:529–33. https://doi.org/10.1016/j.socscimed.2010.05.003.

[96] Stice E, Presnell K, Bearman SK. Relation of early menarche to depression, eating disorders, substance abuse, and comorbid psychopathology among adolescent girls. Dev Psychol 2001;37:608–19. https://doi.org/10.1037/0012-1649.37.5.608.

[97] Joinson C, Heron J, Lewis G, Croudace T, Araya R. Timing of menarche and depressive symptoms in adolescent girls from a UK cohort. Br J Psychiatry 2011;198:17–23. https://doi.org/10.1192/bjp.bp.110.080861.

[98] Angold A, Carol W, Costello EJ. Puberty and depression. Gend Differ Puberty 2003;15:137–64. https://doi.org/10.1017/CBO9780511489716.009.

[99] Dorn LD, Negriff S, Huang B, Pabst S, Hillman J, Braverman P, et al. Menstrual Symptoms in Adolescent Girls: Association with Smoking, Depressive Symptoms, and Anxiety. J Adolesc Heal 2009;44:237–43. https://doi.org/10.1016/j.jadohealth.2008.07.018.

[100] Rey JM, Bella-awusah TT, Liu J. IACAPAP Textbook of Child and Adolescent Mental Health. Mood Disorders: Depression in Children and Adolecents 2015:1–36.

[101] Graber JA. Pubertal timing and the development of psychopathology in adolescence and beyond. Horm Behav 2013;64:262–9. https://doi.org/10.1016/j.yhbeh.2013.04.003.

[102] Hamilton JL, Hamlat EJ, Stange JP, Abramson LY, Alloy LB. Pubertal timing and vulnerabilities to depression in early adolescence: Differential pathways to depressive symptoms by sex. J Adolesc 2014;37:165–74. https://doi.org/10.1016/j.adolescence.2013.11.010.

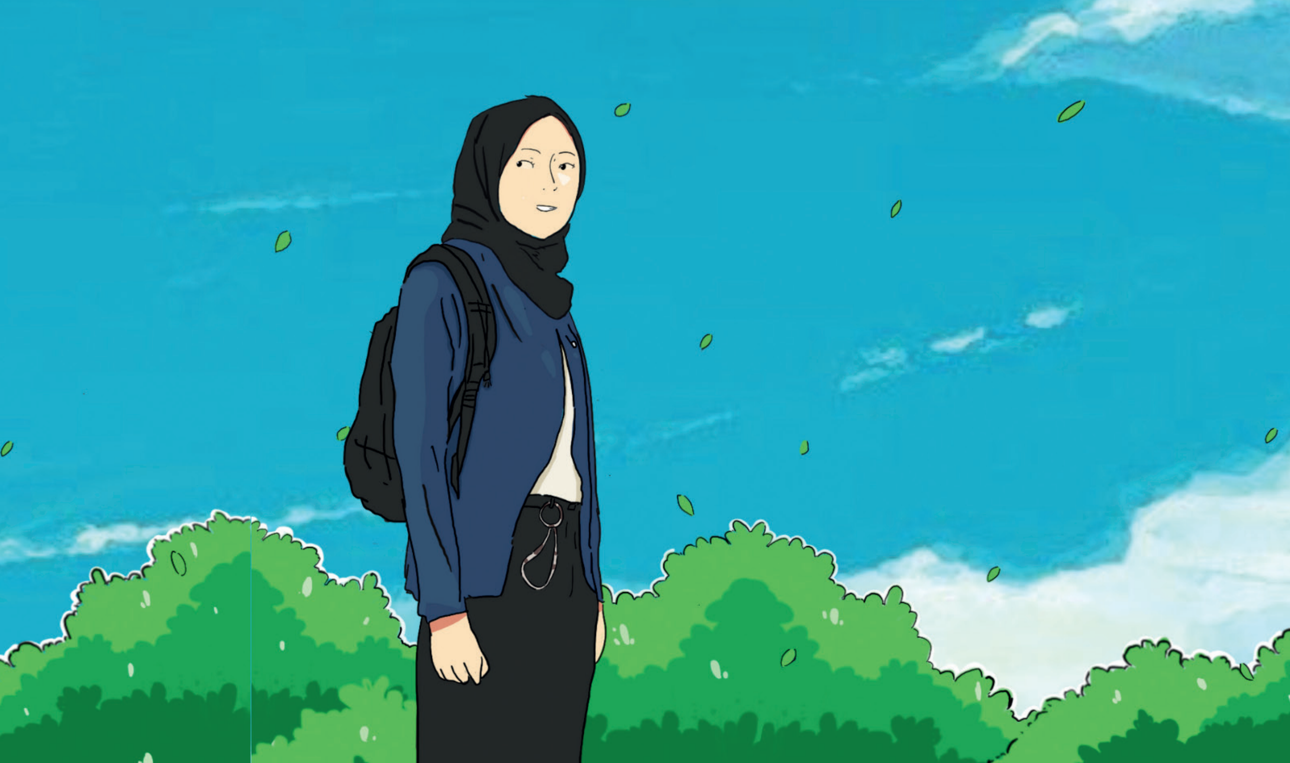
[103] Stubbs ML. Cultural perceptions and practices around menarche and adolescent menstruation in the United States. Ann N Y Acad Sci 2008;1135:58–66. https://doi.org/10.1196/annals.1429.008.
[104] Maehara M, Rah JH, Roshita A, Suryantan J, Rachmadewi A, Izwardy D. Patterns and risk factors of double burden of malnutrition among adolescent girls and boys in Indonesia. PLoS One 2019;14:15–8. https://doi.org/10.1371/journal.pone.0221273.
[105] Madjdian DS, Azupogo F, Osendarp SJM, Bras H, Brouwer ID. Socio-cultural and economic determinants and consequences of adolescent undernutrition and micronutrient deficiencies in LLMICs: a systematic narrative review. Ann N Y Acad Sci 2018;1416:117–39. https://doi.org/10.1111/nyas.13670.
[106] van Zutphen KG, Kraemer K, Melse-Boonstra A. Knowledge Gaps in Understanding the Etiology of Anemia in Indonesian Adolescents. Food Nutr Bull 2021;42:S39–58. https://doi.org/10.1177/0379572120979241.

Chapter 2

Trend in age at menarche and its association with body weight, body mass index and non-communicable disease prevalence in Indonesia: Evidence from the Indonesian Family Life Survey (IFLS)

Muhammad Asrullah, Monique L'Hoir, Edith JM Feskens, Alida Melse-Boonstra

Published in BMC Public Health Journal
DOI: 10.1186/s12889-022-12995-3



ABSTRACT

In western countries age at menarche (AAM) is nowadays lower than a century ago, coinciding with increased Body Mass Index (BMI) and prevalence of non-communicable diseases (NCD). This study aimed to determine the time trend in AAM and its association with BMI and NCD prevalence at later age, in Indonesia. We used secondary data of 15,744 women aged 15-65 years from the Indonesian Family Life Survey (IFLS) conducted in the period 1993 to 2015. Multiple linear regression was applied to determine the association of AAM with BMI, and Poisson regression with robust variance for investigating the association of AAM with NCD prevalence ratios. Models were adjusted for age, and effect modification by wealth status, living area, and region was investigated. AAM has significantly declined from 14.4 (SD:2.1) years of age in the 1940s to 13.4 (SD:1.5) in the 1990s. AAM was inversely associated with BMI (β: -0.30 kg/m^2, 95%CI: -0.37, -0.22) and body weight (β: -0.67 kg, 95%CI: -0.75, -0.54), but was not associated with height. After adjustment for age, AAM was not associated with NCD, i.e., hypertension, type 2 diabetes mellitus, liver diseases, asthma, chronic lung diseases, cardiovascular diseases, stroke, cancer, or arthritis. Including BMI in the models did not change the results. From the 1940s to 1990s, AAM has declined with 1 year in Indonesia. Women with earlier AAM had higher BMI and body weight at later age, but AAM was not associated with NCD prevalence in later life in the Indonesian population. Further longitudinal research is needed to disentangle the direction of causality of the associations.

Keywords: Menarche, Nutritional status, Non-Communicable Diseases, Indonesia

INTRODUCTION

In recent decades, non-communicable diseases (NCD) have emerged as the leading cause of death in both developing and developed countries. In Indonesia, six of the top ten leading causes of death consisted of NCD in 2017, of which stroke was the number one cause from 2007 to 2017 [1]. Based on Indonesian National Health survey data, the prevalence of NCD increased significantly from 2013 to 2018. For example, the prevalence of stroke among people aged 15 years or older increased from 7.0 to 10.9 percent, type 2 diabetes mellitus (DM) from 6.9 to 8.5 percent, and hypertension from 25.8 to 34.1 percent. The prevalence of cancer, arthritis, and cardiovascular diseases (CVD) also increased, especially among the older age groups (> 55 years).

The aetiology of NCD is explained by a multitude of factors such as ethnicity, age, physical activity, dietary patterns, smoking status, as well as early biological maturation [2]. Overweight and obesity, which have globally increased over the past fourty years [3], are known as the most important proximal risk factors for NCD [4]. Any increase in the prevalence of overweight and obesity should therefore be of concern. The prevalence of overweight, obesity and abdominal obesity among people aged 15 years or older in Indonesia increased from 8.6, 10.5 and 18.8 percent in 2007 to 13.6, 21.8, and 31.0 percent in 2018, respectively [5]. Overweight and obesity during childhood have been associated with accelerated pubertal maturation [6]. Obese girls experience earlier age at menarche (AAM) than normal [7], but it is not clear if higher BMI is either a cause or a consequence of earlier menarche, or both. In addition, some studies have reported that earlier AAM is associated with increased risk of NCDs in later life such as stroke, cardiovascular diseases [8], and diabetes [9]. Moreover, AAM has shown to be predictive for cardiovascular disease events and mortality [8].

In Indonesia, a previous study showed that higher Body Mass Index (BMI), higher parental income, and living in an urban area were associated with earlier puberty in both girls and boys based on Tanner scale assessment (pubic hair, female breast development, and male external genitalia) [10]. Globally, menarche occurs at an earlier age than in previous decades [11,12]. For example, in Mexico mean AAM decreased from 13.6 to 12.6 years of age from 1900s to 1980s, while undergoing rapid economic transition, and earlier AAM was associated with diabetes and hypercholesterolemia [13]. Therefore, early AAM may be an intermediary factor between childhood obesity and the development of NCD.

We aimed to identify the association of AAM with obesity and NCD among women from diverse socio-economic groups, living areas, and regions in Indonesia by analysing nationally representative data from the Indonesian Family Life Survey. We expected these associations to be inverse.

2

MATERIAL AND METHODS

Indonesian Family Life Survey

Data collection. The Indonesian Family Life Survey (IFLS) has so far been conducted in 5 waves, namely in 1993, 1997-1998, 2000, 2007-2008, and 2014-2015. IFLS is the only large longitudinal survey in Indonesia and represents 83 percent of the Indonesian population. Administration of questionnaires and health measurements, such as anthropometry and blood analysis, has been conducted under supervision of the non-profit RAND Corporation (Santa Monica, CA, USA). The aim of the IFLS survey is to provide multi-factorial data on economic and non-economic behavioural variables and outcomes such as food consumption, health status, and insurance utilization.

The first wave of IFLS included 13 out of 27 provinces and included 22,000 individuals living in 7,244 households, using a stratified random sampling technique. The sampling method considered the heterogeneity of the population and represents four out of the five largest islands of Indonesia: Sumatra, Java, Kalimantan, and Sulawesi. Data collection areas were adapted from the areas covered by the National Socioeconomic Survey (SUSENAS) in 1993, which was based on the 1990 census. The details of the sampling frame have been described previously in an online IFLS report [14].

IFLS wave 2 collected data from the same individuals as in 1997, covering approximately 94.4% of the first wave. The next IFLS data collection rounds (wave 3-5) mostly interviewed dynasty households, which means that they already participated in any of the previous IFLS data collection rounds. The proportion of dynasty data was 95.3 percent in 2000 (wave 3), 93.6 percent in 2007 (wave 4), and 92 percent in 2014 (wave 5). The proportion of successfully re-contacted households was higher for the IFLS than generally seen in surveys conducted in the United States and Europe. Data collection, comprising self-reported data and direct measurements, was conducted by duly trained data collectors.

Participants. For the aim of the present analysis, data were selected of all women aged 15 years and older with a complete record for AAM, age, anthropometric indicators, and NCD from each IFLS wave. Information on AAM was only collected from married women, while NCD was assessed for all women, albeit only in wave 4 and 5. For women participating in multiple survey waves only data of the most recent survey were included (Supplemental Figure 1).

Explanatory and outcome variables

AAM was assessed using a questionnaire by asking: "*how old were you (in years) at your first menstruation?*" We classified early AAM as <12 years of age, normative AAM as in the range ≥12 – <16 years, and late AAM as ≥16 years. This classification is based on the AAM distribution in our population which was defined as normative of AAM between plus and minus one standard deviation of the mean (mean: 13.75 and SD: 1.80). The same age classification of AAM has been used in previous studies [15,16].

Trained data collectors measured body weight of each participant using a body weight scale up to the nearest tenth of a kilogram or one single decimal, while height was measured using a Seca plastic height board (model 213) up to the nearest millimetre. BMI was calculated as weight (kg)/height $(m)^2$ and classified into overweight (BMI ≥25 - <30) and obese (BMI ≥30) categories.

Occurrence of NCD was assessed by questionnaire, asking whether or not participants had been diagnosed with any of the following chronic conditions: hypertension, type 2 diabetes mellitus, asthma, chronic lung disease, cardiovascular disease, liver disease, stroke, cancer and arthritis. Because not all waves collected these data, only waves 4 and 5 were included in the analysis relating AAM to NCD.

Other variables that were included in our analysis were household socio-economic status, living area, and region. Socio-economic status (SES) was constructed by assigning weights of eleven household assets (ownership of the house, ownership of another building, possession of farmland, fishpond or poultry, vehicles, electronic devices (e.g., radio, tv, refrigerator or washing machine), savings, jewellery, and other assets) into a five-quintile wealth index by Principal Component Analysis (PCA). For the present analysis, we categorized this index further into three groups: poor for the two bottom quintiles, average for the two middle quintiles, and rich for the highest quintile. The same classification of SES has been used for IFLS data in previous studies [17]. Participants were categorized into rural and urban areas of living using classification of Indonesia's Bureau of Statistics [18], which is based on population density, percentage of agricultural households, and presence/access to facilities.

Statistical analysis

Data were analysed using STATA statistical software version 14. Data cleaning was employed at two levels; the first level was the data cleaning for AAM and BMI data which were extracted from all IFLS waves, and the second level was conducted for NCD data which were additionally extracted only from the last two waves (wave 4 and 5), since these were not available for the earlier waves. (Supplementary Figure 1). Data on AAM were used to determine the time trend of AAM and its association with BMI, while NCD data were used to assess associations between AAM and NCD. Completeness of variables such as AAM, BMI, age, wealth index, and unrealistic AAM and body weights because of input errors were considered in data cleaning. Wealth index, BMI and NCD were taken from the last wave in which the respondent was enrolled since these outcomes are influenced by age. Unrealistic data were removed, and the normality assumption and completeness of the variables have been checked by conducting Q-Q plots. In addition, the multicollinearity was checked by plotting the correlation matrix of all the independent variables and identifying the variance Inflation Factor (VIF) for each variable. The correlation matrix showed all the correlations were less than 0.4 and the average of VIF was less than 2.

AAM, women's weight, height, and BMI were described using means and standard deviations. We determined a mean AAM based on the birth year of participants to investigate the time trend per decade. The analysis of the determinant variables in each wave was done by ANOVA and Chi-square test. Furthermore, associations between AAM and nutritional status (BMI, weight, and height) were determined by multiple linear regression and Poisson regression models with robust variance, adjusted for age. The data were stratified by wealth index, living area, and region since these variables were found to be effect modifiers. Finally, we used Poisson regression models with robust variance to determine the association of AAM with the prevalence of NCD, while adjusting for age as well as for BMI as a potential intermediate.

RESULTS

Characteristics of the respondents in all waves

Characteristics of respondents are shown in Table 2.1. The total number of respondents was 15,744 women and the average age of the respondents was 36 years old (SD:10.1). Most respondents were classified in the poor and average wealth index categories. More than half of respondents lived in urban areas and in the region of Java and Bali islands.

Time Trend of AAM

AAM decreased with approximately one year from 14.4 (SD:2.1) years for women born in the 1940s to 13.4 (SD:1.5) years for women born in the 1990s. Mean AAM over the entire period of 1940s to 1990s was 13.8 years (SD:1.8). Of all respondents, 5.8 percent were categorized as having early AAM (<12 years), 81.6 percent as normative (≥12 – <16 years), and 12.5 percent as late (≥16 years). AAM was not significantly different between women who lived in urban (mean:13.7 SD:1.7) and rural areas (mean:13.9 SD:1.8; p:0.08), who lived on the two main islands Java or Bali (mean:13.7 SD:1.9) and elsewhere (mean:13.8 SD:1.7; p:0.10), or who fell in different wealth status classifications; poor (mean:13.7 SD:1.8), average (mean:13.8 SD: 1.8), and rich, (mean:13.8 SD:1,9 ; p:0.10) (Figure 2.1).

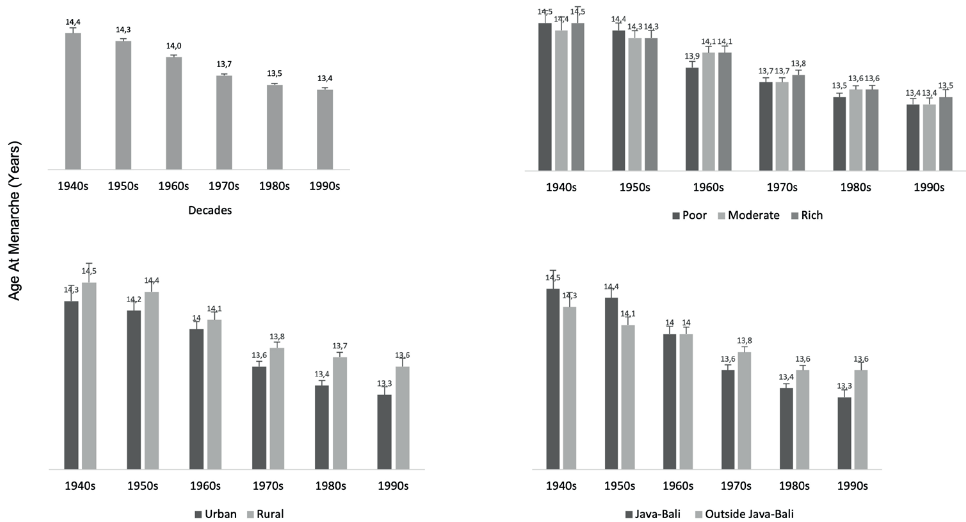


Figure 2.1. Time trend of AAM based on year of birth, wealth index, living area, and region among 15,744 respondents from IFLS waves 1-5.

Table 2.1. Characteristics of the selected female respondents according to IFLS wave (N= 15,744)

	IFLS 1 (n = 33)		IFLS 2 (n = 100)		IFLS 3 (n = 1,396)		IFLS 4 (n = 2,168)		IFLS 5 (n = 12,047)		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P-value**
Age, years	36.5	9.4	41.8	10.7	36.9	12.9	40.1	13.4	36.1	10.0	<0.001
Age at Menarche, years	14.9	2.7	14.0	2.4	14.1	1.9	14.0	1.8	13.7	1.8	<0.001
Nutritional status											
BMI, kg/m^2	21.64	4.23	21.59	4.03	22.35	3.96	24.40	14.22	24.88	4.70	<0.001
Weight, kg	49.7	9.9	47.4	9.5	50.5	9.8	53.4	11.4	57.0	11.52	<0.001
Height, cm	151.5	6.1	148.0	6.1	150.2	5.3	149.9	8.9	151.4	5.5	<0.001
	%		%		%		%		%		
Wealth Index, %											
Poor	39.4		26.0		33.4		35.2		42.1		<0.001
Average	36.4		39.0		38.4		42.5		40.4		
Rich	24.2		35.0		28.2		22.3		17.5		
Living area, %											
Urban	36.4		29.0		45.9		51.8		57.3		<0.001
Rural	63.6		71.0		54.1		48.2		42.7		
Region, %											
Java and Bali	60.6		64.0		62.7		61.2		55.1		<0.001
Outside Java and Bali	39.4		36.0		37.3		38.8		44.9		

Note: ANOVA was used to analyse the age, Age at Menarche, and nutritional status in each wave; Chi-square was applied for wealth index, living area, and region

AAM and risk factors for BMI, weight, and height

Table 2.2 shows the results of multiple linear regression models investigating the association between AAM and BMI. In unadjusted as well as in age-adjusted analysis, AAM (in years) was inversely associated with BMI (adjusted β: -0.30 kg/m^2 per year of AAM, 95%CI: -0.37, -0.22). When stratifying this analysis, the association appeared to be stronger in the highest wealth category (β: -0.39 kg/m^2 per year, 95%CI: -0.43, -0.26), in the urban area (**β: -0.35 kg/m^2** per year, 95%CI: -0.43, -0.26) and at the two main islands (Java and Bali; **β: -0.33 kg/m^2** per year, 95%CI: -0.40, -0.24) compared to the other socio-demographic categories. Further analysis using Poisson regression models adjusted for age shows that in later life, overweight and obesity were more prevalent among women with early age at menarche (overweight: PR: 1.11 95%CI: 1.02-1.22; and obesity: PR: 1.35 95%CI: 1.35-1.76) as compared to women with normative age at menarche, whereas the prevalence ratio of overweight and obesity among women with late age at menarche was lower (overweight: PR: 0.86 95%CI: 0.81-0.94; and obesity: PR: 0.77 95%CI: 0.67-0.87).

Table 2.2. Age-adjusted association between AAM and BMI at later age among female respondents of IFLS waves 1-5 (N=15,744).

Variables	n (%)	BMI (kg/m^2) Unadjusted β	(95% CI)	Age-adjusted β	(95% CI)
Total population	15,744 (100)	-0.23	-0.31; -0.16	-0.30	-0.37; -0.22
Wealth index[1]					
Poor	6,345 (40.3)	-0.21	-0.31; -0.11	-0.29	-0.39; -0.19
Average	6,371 (40.5)	-0.20	-0.27; -0.12	-0.24	-0.31; -0.17
Rich	3,028 (19.2)	-0.33	-0.49; -0.17	-0.39	-0.54; -0.23
Living area[1]					
Urban	8,705 (55.3)	-0.26	-0.34; -0.17	-0.33	-0.41; -0.25
Rural	7,039 (44.7)	-0.17	-0.25; -0.08	-0.26	-0.34; -0.17
Region[2]					
Java and Bali	8,931 (56.7)	-0.25	-0.32; -0.16	-0.33	-0.40; -0.24
Outside Java and Bali	6,813 (43.3)	-0.22	-0.30; -0,13	-0.26	-0.34; -0.16

[1] p-value variable interaction: <0.001; [2] p-value interaction: <0.050

AAM was also inversely associated with current weight (adjusted β: -0.67 kg per year of AAM, 95%CI: -0.75, -0.54) (Table 2.3). The association was stronger in urban (**β** -0.68 kg per year of AAM, 95%CI: -0.81, -0.54) versus rural women (**β**: -0.52 kg per year, 95%CI: -0.67, -0.38), whereas differences between other sociodemographic categories were small. The association between AAM and height was either small or absent (β: -0.03 cm per year of AAM, 95%CI: -0.09, 0.02). (Table 2.4).

Table 2.3. Age-adjusted association between AAM and body weight at later age among female respondents from IFLS waves 1-5 (N=15,744).

Variables	Body Weight (kg)				
	n (%)	Unadjusted		Age-adjusted	
		β	(95% CI)	β	(95% CI)
AAM (years)	15,744 (100)	-0.58	-0.68l; -0.48	-0.67	-0.75; -0.54
Wealth index[1]					
Poor	6,345 (40.3)	-0.55	-0.71; -0.40	-0.67	-0.83; -0.50
Average	6,371 (40.5)	-0.60	-0.75; -0.48	-0.67	-0.83; -0.51
Rich	3,028 (19.2)	-0.53	-0.74; -0.32	-0.57	-0.78: -0.35
Living area[1]					
Urban	8,705 (55.3)	-0.54	-0.67; -0.39	-0.68	-0.81; -0.54
Rural	7,039 (44.7)	-0.50	-0.64; -0.35	-0.52	-0.67; -0.38
Region[2]					
Java and Bali	8,931 (56.7)	-0.52	-0.64; -0.38	-0.61	-0.74; -0.48
Outside Java and Bali	6,813 (43.3)	-0.67	-0.82; -0,50	-0.73	-0.88; -0.56

[1] p-value interaction: <0.001; [2] p-value interaction: <0.001

Table 2.4. Age-adjusted association between AAM and body height at later age among female respondents from IFLS waves 1-5 (N=15,744).

Variables	Body Height (cm)				
	n (%)	Unadjusted		Age-adjusted	
		β	(95% CI)	β	(95% CI)
AAM (years)	15,744 (100)	-0.10	-0.15; -0.04	-0.03	-0.09; 0.02
By wealth[1]					
Poor	6,345 (40.3)	-0.09	-0.17; 0.01	-0.01	-0.10; 0.07
Average	6,371 (40.5)	-0.11	-0.20; -0.04	-0.06	-0.13; 0.03
Rich	3,028 (19.2)	-0.06	-0.18; -0.06	-0.03	-0.11; 0.12
By area[2]					
Urban	8,705 (55.3)	-0.07	-0.14; <0.01	<0.01	-0.06; 0.08
Rural	7,039 (44.7)	-0.09	-0.17; -0.01	-0.02	-0.10; 0.05
By region[3]					
Java and Bali	8,931 (56.7)	-0.09*	-0.16; -0.02	<-0.01	-0.07; 0.06
Outside Java and Bali	6,813 (43.3)	-0.10*	-0.18; -0,02	-0.06	-0.14; 0.02

[1] p-value interaction: 0.911; [2] p-value interaction: 0.100; [3] p-value interaction: 0.330

AAM and Risk of NCD

Hypertension was the NCD with the highest prevalence (14.7 percent) while liver disease and stroke were less prevalent (0.8 and 0.6 percent respectively) in the study population. Although AAM was associated with an increased prevalence of hypertension, cardiovascular diseases and arthritis in crude models, these associations disappeared after adjusting for age and BMI (Table 2.5).

Table 2.5. Prevalence ratio of NCD outcomes with AAM (in years) among female respondents from IFLS wave 4 and 5 (N= 13,267).

Diseases Outcome	Frequency[1]	Crude model			Age-Adjusted			Age and BMI-adjusted		
	n (%)	PR	95% CI		PR	95% CI		PR	95% CI	
Hypertension	1,950 (14.7)	1.03	1.01	1.06	0.98	0.96	1.01	0.99	0.97	1.01
Diabetes Mellitus	283 (2.2)	1.04	0.97	1.12	0.97	0.91	1.03	0.97	0.91	1.03
Asthma	399 (3.0)	1.02	0.96	1.08	1.03	0.97	1.1	1.03	0.97	1.1
Chronic lung diseases	197 (1.5)	0.98	0.90	1.06	0.97	0.90	1.05	0.95	0.88	1.03
Cardiovascular diseases	242 (1.8)	1.09	1.02	1.16	1.03	0.97	1.1	1.03	0.97	1.1
Liver diseases	99 (0.8)	1.08	0.97	1.2	1.08	0.99	1.22	1.09	1.001	1.23
Stroke	71 (0.6)	1.01	0.88	1.15	0.94	0.83	1.06	0.94	0.83	1.06
Cancer	134 (1.0)	0.97	0.89	1.05	0.96	0.88	1.04	0.96	0.89	1.04
Arthritis	826 (6.3)	1.1	1.06	1.14	1.02	0.99	1.06	1.02	0.99	1.06

Note: [1]percentage was measured from total respondents; [2]percentage was measured from total respondents in each wave (column percentages); PR: prevalence ratio. Independent variable: AAM; dependent variable: NCD

2

DISCUSSION

In this study, we found that among Indonesian women AAM declined over birth decades from 14.4 years in the 1940s to 13.4 years in the 1990s. Furthermore, AAM was inversely associated with BMI and body weight in later life, independently of age. AAM was also associated with a higher prevalence of several NCDs such as hypertension, CVD, and arthritis, but this depended on age. Additional adjustment for BMI did not alter these results.

A previous study that reviewed published data indicated a similar time trend of AAM in Indonesia, with a decline from 14.4 y to 13.6 y since 1970 [19]. For China, also a decline in AAM is reported, with an average of 16.2 y for women born before 1950 to 14.7 y for those born after 1959 [20]. Whereas AAM in China is estimated at 15.4 years for the period of 2004-2008, for Taiwan, this is 13.9 years for the same period of time; this disparity may have been influenced by the economic development in Taiwan since the mid-1980s, leading to changes in lifestyle and nutritional status, and thereby to earlier maturation of women [21]. Decline in AAM in both developed and developing countries has been associated with factors such as wealth index, access to health facilities, and intake of food, and it varies within a population based on the local context [22]. Nevertheless, AAM did neither differ between rural and urban areas, nor between different wealth groups in our study.

We observed a significant inverse association of AAM with BMI and body weight, indicating that each year of earlier menarche was associated with a higher BMI of 0.30 kg m^{-2} and of 0.67 kg in adult body weight after adjustment for age. Previous research, both in western and Asian countries, showed a similar pattern [8,23]. A systematic review showed that the mean difference in BMI of adult women with earlier compared to later menarche (menarche <12 vs ≥12 years) was 0.34 kg m^{-2} [23]. This is less than what we found in the current study (1.13 kg m^{-2}) when using the same classification. In a survey among 12,336 Korean women it was reported that early AAM (defined as ≤11 years) was correlated with a higher BMI [24]. The same trend was also seen in a number of longitudinal studies from the UK that made use of mendelian randomization by genetic traits related to pubertal onset, although in one of these cohorts the association attenuated after adjusting for pre-pubertal BMI [25,26].

The question arises whether increased body mass predisposes girls to earlier puberty, or that earlier puberty in physical and hormonal changes contributes to increased body (fat) mass in later life. In support of the prior pathway, a longitudinal study showed that girls with a higher percentage of body fat at 5 years of age, and higher BMI and waist circumference at 7 years of age, were more likely to be classified with earlier pubertal development at 9 years of age. Earlier pubertal development was assessed by breast development, level of oestradiol, and pubertal developmental scale (PDS) [27]. Also, a higher BMI-for-age z score at 9 and 43 months of age and rapid increase in BMI during childhood were associated with having menarche before 12 years of age among 2,083 women in Southern Brazil [28]. Furthermore, fast increases in BMI at 4 months, 1 year, and 4 year of age were associated with increased likelihood of having a 4.6-month earlier menarche in the United States [29]. This may be explained by the fact that children with higher BMI are exposed to higher circulating concentrations of leptin, which could stimulate gonadotropin releasing hormone and premature secretion of sex hormones [30]. A 4-year longitudinal study among adolescents showed that AAM indeed declined by approximately 1 month per 1-ng/mL increase in leptin concentration [31]. In contrast, however, cohort data from India, Peru, and Vietnam consistently showed that increases in BMI during childhood (1-8 years of age) were not associated with earlier menarche [32]. The discrepancy between findings might be explained by lower obesity prevalence in low- and middle-income countries (LMICs) compared to advanced economies such as the United States and some Latin American and European countries [33,34]. Despite rapid increases in the prevalence of childhood overweight in LMICs, the prevalence of undernutrition also remains high [32].

There is also evidence that early maturation may induce higher BMI in later life [35]. Prospective cohort studies conducted in the UK and in Australia showed that earlier menarche was related to higher BMI in middle age, independent of their BMI at 4-6 years of age, and at 20 years of age, independent of their BMI at 8 years of age, respectively [36,37]. Furthermore, a systematic review on genetic predisposition of pubertal timing by mendelian randomization found that earlier pubertal timing assessed by several pubertal traits such as age at menarche, age at voice breaking, male genital and female breast development, was related to increased BMI at adult age [38]. Therefore, both pathways may play a role in the relationship between AAM and BMI which cannot be disentangled by our cross-sectional data.

Although we did not find any association with height, a previous large prospective study with data from 286,205 women from nine European countries found that they were 0.31 cm taller for each year of later menarche [39]. A prospective study in South Africa also showed an increase in adult height of 1.15 cm per year of later menarche after adjusting for prepubertal height and BMI [40]. It has been hypothesized that women with early menarche experience premature closure of the epiphyseal growth plate which is responsible for elongation of the bones. Therefore, later menarche would allow further development of the long bones resulting in a greater adult height [39].

Regarding NCD, a number of large studies did find associations between AAM and cardiovascular diseases, hypertension, and stroke, both in developed and developing countries [8,20,24], whereas some others, consistent with our findings, did not [13,41]. Among 118,964 women with breast cancer from 117 epidemiological studies, it was shown that with every year decline in AAM, the risk for breast cancer increased with 5% [42]. Early menarche (<12 years) was also identified to increase the risk of asthma [43]. Furthermore, a one-year earlier menarche was associated with a higher risk of Non-Alcoholic Fatty Acid Disease (NAFLD) [9,44]. The effect of AAM on rheumatoid arthritis is still under debate, with some studies showing a protective effect for early AAM [45], as well as for late AAM [46], whereas others reported no association [41]. The longer oestrogen exposure among women with earlier AAM may provide a possible mechanism for the related higher risk of NCD [39]. In addition, the higher BMI in middle age seen with earlier AAM may mediate the association with NCD. The prevalence of obesity among Indonesian women has increased while AAM has declined, as shown in this study. Even though the prevalence of NCD has also risen, it may not be at its highest point yet. The incidence of high blood pressure, type 2 diabetes mellitus and stroke is still much lower in Indonesia than for example in the UK [8], China [20], and Korea [24]. This may explain why an association between AAM and NCD for Indonesia could not yet be shown, although an association between AAM and BMI has been clearly demonstrated. More studies with large sample sizes and small confidence intervals are needed in similar populations to clarify the relationship between AAM and NCD.

This is the first study using nationally representative data to explore the trend of AAM and its association with nutritional status and disease outcomes in Indonesia. The longitudinal nature of this study allowed us to assess the trend in AAM over six decades based on the year of birth. This study highlights an inverse association between AAM and BMI, with the latter known to be the most important proximal risk factor for Non-Communicable Diseases. There are some limitations to our study. For instance, the retrospective recall of NCDs or AAM might not be accurate, although the respondents of IFLS were generally healthy and able to remember their health history. Self-reported AAM collected by personal interview, like we used for this study, was shown to be consistent with AAM recall 30 years earlier in a retrospective follow-up study [47], as well as in a study with repeated interviews of menstrual history in the period of 1985-1993 [48]. To better understand the associations between AAM, BMI and NCD, prospective, longitudinal research with more details on pubertal stage and measurement of sex hormones and other biological factors are needed. Full characterization of body composition would also be needed instead of relying on BMI alone [35]. In the current study, no data on prepubertal BMI was available from the women included in the first two waves, nor for NCD data in the first three waves of IFLS. Possible selection bias may have occurred since data on AAM was only collected from married women. The analysis may have selectively excluded women due to early mortality or non-response; nevertheless, the number of missing cases was relatively small and therefore we do not expect it would change our conclusion.

CONCLUSION

In Indonesia, AAM declined over birth decades from 14.4 years in the 1940s to 13.4 years in the 1990s. We found that women from the Indonesian Family Life Survey with earlier AAM had a higher BMI and body weight later in life. Nevertheless, AAM was not independently associated with any of the NCD outcomes. With the prospect of rising overweight and obesity prevalence, future longitudinal cohort studies should include pubertal stage with comprehensive indicators and its risk factors of early AAM as a common variable, to unravel causal pathways.

ABBREVIATION

AAM: Age At Menarche; BMI: Boddy Mass Index; NCD: Non-Communicable Diseases; SD: Standard Deviation; IFLS: Indonesian Family Life Survey; SUSENAS: The Indonesia National Socio-economic Survey; PCA: Principal Component Analysis; SES: Socio-economic Status; LMIC: Low-and-Middle Income Countries; NAFLD: Non-alcoholic Fatty Acid Disease.

ACKNOWLEDGMENTS

The author would like to thank RAND, who provided the dataset online.

AUTHORS' CONTRIBUTIONS

All authors had an essential role in formulation of the research questions; MA and AMB wrote the first draft of the paper, MA analysed the data; MA, MLH, AMB, and EJMF were involved in interpretation of the data and revision of the manuscript. All authors have read and approved the final paper.

FUNDING

This study was performed as part of PhD studies for which MA received a scholarship from Lembaga Pengelola Dana Pendidikan (LPDP), Republic of Indonesia. LPDP had no role in the design and writing process of this article.

AVAILABILITY OF DATA AND MATERIALS

The data are available at https://www.rand.org/well-being/social-and-behavioral-policy/data/FLS/IFLS.html

ETHIC APPROVAL AND CONSENT TO PARTICIPATE

The IFLS and the survey protocol were reviewed and approved by Institutional Review Boards in the USA and the Ethics committee of *Universitas Indonesia* based in Jakarta for the first wave of IFLS, and by *Universitas Gadjah Mada* in Yogyakarta for IFLS waves two to five. All methods were performed in accordance with the relevant guidelines and regulations by including a statement in the Ethics approval and informed consent paper. Informed consent was obtained from all participants to participate after explanation of the study.

CONSENT FOR PUBLICATION

Not applicable

CONFLICT OF INTERESTS

All authors stated no conflict of interest

REFERENCES

[1] The Institute for Health Metrics and Evaluation. Indonesia: What Cause Death the Most? 2019. http://www.healthdata.org/indonesia.

[2] Masana LS, Ros E, Sudano I, Angoulvant D, Ibarretxe Gerediaga D, Murga Eizagaechevarria N, et al. Is there a role for lifestyle changes in cardiovascular prevention? What, when and how? Atheroscler Suppl 2017;26:2–15. https://doi.org/10.1016/S1567-5688(17)30020-X.

[3] Bentham J, Di Cesare M, Bilano V, Bixby H, Zhou B, Stevens GA, et al. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet 2017;390:2627–42. https://doi.org/10.1016/S0140-6736(17)32129-3.

[4] Nyberg ST, Batty GD, Pentti J, Virtanen M, Alfredsson L, Fransson EI, et al. Obesity and loss of disease-free years owing to major non-communicable diseases: a multicohort study. Lancet Public Heal 2018;3:e490–7. https://doi.org/10.1016/S2468-2667(18)30139-7.

[5] Kementerian Kesehatan Republik Indonesia. Laporan Nasional Riset Kesehatan Dasar 2018 (Report of Indonesian Basic Health Survey 2018). 2018.

[6] World Health Organization (WHO). Consideration of the evidence on childhood obesity for the Commission on Ending Childhood Obesity: Report of the Ad hoc Working Group on Science and Evidence for Ending Childhood Obesity. World Heal Organ 2016:219. https://doi.org/ISBN 978 92 4 151006 6.

[7] Kaplowitz P. Pubertal development in girls: Secular trends. Curr Opin Obstet Gynecol 2006;18:487–91. https://doi.org/10.1097/01.gco.0000242949.02373.09.

[8] Lakshman R, Forouhi NG, Sharp SJ, Luben R, Bingham SA, Khaw KT, et al. Early age at menarche associated with cardiovascular disease and mortality. J Clin Endocrinol Metab 2009;94:4953–60. https://doi.org/10.1210/jc.2009-1789.

[9] Mueller NT, Duncan BB, Barreto SM, Chor D, Bessel M, Aquino EML, et al. Earlier age at menarche is associated with higher diabetes risk and cardiometabolic disease risk factors in Brazilian adults: Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Cardiovasc Diabetol 2014;13:1–8. https://doi.org/10.1186/1475-2840-13-22.

[10] Hariadi Edi Saputra, Hakimi, Melda Deliana, Siska Mayasari Lubis KSA. Puberty onset in rural and urban children. Paediatr Indones 2011;51:207–12. https://doi.org/10.14238/pi.

[11] Krieger N, Kiang M V., Kosheleva A, Waterman PD, Chen JT, Beckfield J. Age at menarche: 50-year socioeconomic trends among US-born black and white women. Am J Public Health 2015;105:388–97. https://doi.org/10.2105/AJPH.2014.301936.

[12] Hosokawa M, Imazeki S, Mizunuma H, Kubota T, Hayashi K. Secular trends in age at menarche and time to establish regular menstrual cycling in Japanese women born between 1930 and 1985. BMC Womens Health 2012;12:1. https://doi.org/10.1186/1472-6874-12-19.

[13] Petersohn I, Zarate-Ortiz A, Cepeda-Lopez A, Melse-Boonstra A, Petersohn I, Zarate-Ortiz AG, et al. Time Trends in Age at Menarche and Related Non-Communicable Disease Risk during the 20th Century in Mexico. Nutrients 2019;11:394. https://doi.org/10.3390/nu11020394.

[14] Strauss J, Beegle K, Sikoki B, Dwiyanto A, Herwati Y, Witoelar F, et al. The 5th Wave of the Indonesia Family Life Survey (IFLS): Overview and Field Report 2016.

[15] Lee MH, Kim SH, Oh M, Lee KW, Park MJ. Age at menarche in Korean adolescents: Trends and influencing factors. Reprod Health 2016;13:1–7. https://doi.org/10.1186/s12978-016-0240-y.

[16] Lim SW, Ahn JH, Lee JA, Kim DH, Seo JH, Lim JS. Early menarche is associated with metabolic syndrome and insulin resistance in premenopausal Korean women. Eur J Pediatr 2016;175:97–104. https://doi.org/10.1007/s00431-015-2604-7.

[17] Rachmi CN, Agho KE, Li M, Baur LA. Stunting, underweight and overweight in children aged 2.0-4.9 years in Indonesia: Prevalence trends and associated risk factors. PLoS One 2016;11:1–17. https://doi.org/10.1371/journal.pone.0154756.

[18] Badan Pusat Statistik Indonesia. Regulation of the Head of Indonesia's Bureau of Statistics, Number 37 of 2010 concerning Urban and Rural Classification in Indonesia (Peraturan Kepala Badan Pusat Statistik Nomor 37 Tahun 2010 tentang Klasifikasi Perkotaan dan Perdesaan di Indonesia). 2010.

[19] Wahab A, Wilopo SA, Hakimi M, Ismail D. Declining age at menarche in Indonesia: A systematic review and meta-analysis. Int J Adolesc Med Health 2018:1–9. https://doi.org/10.1515/ijamh-2018-0021.

[20] Yang L, Li L, Millwood IY, Peters SAE, Chen Y, Guo Y, et al. Age at menarche and risk of major cardiovascular diseases: Evidence of birth cohort effects from a prospective study of 300,000 Chinese women. Int J Cardiol 2017;227:497–502. https://doi.org/10.1016/j.ijcard.2016.10.115.

[21] Chang CJ, Lai MM, Lin CC, Liu CS, Li TC, Li CI, et al. Age at menarche and its association with the metabolic syndrome in Taiwan. Obes Res Clin Pract 2016;10:S26–34. https://doi.org/10.1016/j.orcp.2015.10.003.

[22] McDowell MA, Brody DJ, Hughes JP. Has Age at Menarche Changed? Results from the National Health and Nutrition Examination Survey (NHANES) 1999-2004. J Adolesc Heal 2007;40:227–31. https://doi.org/10.1016/j.jadohealth.2006.10.002.

[23] Prentice P, Viner RM. Pubertal timing and adult obesity and cardiometabolic risk in women and men: A systematic review and meta-analysis. Int J Obes 2013;37:1036–43. https://doi.org/10.1038/ijo.2012.177.

[24] Won JC, Hong JW, Noh JH, Kim D-J. Association Between Age at Menarche and Risk Factors for Cardiovascular Diseases in Korean Women. Medicine (Baltimore) 2016;95:e3580. https://doi.org/10.1097/md.0000000000003580.

[25] Bell JA, Carslake D, Wade KH, Richmond RC, Langdon RJ, Vincent EE, et al. Influence of puberty timing on adiposity and cardiometabolic traits: A Mendelian randomisation study. PLoS Med 2018;15:1–25. https://doi.org/10.1371/journal.pmed.1002641.

[26] Gill D, Brewer CF, Del Greco M F, Sivakumaran P, Bowden J, Sheehan NA, et al. Age at menarche and adult body mass index: a Mendelian randomization study. Int J Obes 2018;42:1574–81. https://doi.org/10.1038/s41366-018-0048-7.

[27] Davison KK, Susman EJ, Birch LL. Percent Body Fat at Age 5 Predicts Earlier Pubertal Development Among Girls at Age 9 2003;111:815–21.

[28] Martínez J, Araújo C, Horta BL, Gigante DP. Growth patterns in early childhood and the onset of menarche before age twelve. Rev Saude Publica 2010;44:249–60. https://doi.org/10.1590/s0034-89102010000200004.

[29] Flom JD, Cohn BA, Tehranifar P, Houghton LC, Wei Y, Protacio A, et al. Earlier age at menarche in girls with rapid early life growth: cohort and within sibling analyses. Ann Epidemiol 2017;27:187-193.e2. https://doi.org/10.1016/j.annepidem.2017.01.004.

[30] Shalitin S, Phillip M. Role of obesity and leptin in the pubertal process and pubertal growth - A review. Int J Obes 2003;27:869–74. https://doi.org/10.1038/sj.ijo.0802328.

[31] Matkovic V, Ilich JZ, Skugor M, Badenhop NE, Goel P, Clairmont A, et al. Leptin is inversely related to age at menarche in human females. J Clin Endocrinol Metab 1997;82:3239–45. https://doi.org/10.1210/jc.82.10.3239.

[32] Aurino E, Schott W, Penny ME, Behrman JR. Birth weight and prepubertal body size predict menarcheal age in India, Peru, and Vietnam. Ann N Y Acad Sci 2018;1416:107–16. https://doi.org/10.1111/nyas.13445.

[33] Walvoord EC. The timing of puberty: Is it changing? Does it matter? J Adolesc Heal 2010;47:433–9. https://doi.org/10.1016/j.jadohealth.2010.05.018.

[34] Currie C, Ahluwalia N, Godeau E, Nic Gabhainn S, Due P, Currie DB. Is obesity at individual and national level associated with lower age at menarche? Evidence from 34 countries in the health behaviour in school-aged children study. J Adolesc Heal 2012;50:621–6. https://doi.org/10.1016/j.jadohealth.2011.10.254.

[35] Kaplowitz PB. Link Between Body Fat and the Timing of Puberty. Pediatrics 2008;121:S208–17. https://doi.org/10.1542/peds.2007-1813f.

[36] Pierce MB, Leon DA. Age at menarche and adult BMI in the Aberdeen Children of the 1950s Cohort Study. Am J Clin Nutr 2005;82:733–9.

[37] Le-Ha C, Beilin LJ, Burrows S, Huang RC, Hickey M, Mori TA, et al. Age at menarche and childhood body mass index as predictors of cardio-metabolic risk in young adulthood: A prospective cohort study. PLoS One 2018;13:1–12. https://doi.org/10.1371/journal.pone.0209355.

[38] Chan YM, Feld A, Jonsdottir-Lewis E. Effects of the Timing of Sex-Steroid Exposure in Adolescence on Adult Health Outcomes. J Clin Endocrinol Metab 2019;104:4758–86. https://doi.org/10.1210/jc.2019-00569.

[39] Onland-Moret NC, Peeters PHM, Van Gils CH, Clavel-Chapelon F, Key T, Tjønneland A, et al. Age at menarche in relation to adult height: The EPIC study. Am J Epidemiol 2005;162:623–32. https://doi.org/10.1093/aje/kwi260.

[40] Lundeen EA, Norris SA, Martorell R, Suchdev PS, Mehta NK, Richter LM, et al. Early life growth predicts pubertal development in South African adolescents. J Nutr 2016;146:622–9. https://doi.org/10.3945/jn.115.222000.

[41] Merlino LA, Cerhan JR, Criswell LA, Mikuls TR, Saag KG. Estrogen and Other Female Reproductive Risk Factors Are Not Strongly Associated With the Development of Rheumatoid Arthritis in Elderly Women. Semin Arthritis Rheum 2003;33:72–82. https://doi.org/10.1016/S0049-0172(03)00084-2.

[42] Hamajima N, Hirose K, Tajima K, Rohan T, Friedenreich CM, Calle EE, et al. Menarche, menopause, and breast cancer risk: Individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol 2012;13:1141–51. https://doi.org/10.1016/S1470-2045(12)70425-4.

[43] Lieberoth S, Gade EJ, Brok J, Backer V, Thomsen SF. Age at menarche and risk of asthma: Systematic review and meta-analysis. J Asthma 2014;51:559–65. https://doi.org/10.3109/02770903.2014.903966.

[44] Lu J, Zhang J, Du R, Wang T, Xu M, Xu Y, et al. Age at menarche is associated with the prevalence of non-alcoholic fatty liver disease later in life: J Diabetes 2017;9:53–60. https://doi.org/10.1111/1753-0407.12379.

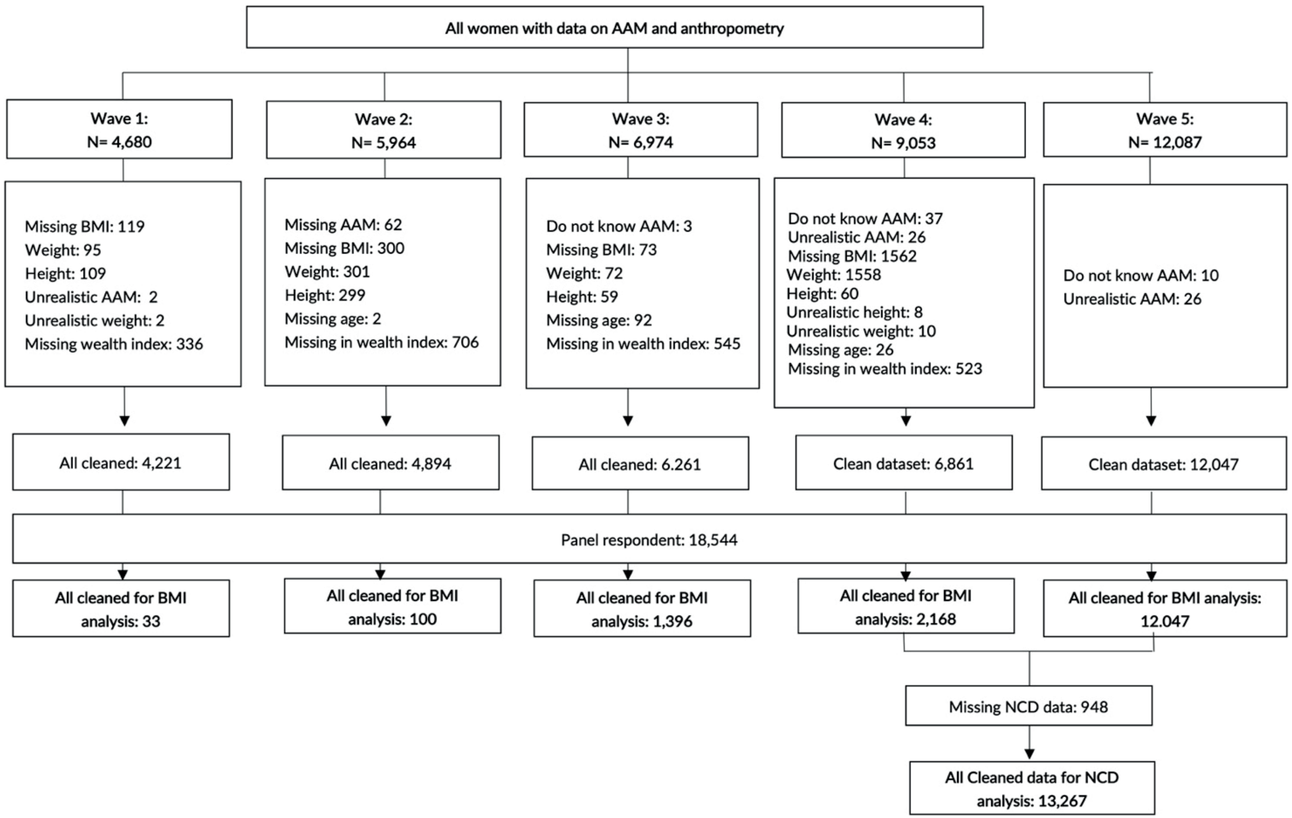
[45] Karlson EW, Mandl LA, Hankinson SE, Grodstein F. Do breast-feeding and other reproductive factors influence future risk of rheumatoid arthritis? Results from the nurses' health study. Arthritis Rheum 2004;50:3458–67. https://doi.org/10.1002/art.20621.

[46] Pedersen M, Stripp C, Klarlund M, Olsen SF, Tjønneland AM, Frisch M. Diet and risk of rheumatoid arthritis in a prospective cohort. - Travel Doctor Online 2005;32.

[47] Must A, Phillips SM, Naumova EN, Blum M, Harris S, Dawson-Hughes B, et al. Recall of early menstrual history and menarcheal body size: After 30 years, how well do women remember? Am J Epidemiol 2002;155:672–9. https://doi.org/10.1093/aje/155.7.672.

[48] Bosetti C, Tavani A, Negri E, Trichopoulos D, La Vecchia C. Reliability of data on medical conditions, menstrual and reproductive history provided by hospital controls. J Clin Epidemiol 2001;54:902–6. https://doi.org/10.1016/S0895-4356(01)00362-6.

SUPPLEMENTARY INFORMATION



Supplementary Figure 2.1. Overview of study population and results of data cleaning

Chapter 3

Intra-uterine maternal haemoglobin concentration is associated with impaired cognitive function in stunted adolescents: results from a 17-year longitudinal cohort study in Indonesia

Muhammad Asrullah, Hastrin Hositanisita, Siti Muslimatun, Monique L'Hoir, Edith JM Feskens, Alida Melse-Boonstra

Under review of journal

ABSTRACT

Maternal anaemia is a major public health problem that has a negative impact on the neurodevelopment of children under five years, but its impact on long-term cognitive performance is largely unknown. This study aims to investigate the association between intra-uterine maternal haemoglobin (Hb) concentration and cognitive function of their offspring during adolescence. We performed secondary analysis of longitudinal cohort data of 363 paired pregnant mothers and their offspring at 10-14 years of age from the Indonesia Family Life Survey (IFLS) conducted in 1997-2014. Multiple linear regression models with maternal Hb as exposure and cognitive function (Raven's Progressive Matrices test) as outcome were explored, with adjustments for maternal age, maternal height, and socioeconomic status. The weighted anaemia prevalence was 49.3% in pregnant mothers and 22.2% in adolescents. The mean total cognitive score of adolescents was 12.4 points out of 17. Adolescents who were stunted, anaemic, or living in a rural area had a significantly lower cognitive score than their counterparts. In the adjusted model, maternal Hb was not associated with adolescent cognitive function (β: 0.14; 95%CI: -0.052 – 0.340). However, the effect of maternal Hb concentration on cognitive function of their offspring was modified by stunting status (β, stunted: 0.44; 95%CI: 0.05 – 0.82 and β, non-stunted: 0.01; 95%CI: -0.02 – 0.24, p-interaction 0.039). This study shows that adverse cognitive outcomes at adolescent age is likely to be multi-causal and may best be addressed by tackling pregnancy-related anaemia as well as warranting good nutrition for growth and development during childhood.

Keywords: Pregnancy, Anaemia, Adolescent, Cognition, Indonesia

INTRODUCTION

About one-third of the world's population, especially in Low-and Middle-Income Countries (LMICs), is suffering from iron deficiency anaemia, a condition with abnormally small-sized red blood cells and reduced haemoglobin (Hb) concentration [1]. Anaemia affects around 800 million children and women in the world, with almost half of all pregnant women being affected [2]. In Indonesia, anaemia is considered a moderate public health problem with a prevalence among pregnant women of 37.1% in 2013, which increased to 48.9% in 2018 based on the Indonesian National Basic Health Survey [3].

Pregnancy is a vital stage in human development, and maternal anaemia during the intra-uterine period can affect growth and development of the offspring. A meta-analysis of 26 cohort studies (both with prospective and retrospective study designs) conducted in LMICs confirmed that anaemia during pregnancy is associated with low birth weight, preterm birth, and perinatal mortality [4]. A cohort study in India among 1,007 pregnant women found that women who were anaemic in the second trimester of gestation gave birth to infants with lower birth weight [5]. Low birth weight is an important determinant of stunting later in life, as also shown for children aged 0 – 23 months in Indonesia based on three waves of data (2000, 2007, and 2014) from the Indonesian Family Life Survey (IFLS) [6]. Previous studies also found that maternal anaemia is associated with anaemia in the offspring. For instance, a study in China found that infants at the age of 5-7 months and 11-13 months had a higher risk of anaemia when their mothers had been anaemic during mid-pregnancy [7]. An intervention study among 359 Filipino pregnant women found that maternal iron deficiency anaemia is linked to an increased risk of iron deficiency during infancy [8].

More importantly, children tend to have delayed neurocognitive development, including mental and motor development, at young age if their mothers had been anaemic during pregnancy [9]. This may be due to the non-reversible nature of neurodevelopmental damage incurred during early stages of life [10]. Also, anaemia during infancy, which is predominantly caused by iron deficiency worldwide [11], is associated with poorer cognitive and motor development [12,13]. The potential mechanism underlying an iron deficiency-related cognitive deficit is not yet well studied in humans [14], but animal studies showed that iron deficiency may interfere with neurogenesis, myelination, dendrite growth, and protein expression during neurodevelopment [15–17]. A study in India showed that 3-week old infants whose mothers had not been anaemic during pregnancy scored 3.9 times higher on behavioural outcomes such as attention and interactive abilities [18]. A nationwide prospective cohort study over 30 years conducted among 11,656 Finnish women found that low maternal Hb, especially during late gestation, was associated with lower educational performance of their offspring at the ages of 14 and 16 years [19].

Evidence on the persistent impact of early-life anaemia on cognitive performance in later life has been summarized in a systematic review including 27 observational and randomized controlled trials (RCT), but it was concluded that there is a scarcity of studies with long-term follow-up into adolescence and adulthood [20,21]. We therefore aimed to evaluate the relationship between intra-uterine maternal Hb concentration and cognitive function of their offspring at adolescent age (10-14 years), using longitudinal data from the Indonesian Family Life Survey (IFLS).

MATERIAL AND METHODS

Indonesian Family Life Survey (IFLS)

IFLS is a longitudinal survey in Indonesia that started in 1993/1994 (IFLS 1). The IFLS used a multistage stratified sampling design and collected data at individual and household level [22]. The total sample of IFLS comprises >30,000 individuals from 13 out of 27 provinces in Indonesia and represents about 83% of the Indonesian population. IFLS 2 was performed in 1997/1998, IFLS 3 in 2000, IFLS 4 in 2007/2008, and IFLS 5 in 2014/2015. For the current analysis, we only used data from IFLS waves 2 to 5, since maternal Hb concentration was not assessed in the first wave.

Participants

Subjects were adolescents aged 10-14 years from IFLS waves 4 and 5, who had a complete cognitive score record (n= 8,109). Participants without weight and height measurements (n= 22) and Hb data (n= 349) were excluded, yielding 7,712 adolescents. A total of 867 pregnant women >15 years with complete Hb data from waves 2 and 3 were then paired with their children at adolescent age (n= 363; Figure 3. 1).

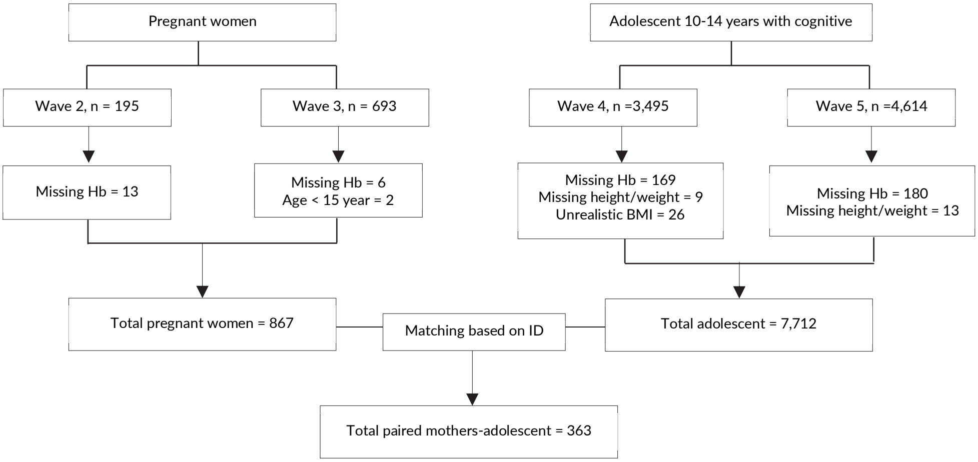


Figure 3.1. Flowchart of participant selection based on data availability

Assessment of cognitive function

Cognitive function was measured using a subset of questions from Raven's Progressive Matrices (RPM). RPM is the most commonly used nonverbal test to measure general intellectual ability, or cognitive function. It relates to several abilities such as analysing, reasoning, and understanding of unconcret concepts [23]. This intelligence test has been validated for use in different socio-economic groups, ethnicities, and cultures [24]. Two members of the testing division of the Indonesian Ministry of Education adapted the test for the Indonesian setting by drawing items from the National Achievement Test [25]. In IFLS, an RPM module (EK1) was developed for participants aged 7-14 years while a larger module including EK1 items was developed for participants aged 15 years or older. EK1, as used for the present study, consists of 17 questions; 12 questions to test cognitive abilities, such as general intelligence and non-concrete reasoning, and 5 questions to test mathematic skills. Correct answers were scored as '1' and incorrect answers as '0', so that the maximum total score was 17.

Assessment of maternal anaemia

Hb concentrations were determined from finger prick blood. Hb was measured consistently in all waves using a Hemocue (HemoCue Hb201+) [22]. Based on WHO guidance, anaemia status was defined as Hb <11.5 g/dl for adolescents aged 10-11 years, < 12.0 g/dL for adolescents aged 12-14 years, and <11 g/dL for pregnant women [26]. In the present study, Hb concentrations were not adjusted for altitude or smoking.

Assessment of other variables

Body Mass Index (BMI)-for-age and height-for-age z-scores were calculated using the WHO growth standard for children aged 5-19 years, with a BMI-for-age z-score <-2 SD classified as thin, ≥-2 SD to ≤1 SD as normal body weight, >1 SD as overweight, and >2SD as obese [27]. Height-for-age z score (HAZ) <-2 SD defined stunting [28]. Per capita expenditure (PCE) was used to indicate socioeconomic status (SES) [28]. The PCE was formulated based on all household expenditures (expenditures for food and non-food items, education and housing) over a month, divided by the number of household members [29]. To correct for inflation rate and to standardize the value, PCE of waves 2 and 3 were converted to Jakarta's price level in December 2000 [29]. Missing values (n=2) were imputed with the median value of PCE in the sub-district where they lived. PCE is presented as tertiles, with the first tertiles representing the lowest per capita expenditure class [30].

Statistical analysis

The statistical analysis was performed using STATA version 16 [31]. Data analysis was done based on complete cases (Figure 1). A comparison was made between included (n=363) and excluded cases (n=9) to verify that this approach did not lead to selection bias (Supplementary Table 3.1). Subjects' characteristics such as age, sex, living area, BMI z-score, and HAZ were first analysed descriptively. Before regression analysis, the assumption of normal value distribution was checked for continuous data by inspecting the Q-Q plot of regression standardized residuals, and multicollinearity was checked by variance inflation factor (VIF<10), with VIF < 10 reflecting no collinearity. A one-way ANOVA was performed to analyse differences in total cognitive scores between groups. Multiple linear regression was used to relate maternal Hb concentration during pregnancy to adolescents' total cognitive score before and after adjusting for maternal age, maternal height, and SES**.**

Adolescent characteristics, such as Hb concentration, HAZ, and BMI-for-age-z-score were tested to be effect modifiers or mediating factors, since these factors may either be more proximate predictors in the pathway between maternal Hb and cognitive outcomes, or they may amplify or downplay any effects. This was done by including interaction terms between maternal Hb concentration and children's Hb concentration, HAZ, and BMI-for-age-z-scores to identify the effect modifiers, and a mediation analysis [32] to identify the mediating factors. Variables with a P-value <0.05 in the interaction model were used for stratification to estimate the group-specific regression coefficients with their 95% confidence intervals.

RESULTS

In Table 3.1, characteristics of the 363 paired mothers-adolescents are summarized. Almost half of the pregnant women (49.3%) were anaemic. Anaemia prevalence among adolescents was 22.2%, and 32.3% of the adolescents were stunted. The mean cognitive score of the adolescents was 12.35 out of 17 (Table 3.2). Adolescents who were stunted, anaemic or lived in a rural area had lower cognitive test scores than their counterparts who were non-stunted (11.68 ± 3.01 vs 12.66 ± 2.86, P=0.003), non-anaemic (11.33 ± 3.28 vs 12.66 ± 2.74, P<0.001), or lived in an urban area (11.92 ± 3.27 vs 12.68 ± 2.62, P=0.015). Cognitive score did not differ between adolescents whose mothers had been anaemic or non-anaemic during pregnancy, nor for any of the other characteristics.

Table 3.1. Characteristics of pregnant women and their 10-14 y old adolescents (n=363) from IFLS waves 2-5 who were included in the data analysis.

	Characteristics	Values[1]
Household	Per capita expenditure, IDR	
	• Low	91 (25.07)
	• Medium	182 (50.14)
	• High	90 (24.79)
	Living area	
	• Urban	214 (58.63)
	• Rural	148 (40.55)
Pregnant women	Age, y	
	• < 20 y	50 (13.77)
	• 20 – 35 y	279 (76.86)
	• > 35 y	33 (9.09)
	Haemoglobin concentration, g/dL	11.06 ± 1.55
	• Anemic	179 (49.31)
Adolescents	Age, y	13.17 ± 1.24
	Sex (boys / girls)	179 (49.31) / 184 (50.69)
	BMI-for-age z-score	0.002 ± 1.00
	• Thin	0 (0)
	• Normal weight	316 (87.05)
	• Overweight	28 (7.71)
	• Obese	19 (5.23)
	Height-for-age z-score	-1.52 ± 1.02
	• Stunted	117 (32.23)
	Hemoglobin concentration, g/dL	12.90 ± 1.47
	• Anemic	81 (22.19)

[1] Values are means ± SD for continuous variables, and n (%) for categorical data; IFLS = Indonesian Family Life Survey; IDR = Indonesian Rupiah based on December 2000 Jakarta baseline

Table 3.2. Mean (± SD) total cognitive score on the Raven's Progressive Matrices (RPM) test of adolescents (n=363) from IFLS in relation to household, maternal and individual characteristics.

	Characteristics	Cognitive Score (Mean ± SD)	P Value
Household	Per capita expenditure, IDR		
	• Low	12.07 ± 2.89	0.581
	• Medium	12.43 ± 3.01	
	• High	12.46 ± 2.89	
	Living area		0.015
	• Urban	12.68 ± 2.62	
	• Rural	11.92 ± 3.27	
Pregnant women	Age, y		
	• < 20 y	11.71 ± 2.84	0.171
	• 20 – 35 y	12.50 ± 2.92	
	• > 35 y	12.03 ± 3.26	
	Haemoglobin concentration		
	• Anaemic	12.15 ± 2.88	0.204
	• Non-anaemic	12.66 ± 2.74	
Adolescents	Sex		
	• Boys	12.47 ± 2.93	0.426
	• Girls	12.22 ± 2.97	
	BMI-for-age z-score		
	• Thin	-	0.212
	• Normal weight	12.26 ± 2.99	
	• Overweight	13.28 ± 2.62	
	• Obese	12.31 ± 2.45	
	Height-for-age z-score		
	• Stunted	11.68 ± 3.01	0.003
	• Non-stunted	12.66 ± 2.86	
	Haemoglobin concentration, g/dL		
	• Anaemic	11.33 ± 3.28	0.000
	• Non-anaemic	12.66 ± 2.74	

IFLS = Indonesian Family Life Survey; IDR = Indonesian Rupiah currency based on December 2000 Jakarta baseline

No association was found between maternal Hb and adolescent's cognitive score in unadjusted and adjusted models (Table 3.3). We did not find any mediation of adolescent Hb, BMI-Z score, and HAZ in the association between maternal Hb and adolescent cognitive scores (supplementary Table 2). However, we observed an interaction between maternal haemoglobin concentration and stunting (P=0.039), as well as a difference in cognitive scores between stunted and non-stunted adolescents among the group of anaemic mothers (Supplementary Table 3). Therefore, we continued with stratifying the analysis for stunted and non-stunted adolescents separately. In contrast to the non-stunted population, we found a positive association between maternal haemoglobin concentration and cognitive score in stunted adolescents both in the unadjusted model (β= 0.46, 95%CI 0.08 – 0.84) as well as in the model adjusted for maternal age, maternal height, and socioeconomic status (β= 0.44, 95%CI 0.05 – 0.82) (Table 3). No interaction was observed for maternal Hb and adolescent BMI (p= 0.830), and maternal Hb and adolescent Hb (p=0.844).

Table 3.3. Multiple linear regression of the association between maternal haemoglobin concentration (g/L) during pregnancy and cognitive score of her adolescent child aged 10-14 years from IFLS waves 2-5, adjusted for maternal age, maternal height, and socioeconomic status

	Cognitive Score[1]					
	Unadjusted			Adjusted		
	β	(95% CI)	P-value	β	(95% CI)	P-value
Total study population (n=363)	0.14	-0.06 , 0.34	0.165	0.14	-0.05 , 0.34	0.160
Stunted adolescents (n=117)	0.46	0.08 , 0.84	0.018	0.44	0.05 , 0.82	0.026
Non-stunted adolescents (n=246)	0.01	-0.22 , 0.23	0.960	0.01	-0.22 , 0.24	0.922

[1]Cognitive score was assessed using the EK1 module from the Raven's Progressive Matrices test in IFLS

DISCUSSION

In this study, we examined the association between maternal Hb concentration and her offspring's cognitive function presented as RPM total scores at adolescent age (10-14 years). We found that adolescents who suffered from anaemia, were stunted, or lived in a rural area had lower total cognitive scores. Maternal Hb was not associated with adolescent cognitive function. However, the association between maternal Hb concentration and cognitive function of their offspring was modified by stunting status of the adolescents and showed a positive association in stunted adolescents indicating synergy.

Our study showed that almost half of pregnant women were anaemic (49.3%), and the overall anaemia prevalence in adolescents was 22.9%. This shows that, based on WHO classification, anaemia was a moderate (adolescents) to severe (pregnant women) public health problem in the population under study [11]. It should be noted that the data from pregnant women in this study originated from IFLS waves 2 and 3, conducted in 1997 and 2000. Another study also reported that the prevalence of anaemia during pregnancy in this period was high (45.1-46.5%) [33]. An explanation for the high prevalence of maternal anaemia during this time period could be the Indonesian economic crisis, in which the poverty increased from 17% to 24% from 1996 to 1999 [34]. Although there has been a dip in the prevalence of maternal anaemia recorded by the national basic health survey (Riskesdas; Riset Kesehatan Dasar) in 2013, i.e. 37.1%, data from the most recent Riskesdas conducted in 2018, shows a similarly high prevalence of maternal anaemia, i.e. 48.9%, despite the fact that a nationwide iron-folic acid (IFA) supplementation program has been implemented since 1990 [3]. Incomplete coverage of the IFA supplementation program, with a national coverage of ~78% from 2002 to 2007, might be a reason for

3

the lack of decline in the prevalence of maternal anaemia. It should also be noted that IFA supplementation has not been distributed equally over the population, i.e. pregnant women who were higher educated and those who lived in urban areas took IFA supplementation more often than pregnant women with a lower educational level and who lived in rural areas [35]. Populations living in rural areas often experience more health disparities [36]. This may be related to geographic isolation, lower SES, limited access to medical and preventive care, and less job opportunities. A previous study confirmed that low SES was associated with anaemia during pregnancy in Indonesia [37].

Our finding on the prevalence of anaemia among adolescents is largely in line with the most recent Riskesdas (2018), showing that the prevalence of anaemia was 26.8% among those aged 5-14 years and 32.4% among those aged 15-24 years [3]. Anaemia among adolescents can be due to the increased need for iron and other micronutrients in support of their physical growth and, for girls, to compensate for menstrual loss of iron [38] and the adoption of unhealthy eating habits in a time period of physical, mental, and emotional change [39].

We did not find an overall association between maternal Hb concentration and total cognitive scores among adolescents either in unadjusted or adjusted models. The limited number of studies on this topic performed to date have shown inconsistent findings [20,21]. Some observational studies found a negative/inverse association [9,40,41], or an inverted U-shaped association [42] when developmental outcomes were measured in infancy. The largest 30-year prospective cohort study to date, including 11,656 Finnish women, showed that low maternal haemoglobin, especially during late pregnancy, was linked to lower educational achievement of their offspring at the age of 14 and 16 years [19]. This is in line with study findings from 850 women and their children in China, showing that maternal anaemia, especially in the third trimester, was associated with worse neurodevelopment in their children [7]. We could not differentiate between anaemia across trimesters of pregnancy since data on gestational age at the time point of Hb testing were not collected. Discrepancies between study findings may also be explained by certain contextual differences, such as differences in SES, prevalence of malnutrition, health status, and health care access.

It should be emphasized that Hb cannot be interpreted as a direct measure of iron deficiency, and therefore it is also worthwhile to look at studies that used indicators of iron status. Iron plays an important role during foetal development in cell maturation and myelination of the frontal lobes [43]. Iron-containing enzymes are crucial especially in the development of the striatum and hippocampus, [21] which are important for memory, optimal learning, processing speed, and decision making [44]. Iron deficiency during specific time windows of pregnancy may importantly modify *in utero* neurodevelopment

[21]. A rapid growth of the hippocampus in humans starts in late pregnancy throughout the first year of life [21]. There is some evidence that low maternal iron status especially in the late gestational period is adversely associated with offspring's neurodevelopment from infancy (<1 year) till adulthood (>18 years) [18]. Furthermore, iron deficiency together with low haemoglobin concentration is more clearly associated with long-term deficits in cognitive and motor function of children than low iron status only. Children with IDA and haemoglobin concentration ≤ 105 g/L had consistently lower cognitive abilities as compared to non-anaemic iron deficient children [45]. In children with IDA and low haemoglobin concentration (Hb < 115 g/L for 5–11 years old; Hb < 120 g/L for 12–13 years old), still a positive association between haemoglobin concentration and cognitive performance was shown, although no such association existed in non-anaemic iron-deficient children [46]. A RCT found a beneficial effect of correction of iron status during late pregnancy on developmental child outcomes [7]. In the present study, we did not have information on iron metabolism indicators and therefore could not assess the association between maternal iron status and cognitive outcomes.

The present study only showed a significant association between maternal Hb and cognitive function for adolescents who were stunted. Collective data from 137 countries found that maternal anaemia is one of the key factors of child stunting [47]. About one-third of adolescents in our study were stunted, and it has been shown before that stunted children also have a higher risk of being anaemic [48,49]. Moreover, stunting has been associated with a lower cognitive functioning at school age and adulthood, along with other risk factors, such as poverty and poor home environment [50]. A prospective birth cohort study among 1,291 children conducted in eight countries in Asia, America, and Africa showed that early-onset persistent stunting was associated with lower cognitive development scores at 5 years of age [51]. The effects might persist to adolescent age, since a study from the Philippines showed lower cognition scores at early adolescent age (8 and 11 years) after recovering from stunting [8]. Another study found that stunted Jamaican children still had lower cognitive scores at adolescent age (17-18 years) despite nutritional supplementation and stimulation at the age of 9-24 months [52]. Thus, stunting may be an important explanatory factor in the pathway between maternal anaemia and cognitive function. Nevertheless, our analysis revealed that stunting was rather an effect modifier than a mediating factor between maternal Hb and cognitive outcomes at adolescent age. The results suggested that stunting exacerbates the effect of maternal anaemia on adolescent cognitive function.

Since adolescents in the present study were born during the economic crisis, their parents' economic status may have been affected. The Young Lives study, an observational cohort study among 3000 children in four developing countries (Ethiopia, Peru, India, and Vietnam), found that three factors were strongly associated with cognitive function at adolescent age: child growth (including stunting status), parental education and socioeconomic status [53]. Previous studies in Indonesia found a stronger and more consistent association of adolescents' cognitive scores with socioenvironmental risk factors including stunting than with biomedical factors [54]. Previous IFLS studies found only a weak association of household expenditure with children's cognitive function [55,56]. It should be noted that stunting in adolescents is multi-causal and can be the result of infection, poor nutrition, and environmental stress starting from the foetal period to later in life [57]. Furthermore, inequalities in education and learning outcomes exist, with rural areas lagging behind compared to urban areas in Indonesia [58]. Thus, the lower cognitive function of adolescents who were both exposed to maternal anaemia and were stunted in this study may be attributable to the same root causes of long-term poverty.

To our knowledge, this is one of few studies which evaluated the long-term effects of maternal anaemia on cognitive function in adolescence, using a prospective longitudinal study design. However, gestational age at the time point of Hb testing was not assessed, and no indicators of iron status were measured in this study. Furthermore, this study also did not take into account the altitude and smoking status to correct Hb concentrations as suggested by the WHO [26]. There may also be unmeasured confounding, e.g., by other maternal exposures and variables that impact both maternal nutritional status and child development. In that case, there is a possibility that maternal anaemia may not be causal to poor cognitive development of her stunted adolescent child, but rather is a result of the same cause, i.e., poverty. The RPM is a standardized method to measure non-verbal cognitive ability that has previously been used in Indonesia [59] and is not biased by educational background or by cultural or linguistic deficiencies [60], but we acknowledge that we cannot compare cognitive function measured by RPM with other tools.

CONCLUSION

In conclusion, maternal Hb concentration was, overall, not associated with cognitive function in adolescents aged 10-14 years, but it was associated in those who were stunted. For each 1 g/dL increase in Hb, cognitive scores increased by 0.44 in stunted adolescents, but not in non-stunted ones. This study reveals that adverse cognitive outcomes at adolescent age is likely to be multi-causal.

ACKNOWLEDGEMENTS

The authors would like to thank RAND, who provided the dataset online. The data are available at https://www.rand.org/well-being/social-and-behavioral-policy/data/FLS/IFLS.html

REFERENCES

[1] Chaparro CM, Suchdev PS. Anemia epidemiology, pathophysiology, and etiology in low- and middle-income countries. Ann N Y Acad Sci 2019. https://doi.org/10.1111/nyas.14092.

[2] WHO. The global prevalence of anaemia in 2011. Who 2011.

[3] Kementerian Kesehatan Republik Indonesia. Laporan Nasional Riset Kesehatan Dasar 2018 (Report of Indonesian Basic Health Survey 2018). 2018.

[4] Rahman MM, Abe SK, Rahman MS, Kanda M, Narita S, Bilano V, et al. Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: Systematic review and meta-analysis. Am J Clin Nutr 2016. https://doi.org/10.3945/ajcn.115.107896.

[5] Nair M, Choudhury MK, Choudhury SS, Kakoty SD, Sarma UC, Webster P, et al. Association between maternal anaemia and pregnancy outcomes: A cohort study in Assam, India. BMJ Glob Heal 2016;1:1–9. https://doi.org/10.1136/bmjgh-2015-000026.

[6] Hanifah L, Wulansari R, Meiandayati R, Achadi EL. Stunting trends and associated factors among Indonesian children aged 0-23 months: Evidence from Indonesian Family Life Surveys (IFLS) 2000, 2007 and 2014. Malays J Nutr 2018.

[7] Chang S, Zeng L, Brouwer ID, Kok FJ, Yan H. Effect of iron deficiency anemia in pregnancy on child mental development in rural China. Pediatrics 2013;131. https://doi.org/10.1542/peds.2011-3513.

[8] Mendez MA, Adair LS. Severity and timing of stunting in the first two years of life affect performance on cognitive tests in late childhood. J Nutr 1999;129:1555–62. https://doi.org/10.1093/jn/129.8.1555.

[9] Tran TD, Tran T, Simpson JA, Tran HT, Nguyen TT, Hanieh S, et al. Infant motor development in rural Vietnam and intrauterine exposures to anaemia, iron deficiency and common mental disorders: A prospective community-based study. BMC Pregnancy Childbirth 2014;14. https://doi.org/10.1186/1471-2393-14-8.

[10] Beard JL. Why iron deficiency is important in infant development. J. Nutr., 2008. https://doi.org/10.1093/jn/138.12.2534.

[11] De Benoist B, McLean E, Egli I, Cogswell M. WHO | Worldwide prevalence on anaemia 1993-2005. 2008.

[12] Sania A, Sudfeld CR, Danaei G, Fink G, McCoy DC, Zhu Z, et al. Early life risk factors of motor, cognitive and language development: A pooled analysis of studies from low/middle-income countries. BMJ Open 2019;9. https://doi.org/10.1136/bmjopen-2018-026449.

[13] Grantham-McGregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. J Nutr 2001;131:649S-668S.

[14] Veena SR, Gale CR, Krishnaveni G V., Kehoe SH, Srinivasan K, Fall CHD. Association between maternal nutritional status in pregnancy and offspring cognitive function during childhood and adolescence; a systematic review. BMC Pregnancy Childbirth 2016. https://doi.org/10.1186/s12884-016-1011-z.

[15] Beard JL, Felt B, Schallert T, Burhans M, Connor JR, Georgieff MK. Moderate iron deficiency in infancy: Biology and behavior in young rats. Behav Brain Res 2006;170:224–32. https://doi.org/10.1016/j.bbr.2006.02.024.

[16] Lozoff B, Beard J, Connor J, Felt B, Georgieff M, Schallert T. Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutr Rev 2006;64. https://doi.org/10.1301/nr.2006.may.S34-S43.

[17] Fretham SJB, Carlson ES, Georgieff MK. The role of iron in learning and memory. Adv Nutr 2011;2:112–21. https://doi.org/10.3945/an.110.000190.

[18] Menon KC, Ferguson EL, Thomson CD, Gray AR, Zodpey S, Saraf A, et al. Effects of anemia at different stages of gestation on infant outcomes. Nutrition 2016. https://doi.org/10.1016/j.nut.2015.07.009.

[19] Fararouei M, Robertson C, Whittaker J, Sovio U, Ruokonen A, Pouta A, et al. Maternal Hb during pregnancy and offspring's educational achievement: A prospective cohort study over 30 years. Br J Nutr 2010;104:1363–8. https://doi.org/10.1017/S0007114510002175.

[20] Janbek J, Sarki M, Specht IO, Heitmann BL. A systematic literature review of the relation between iron status/anemia in pregnancy and offspring neurodevelopment. Eur J Clin Nutr 2019. https://doi.org/10.1038/s41430-019-0400-6.

[21] Alwan N, Hamamy H. Maternal Iron Status in Pregnancy and Long-Term Health Outcomes in the Offspring. J Pediatr Genet 2015. https://doi.org/10.1055/s-0035-1556742.

[22] Strauss J, Witoelar F, Sikoki B. The Fifth Wave of the Indonesia Family Life Survey: Overview and Field Report: Volume 1. vol. 1. 2016. https://doi.org/10.7249/wr1143.1.

[23] Prabhakaran V, Smith JAL, Desmond JE, Glover GH, Gabrieli JDE. Neural substrates of fluid reasoning: An fMRI study of neocortical activation during performance of the Raven's Progressive Matrices Test. Cogn Psychol 1997;33:43–63. https://doi.org/10.1006/cogp.1997.0659.

[24] Raven J. The Raven's Progressive Matrices: Change and Stability over Culture and Time. Cogn Psychol 2000. https://doi.org/10.1006/cogp.1999.0735.

[25] Frankenberg E, Thomas D. The Indonesia Family Life Survey (IFLS): Study Design and Results from Waves 1 and 2. n.d.

[26] World Health Organization. Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity. Miner Nutr Inf Syst World Heal Organ 2013:1–6. https://doi.org/2011.

[27] WHO. World Health Organization. Growth reference data for 5-19 years. WHO 2007. https://doi.org/10.1002/mds.26203.

[28] Preedy VR. Handbook of Anthropometry: Physical Measures of Human Form in Health and Disease. Handb Anthr Phys Meas Hum Form Heal Dis 2012:1–3107. https://doi.org/10.1007/978-1-4419-1788-1.

[29] Witoelar F. Note on the construction of the IFLS consumption expenditure aggregates 2009.

[30] Vaezghasemi M, Razak F, Ng N, Subramanian S V. Inter-individual inequality in BMI: An analysis of Indonesian Family Life Surveys (1993–2007). SSM - Popul Heal 2016. https://doi.org/10.1016/j.ssmph.2016.09.013.

[31] StataCorp. Stata Statistical Software: Release 16 2019.

[32] Mehmetoglu M. Medsem: A Stata package for statistical mediation analysis. Int J Comput Econ Econom 2018;8:63–78. https://doi.org/10.1504/IJCEE.2018.088321.

[33] Barkley JS, Kendrick KL, Codling K, Muslimatun S, Pachón H. Anaemia prevalence over time in Indonesia: Estimates from the 1997, 2000, and 2008 Indonesia Family Life Surveys. Asia Pac J Clin Nutr 2015;24:452–5. https://doi.org/10.6133/apjcn.2015.24.3.22.

[34] Rizky M, Suryadarma D, Suryahadi A. Effect of Growing up Poor on Labor Market Outcomes. ADBI Work Pap Ser 2019.

[35] Fiedler J, D'Agostino A, Sununtnasuk C. Technical Brief a Rapid Initial Assessment of the Distribution and Consumption of Iron – Folic Acid Tablets Through Antenatal Care in Ethiopia 2014.

[36] Irianti S, Prasetyoputra P. Rural–Urban Disparities in Access to Improved Sanitation in Indonesia: A Decomposition Approach. SAGE Open 2021;11. https://doi.org/10.1177/21582440211029920.

[37] Chandra AF, Marsigit J, Pratiwi AA, Akhmad SR, Andrianus A, Priyatini T. Education and Socioeconomic Status as Risk Factors of Anemia in Pregnancy: A Cross-Sectional Study in Puskesmas Kecamatan Duren Sawit. Adv Sci Lett 2018. https://doi.org/10.1166/asl.2018.12765.

[38] de Benoist B, McLean E, Egli I, Cogswell M. Worldwide prevalence of anaemia 1993-2005: WHO global database on anaemia. / Edited by Bruno de Benoist, Erin McLean, Ines Egli and Mary Cogswell. 2008. https://doi.org/10.1017/S1368980008002401.

[39] Agustina R, Nadiya K, El Andini A, Setianingsih AA, Sadariskar AA, Prafiantini E, et al. Associations of meal patterning, dietary quality and diversity with anemia and overweight-obesity among Indonesian schoolgoing adolescent girls in West Java. PLoS One 2020;15:1–19. https://doi.org/10.1371/journal.pone.0231519.

[40] Hernández-Martínez C, Canals J, Aranda N, Ribot B, Escribano J, Arija V. Effects of iron deficiency on neonatal behavior at different stages of pregnancy. Early Hum Dev 2011;87:165–9. https://doi.org/10.1016/j.earlhumdev.2010.12.006.

[41] Aranda N, Hernández-Martínez C, Arija V, Ribot B, Canals J. Haemoconcentration risk at the end of pregnancy: Effects on neonatal behaviour. Public Health Nutr 2017;20:1405–13. https://doi.org/10.1017/S136898001600358X.

[42] Mireku MO, Davidson LL, Koura GK, Ouédraogo S, Boivin MJ, Xiong X, et al. Prenatal hemoglobin levels and early cognitive and motor functions of one-year-old children. Pediatrics 2015;136:e76–83. https://doi.org/10.1542/peds.2015-0491.

[43] Todorich B, Pasquini JM, Garcia CI, Paez PM, Connor JR. Oligodendrocytes and myelination: The role of iron. Glia 2009;57:467–78. https://doi.org/10.1002/glia.20784.

[44] O'Shea A, Cohen RA, Porges EC, Nissim NR, Woods AJ. Cognitive aging and the hippocampus in older adults. Front Aging Neurosci 2016. https://doi.org/10.3389/fnagi.2016.00298.

[45] Carter RC, Jacobson JL, Burden MJ, Armony-Sivan R, Dodge NC, Angelilli ML, et al. Iron deficiency anemia and cognitive function in infancy. Pediatrics 2010;126:427–34. https://doi.org/10.1542/peds.2009-2097.

[46] Sungthong R, Mo-suwan L, Chongsuvivatwong V. Effects of haemoglobin and serum ferritin on cognitive function in school children. Asia Pac J Clin Nutr 2002;11:117–22. https://doi.org/10.1046/j.1440-6047.2002.00272.x.

[47] Danaei G, Andrews KG, Sudfeld CR, Fink G, McCoy DC, Peet E, et al. Risk Factors for Childhood Stunting in 137 Developing Countries: A Comparative Risk Assessment Analysis at Global, Regional, and Country Levels. PLoS Med 2016. https://doi.org/10.1371/journal.pmed.1002164.

[48] Wang JY, Hu PJ, Luo DM, Dong B, Ma Y, Dai J, et al. Reducing Anemia Among School-Aged Children in China by Eliminating the Geographic Disparity and Ameliorating Stunting: Evidence From a National Survey. Front Pediatr 2020. https://doi.org/10.3389/fped.2020.00193.

[49] Rahman MS, Mushfiquee M, Masud MS, Howlader T. Association between malnutrition and anemia in under-five children and women of reproductive age: Evidence from Bangladesh demographic and Health Survey 2011. PLoS One 2019. https://doi.org/10.1371/journal.pone.0219170.

[50] Black MM, Walker SP, Fernald LCH, Andersen CT, DiGirolamo AM, Lu C, et al. Early childhood development coming of age: science through the life course. Lancet 2017;389:77–90. https://doi.org/10.1016/S0140-6736(16)31389-7.

[51] Alam MA, Richard SA, Fahim SM, Mahfuz M, Nahar B, Das S, et al. Impact of early-onset persistent stunting on cognitive development at 5 years of age: Results from a multi-country

cohort study (PLoS One (2020) 15:1 (e0227839) DOI: 10.1371/journal.pone.0227839). PLoS One 2020;15:1–16. https://doi.org/10.1371/journal.pone.0229663.
[52] Walker SP, Chang SM, Powell CA, Grantham-McGregor SM. Effects of early childhood psychosocial stimulation and nutritional supplementation on cognition and education in growth-stunted Jamaican children: Prospective cohort study. Lancet 2005;366:1804–7. https://doi.org/10.1016/S0140-6736(05)67574-5.
[53] Crookston BT, Forste R, McClellan C, Georgiadis A, Heaton TB. Factors associated with cognitive achievement in late childhood and adolescence: The Young Lives cohort study of children in Ethiopia, India, Peru, and Vietnam. BMC Pediatr 2014. https://doi.org/10.1186/1471-2431-14-253.
[54] Prado EL, Sebayang SK, Apriatni M, Adawiyah SR, Hidayati N, Islamiyah A, et al. Maternal multiple micronutrient supplementation and other biomedical and socioenvironmental influences on children's cognition at age 9–12 years in Indonesia: follow-up of the SUMMIT randomised trial. Lancet Glob Heal 2017;5:e217–28. https://doi.org/10.1016/S2214-109X(16)30354-0.
[55] Sartika RAD, Fajarini IA, Fitrianing L. Relationship Between Expenditures for Food Purchasing and Adolescent Anemia in Indonesia. Pakistan J Nutr 2019. https://doi.org/10.3923/pjn.2019.171.177.
[56] Maika A, Mittinty MN, Brinkman S, Lynch J. Effect on child cognitive function of increasing household expenditure in Indonesia: Application of a marginal structural model and simulation of a cash transfer programme. Int J Epidemiol 2015. https://doi.org/10.1093/ije/dyu264.
[57] Christian P, Smith ER. Adolescent Undernutrition: Global Burden, Physiology, and Nutritional Risks. Ann Nutr Metab 2018. https://doi.org/10.1159/000488865.
[58] The World Bank. Improving Education Quality in Indonesia's Poor Rural and Remote Areas 2017.
[59] Sandjaja S, Poh BK, Rojroonwasinkul N, Le Nyugen BK, Budiman B, Ng LO, et al. Relationship between anthropometric indicators and cognitive performance in Southeast Asian school-aged children. Br J Nutr 2013;110. https://doi.org/10.1017/S0007114513002079.
[60] Motta RW, Joseph JM. Group Intelligence Tests. Woodhead Publishing Limited; 2000. https://doi.org/10.1016/b978-008043645-6/50084-7.

Supplementary Table 3.1. Comparison of characteristics of adolescent-mother pairs from IFLS 2-5 who were included (N=363) and excluded (N=9) from analysis due to missing data.[1]

	Characteristics	Excluded cases N=9	Included cases N=363	P value[2]
Household	Per capita expenditure, IDR			
	• Low	3 (33.33)	91 (25.07)	0.573
	• Medium	5 (55.56)	182 (50.14)	0.748
	• High	1 (11.11)	90 (24.79)	0.346
	Living area			
	• Urban	6 (66.67)	214 (58.63)	0.628
	• Rural	3 (33.33)	148 (40.55)	0.663
Pregnant women	Age			
	• < 20 y	2 (22.22)	50 (13.77)	0.316
	• 20 – 35 y	5 (55.56)	279 (76.86)	0.138
	• > 35 y	2 (22.22)	33 (9.09)	0.475
Adolescents	Sex			
	• Boys	2 (22.22)	179 (49.31)	0.108
	• Girls	7 (77.78)	184 (50.69)	

[1]Values are n (%) for categorical data. P values were generated using a two-sample test of proportion.

Supplementary Table 3.2. Mediation analysis results of adolescent Hb, BMI-Z score, and adolescent HAZ in the association between maternal anaemia and adolescents' cognitive score

Moderated mediation results	Coefficient	P value[1]	RIT[2]	RID[3]
Adolescent Hb				
Adolescent Hb: maternal Hb	0.03	0.064	26%	0.35
Total score: adolescent Hb	1.38	<0.001		
Adolescent BMI Z-score				
Adolescent BMI Z-score: maternal Hb	0.09	0.005	12%	0.10
Adolescent BMI Z-score: adolescent Hb	0.18	0.242		
Adolescent HAZ				
Adolescent HAZ: maternal Hb	0.01	0.559	6%	0.10
Adolescent HAZ: adolescent Hb	0.97	0.003		

Note:

[1] P value was generated by mediation analysis using Baron and Kenny's approach, modified by Lacobucci *et al.* (2007) with the *medsem* package in STATA-16 software. Mediation analysis aimed to identify the mediating factors in the association between maternal anaemia and adolescents' cognitive score

[2] RIT is the ratio of the indirect effect to the total effect. Analysis of adolescent Hb as a mediator showed that about 26% of the effect of maternal Hb on cognitive scores is mediated by adolescent Hb.

[3] RID is the ratio of the indirect effect to the direct effect. Analysis of adolescent Hb as a mediator showed that the mediated effect is about 0.3 times as large as the direct effect of maternal Hb on cognitive scores.

Supplementary Table 3.3. Cognitive scores of adolescents, grouped by maternal anaemia and adolescent stunting status

Group	n	Cognitive scores (Mean ± SD)	P-value
Anaemic mother + stunted adolescent	55	11.52 ± 2.95	0.0253
Anaemic mother + non stunted adolescent	110	12.59 ± 2.71	
Non-anaemic mother + stunted adolescent	62	11.80 ± 3.07	
Non-anaemic mother + non stunted adolescent	136	12.72 ± 2.98	

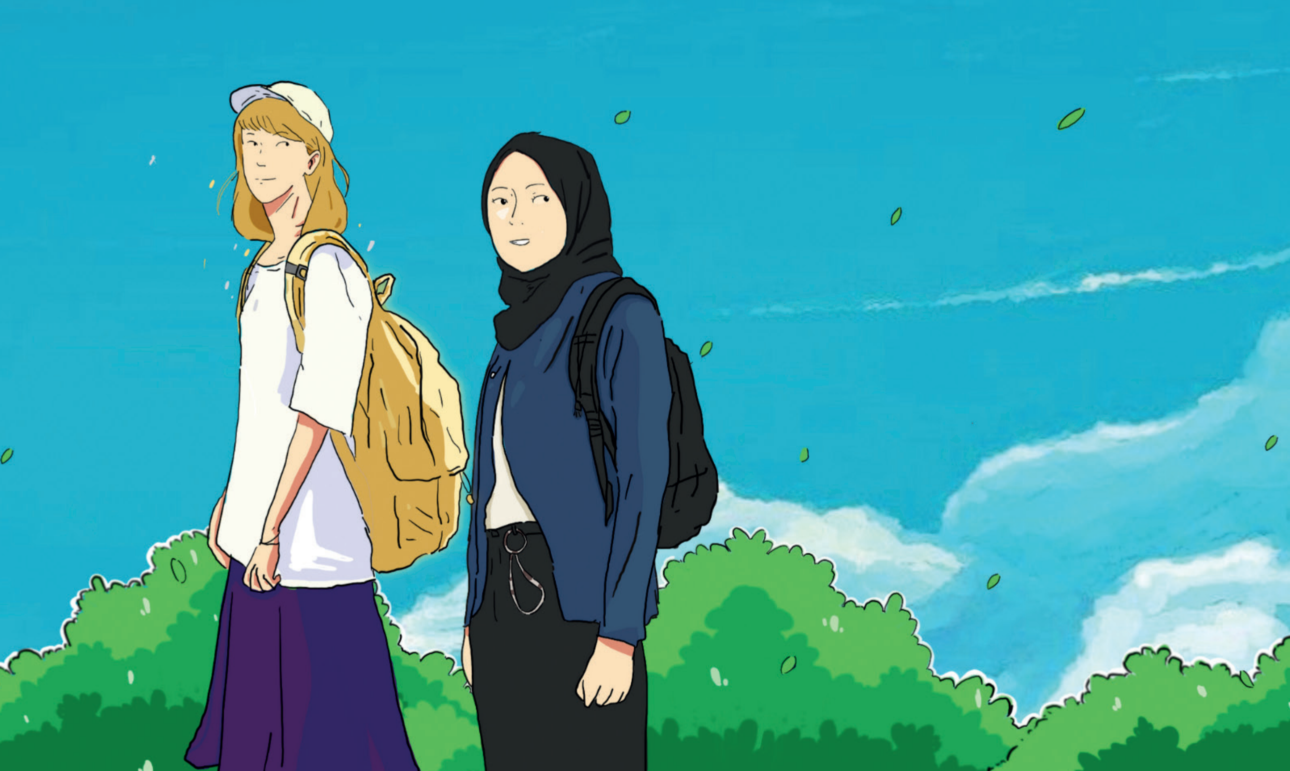
Note: Maternal anaemia was defined as Hb <11 g/dL; Adolescent stunting = height-for-age z score <-2. Adolescents were 10-14 y at the time of cognitive assessment. Cognitive scores were measured by Raven Matrixes. Differences between groups were tested with One-way ANOVA. The result showed that stunting status exacerbates the effect of maternal anaemia on adolescent cognitive function.

Chapter 4

Determinants of Common Mental Disorders (CMD) among adolescent girls aged 15-19 years in Indonesia: analysis of the 2018 National Basic Health Survey Data

Muhammad Asrullah, Maria-João Paulo, Monique L'Hoir, Edith JM Feskens, Alida Melse-Boonstra

Published in PLOS Global Public Health Journal
doi.org/10.1371/journal.pgph.0000232



ABSTRACT

Common Mental Disorders (CMD) are distress conditions which manifest themselves with anxiety, somatic, and depressive symptoms. CMD are highly prevalent in Indonesia especially among adolescents. Adolescent girls have a higher risk to develop CMD than boys. This may be related to anaemia, potentially aggravated by early onset of menstruation. This study aimed to determine the association between haemoglobin concentration and other determinants of CMD among adolescent girls in Indonesia. Data of 1,052 adolescent girls aged 15-19 years old from the Indonesian Basic Health Survey 2018 were analysed. CMD was measured using the Self Reporting Questionnaire (SRQ-20). Principal Component Analysis of main determinants was applied and resulting principal components were investigated as risk factors for CMD. The prevalence of CMD among the study population was 16.5%. Anaemia and Age at Menarche (AAM) were not associated with CMD. Three principal components were significantly associated with higher CMD score: 1) higher parental education, better employment of the father, and living in an urban area (β: 0.16, 95%-CI: 0.02; 0.30); 2) higher consumption of salty foods, high-fat foods, and soft drinks (β: 0.23, 95%-CI: 0.05; 0.40); and 3) having asthma, smoking, and a higher haemoglobin concentration (β: 1.74, 95%-CI: 1.59; 1.89). The strongest clustered associates of CMD among adolescent girls in Indonesia were asthma, smoking status, and higher haemoglobin concentration, whereas anaemia and AAM were not associated. Causality of smoking and diet to CMD could not be disentangled in this cross-sectional study. Our findings imply that adolescent girls who have asthma and smoke, as well as those having parents with higher education and secured occupation, are more likely to have mental disorders.

Keywords: Common Mental Disorders; adolescent girls; asthma; smoking; haemoglobin; Indonesia

INTRODUCTION

Common mental disorders comprise a number of distressing conditions characterized by anxiety and depression that are often seen in primary care and community settings. These disorders are highly prevalent in the global population with around 4.4% being depressive and 3.6% having an anxiety disorder [1]. Adolescents are specifically susceptible for mental disorders, and the prevalence of CMD among this age group is increasing rapidly in developing countries to an estimated 10 - 20% [2]. In Indonesia, the prevalence of depression and other mental health disorders were found to be 6.2 and 10%, respectively, among 15 to 24 year olds in 2018, which is higher than the national average [3].

Patients with psychiatric problems suffer more often from anaemia than the overall population [4]. Anaemia is also consistently reported to be related to depression and other mental disorders in adults [5–7]. The most common cause of anaemia is iron deficiency, but shortage of B-vitamins such as vitamin B12 can also play a role. Loss of oxygen-carrying haemoglobin affects normal brain functioning [8]. In addition, both iron and vitamin B12 are known to be involved in physiological processes affecting mental disorders [9]. Anaemia is common among adolescent girls in view of their higher iron needs to compensate for menstrual loss. Globally, more than 50% of adolescent girls at the age of 12-15 are reported to be anaemic by WHO [10]. However, besides a few reports, there is a dearth of literature on the association between anaemia and CMD in adolescent girls [11].

The aetiology of CMD is multi-factorial and still not fully understood. Puberty and adolescence are characterized by cognitive, physical, social, and emotional changes, and as such it is a vulnerable period in life during which multiple risk factors for CMD coincide. Mental health disorders in adolescents are shaped to a large extent by social determinants, including socioeconomic status and environmental factors [12]. This also concerns quality of parenting and family characteristics that affect children's physical and emotional growth [13]. From a nutritional viewpoint, puberty markedly increases energy and protein requirements [14]. However, girls tend to diet, which may cause mood disturbances because of caloric deprivation [15]. Dieting may also increase depressive symptoms because of failure to control body weight [16]. The global prevalence of CMD is higher in girls than in boys, approximately 38% versus 23%, respectively [17]. This is apparently related to menarche, a major milestone in puberty which can be perceived by girls as a startling realization of their own physical development [18]. Circulation of sex steroids and their physical manifestation during menarche, as well as neurological changes during adolescent growth may therefore increase the risk of developing a depression [19]. Early pubertal onset is one of the factors associated with increased risk of CMD around the world [18,20]. This may be caused by new situations and expectations that girls have to face, leading to shame, distress, and to self-imposed behaviour to keep menstrual status hidden. Experiencing physical changes earlier than peers, such as increases in body mass index, is correlated with Detrimental Psychological Outcomes such as depression and sleep disturbances [21]. It can lead to feelings of sickness and moodiness, hampered school and cognitive performance, psychosomatic symptoms, eating disorders, and lower body satisfaction because of social stigma and peer pressure [22]. Girls that mature early were found to worry more about their menarche, which was correlated with a lower self-esteem, a more external locus of control, and increased anxiety [23].

In this paper, we aim to explore the epidemiologic evidence on anaemia and other potential aetiologic factors as determinants of CMD in Indonesian adolescent girls aged 15-19 years. For this, we analysed data from the Indonesian Basic National Health Survey conducted in 2018. Better understanding of the aetiology of CMD will help us to design preventive interventions and effective programs for adolescent girls in Indonesia.

MATERIAL AND METHODS

Ethics Statement

All procedures were in accordance with the ethical standards to protect the respondent's information and privacy. Ethical approval has been issued by the Health Research Ethics Commission, Ministry of Health, Republic of Indonesia No. LB.02.01/2/KE.267/2017, and informed consent was obtained from all participants and their parent. The dataset was obtained from the National Institute of Health Research and Development (NIRD), Ministry of Health, Republic of Indonesia without respondent's personal information due to data privacy policy, after approval of the proposed data analysis.

Study design and data collection

The Indonesian Basic Health Survey (Riskesdas) is a National Health Survey which represents the Nation, Provinces, and Districts and is conducted every five years on household and individual level. For the present study, the data from Riskesdas conducted in 2018 was analysed because of the availability and completeness of CMD data. The Riskesdas was established by the National Institute of Health Research and Development, Ministry of Health, Republic of Indonesia. Data collection instruments in 2018 had mostly been used in previous Basic National Health Surveys (Riskesdas surveys), conducted in 2007, 2010, and 2013. The validation of these instruments was carried out by a variety of researchers, the Research and Development Agency, academics, and professional organizations. During data collection, field supervision was done by provincial technical and managerial teams in order to monitor interviews, to check the data entry and cleaning process, and to check availability of tools [3].

Cascade training was applied from national level to data collectors on district level to have the same perception on content and procedures. Trained staff collected the data using a one-on-one interview through structured questionnaires on household and individual level, and anthropometry measurements. The households were selected randomly through 4 stages of sampling, based on the representativeness of the population and rural-urban distribution [3,24]. Adolescent girls were recruited from these households with all adolescents in the house being interviewed. Data was collected from 282,654 households, including 1,017,290 household members (the overall recruitment rate of household interviews was 95.58%, while this was 93.2% for individual interviews). For blood collection, a national representative subsample of 24,980 households was selected using a probability proportional to size approach with linear systematic sampling (final sample: 19,418; completion rate: 77.7%). Blood samples were collected by a different team of data collectors who were experienced in medical services. Haemoglobin measurement was done for all household members, but only after signing for informed consent. The respondents for the present analysis were female adolescents aged 15-19 years who were interviewed, amongst others, about their age at menarche (AAM), depression and mental health, and of whom haemoglobin concentration was measured (n=1,274). After removing cases with incomplete data on CMD, AAM, and other individual and parental characteristics, data of 1,052 adolescent girls remained for analysis (S1 Fig).

Variables

CMD was measured using a self-reporting questionnaire (SRQ-20), a psychometric tool developed by the World Health Organization (WHO) that has been used widely in Low and Middle Income Countries (LMIC) [25]. The SRQ-20 has been adopted by the Indonesian Ministry of Health since the first Riskesdas in 2007, and has been locally validated for use among people 15 years and older with a Positive Predictive Value (PPV) of 60% and a Negative Predictive Value (NPV) of 92% [26]. The Indonesian Ministry of Health with WHO and other researchers have used the data to monitor CMD among all age groups at the national level over time [27–29]. In this questionnaire, CMD is determined by 20 yes/no questions related to mental disorders, divided over four subcategories, namely 'depression/anxiety', 'somatic symptoms', 'reduced vital energy', and 'depressive thoughts'. We dichotomized the presence or absence of CMD (cut off point ≥ 6) in order to calculate the prevalence of occurrence and used the continuous CMD score of 0-20 in further analysis to determine associations with potential determinant variables. To see whether the SRQ-20 was reliable in the present study, the reliability coefficient (Cronbach's alpha) was calculated.

Determinants of CMD considered in this study consisted of both adolescent-related and environmental factors (Supplementary Table 4.1). Adolescent-related factors were anaemia status, age at menarche (AAM), Body Mass Index (BMI)-for-age z-score,

4

adolescent occupation, iron supplementation, smoking status, diagnosed respiratory tract infection and asthma, and consumption of unhealthy foods. Environmental factors were factors related to household and living circumstances such as parental education, parental occupation, number of household members, and demographic area.

Adolescent factors

Anaemia status was identified based on haemoglobin concentration which was measured by finger prick method using a portable HemoCue 201+ machine. A haemoglobin concentration <12.0 g/dl was classified as anaemia. AAM was determined by two questions in a structured questionnaire, namely "Have you started to menstruate?" followed by a question "How old (years) were you when you had your first menstruation?" AAM was classified into the following age categories: ≤11 years,12-14 years, 15-17 years, and ≥18 years.

Height was measured by microtoise (SECA 206) and weight by a flat digital weighing scale. BMI-for-age z-score was classified into five categories namely severe thinness (< -3 SD), thinness (≥ -3 SD ≤ -2 SD), normal (>-2 SD to ≤1 SD), overweight (>1 SD to ≤2 SD), and obesity (>2 SD). Smoking status was labelled into "yes" if a respondent smoked every day or sometimes, while respondents who had no smoking experience were labelled into "no" (i.e., non-smoker). Information on any diagnosed communicable and non-communicable diseases was included in the standardized questionnaire by asking the respondent:" Have you been diagnosed with (disease) by medical doctors?" For most diseases the prevalence was 0% among the adolescent girls. Therefore, only two diseases were retained in the analysis: respiratory tract infections and asthma. Unhealthy food consumption, which refers to consumption of salty food, high-fat food, and soft drinks, was determined by a short questionnaire. Each food category was classified based on frequency of consumption with "high" for ≥1 time per day, "moderate" for 1-6 times per week, and "low" for ≤ 3 times per month.

Household factors

Parental education was classified for both parents into 4 categories namely "no education", "elementary school", "senior high school", and "diploma program or higher" if they finished the indicated level of education. With respect to the "no education" group, fathers and/or mothers who were never enrolled in education, or enrolled but did not finish elementary school, were categorized into this category. Parental occupation was classified for both parents into 3 groups, namely unemployed, unsecured job, and secured/paid job. Fathers and mothers who had no job/work were classified as being unemployed, while those who worked as temporary employee in a private company, as entrepreneur, farmer, fisherman, worker, craftsman, driver, or as a housekeeper were classified as having an unsecured job. Furthermore, fathers and mothers were classified as having a secured job if they worked as civil servant, army, or police officer, worked for state companies, or worked as a driver or housekeeper with a monthly based salary. The number of household members was classified into 2 categories, namely adolescents who lived in a home together with < 5 people or with ≥ 5 people. Demographic area was divided into rural and urban using the classification of Indonesia's Bureau of Statistics, which is based on population density, percentage of agricultural households, and presence/access to facilities.

Statistical analysis

All data analysis was conducted with STATA statistical software, version 16 (StataCorp LCC, TX, USA). Complete case analysis was employed, with minor differences between excluded and included cases; excluded cases tended to be slightly more often member of a smaller household, living in urban areas, have a highly educated father and a mother without education (see Supplementary Table 4.2 for missing data analysis). Prevalence and estimation of the proportion of the population having CMD was analysed by using the Survey (Svy) command in STATA to adjust for sampling weights. In Riskesdas, sampling weights at National, Provincial, and District level were generated by adjusting for sampling procedures as well as for intra-household dependency. Both discrete and continuous variables, such as haemoglobin concentration, AAM, BMI-for-age z-score, and number of household members, were included in PCA. We also used categorical variables that were converted into dummy variables. Barlett's test of sphericity was used for the correlation matrix between determinant variables and CMD score. PCA was conducted with, firstly, a scree-test to assess the number of components, which were each explained by eigen values. Secondly, an orthogonal component rotation (varimax) was examined to more clearly distinguish all determinant variables that correlated highly with each component and to aid interpretation. Principal Component Regression (PCR) of CMD as continuous variable (i.e. linear regression) was applied on the resulting principal components. Multiple regression of CMD on the original variables that were part of the components with a high variance proportion in PCR, was employed to see their interactions and understand how these variables were associated with CMD.

4

RESULTS

The scale reliability coefficient (Cronbach's alpha; all indicators) of the SRQ-20 questionnaire was 0.866, indicating good internal consistency. Data from the total of 1,052 included adolescent girls aged 15-19 years show that the anaemia prevalence was 27.3%. Based on BMI-for-age z-score, 26.6% of adolescents were severely thin, 6.2% were overweight, and 20.2% were obese. With respect to food consumption, 49.9% and 41.0% adolescents consumed high-fat food and salty foods more than ≥1 time per day, respectively. Approximately half of the fathers and 45% of mothers had at least completed secondary school, but the majority of mothers were unemployed.

The mean total CMD score was 4.0 (SD: 2.4). Based on CMD classification, the prevalence of CMD was 16.5% (Table 4.1). Among the 287 adolescents with anaemia, 16.8% were suspected to have CMD and this did not differ from those without anaemia (16.4%, p=0.87). Although the prevalence of CMD showed a downward trend with age at menarche, differences between categories were not statistically significant (p=0.59). Prevalence of CMD was significantly higher in adolescents with overweight (22.9%), who smoked (42.2%), who had asthma (40.1%), and who consumed more often salty foods or soft drinks (19.9%). Furthermore, the prevalence of CMD was lower in the group who had a father with only elementary school education (12.6%) and higher in adolescents living in an urban area (19.1%). Among the four subcategories of the SRQ-20 questionnaire, girls with CMD indicated most often to 'feel nervous, tense or worried' (17.8%) in the subcategory 'depression/anxiety', to 'often have headaches' (32.6%) within the category of 'somatic symptoms', to be 'easily tired' (19.3%) in the category 'reduced vital energy', and to have 'lost interest in things' (6.1%) in the category 'depressive thoughts' (Supplementary Table 4.3).

Table 4.1. Prevalence of CMD[1] among Indonesian girls aged 15-19 years old according to adolescent-related and household factors (Riskesdas 2018)

Variables			**Prevalence[2]**	
Adolescent factors	N	n	% (95% CI)	p-value[3]
All	1,052	169	16.5 (14.3; 18.8)	0.000
Anaemia status				
• No	765	122	16.4 (13.4; 18.7)	0.876
• Yes	287	47	16.8 (12.3; 21.2)	
Age at Menarche (years)				
• 9-11	86	16	21.5 (11.1; 28.5)	0.595
• 12-14	834	136	16.2 (13.9; 18.9)	
• 15-17	130	17	15.4 (7.7; 19.8)	
• ≥ 18	2	0		
Nutritional status (BMI z-score)				
• Severe thinness	280	41	15.5 (10.7; 19.4)	
• Thinness	134	15	11.2 (6.4; 17.8)	0.158
• Normal	361	68	18.4 (14.9; 23.3)	
• Overweight	65	14	22.9 (12.3; 33.4)	
• Obese	212	31	16.5 (10.2; 20.2)	
Adolescent Occupation				
• Unemployed	277	39	14.4 (10.2; 18.7)	0.606
• Student	679	116	17.4 (14.3; 20.2)	
• Work (Paid and unpaid)	96	14	16.8 (8.2; 23.3)	
Iron Supplementation				
• Not supplemented	906	146	17.0 (13.8; 18.7)	0.286
• Supplemented (<52 pills)	146	23	13.3 (10.3; 22.7)	
Smoking Status				
• Not Smoking	1,028	161	15.9 (13.5; 18.1)	0.002
• Smoking	24	8	42.2 (15.6; 55.4)	
Diseases diagnosed				

Table 4.1. Continued

Variables			**Prevalence[2]**	
Respiratory infection				
• No	1,019	6	16.3 (13.8; 18.4)	0.400
• Yes	33	163	22.6 (6.9; 35.5)	
Asthma				
• No	1,021	159	15.7 (13.4; 17.9)	0.002
• Yes	31	10	40.1 (16.7; 51.4)	
Risk consumption				
Salty food				
• High	431	31	19.9 (9.6; 19.1)	0.027
• Moderate	397	57	14.6 (11.1; 18.1)	
• Low	224	81	11.9 (15.2; 22.8)	
High-fat food				
• High	525	76	15.4 (11.6; 17.8)	0.356
• Moderate	416	77	18.7 (14.9; 22.6)	
• Low	111	16	13.8 (8.5; 22.4)	
Soft drink				
• High	28	8	36.0 (13.2; 48.7)	0.008
• Moderate	171	34	21.2 (14.2; 26.7)	
• Low	853	127	14.9 (12.6; 17.5)	
Household factors				
Paternal education				
• No education	40	6	20.9 (5.7; 29.8)	0.047
• Elementary school	473	61	12.6 (10.1; 16.3)	
• Senior high school	469	90	19.8 (15.7; 23.1)	
• University	70	12	19.7 (9.2; 28.1)	
Maternal education				
• No education	39	6	20.5 (5.9; 30.5)	0.301
• Elementary school	532	78	14.4 (11.8; 18.0)	
• Senior high school	419	77	19.2 (14.8; 22.4)	
• University	62	8	16.5 (5.7; 23.9)	
Paternal occupation				
• Unemployed	20	3	15.5 (3.2; 37.9)	0.834
• Unsecured job	589	92	15.8 (12.8; 18.8)	
• Secured Job	443	74	17.3 (13.4; 20.5)	
Maternal occupation				
• Unemployed	522	78	15.8 (12.0; 18.3)	0.317
• Unsecured job	389	63	15.8 (12.7; 20.3)	
• Secured job	141	28	21.3 (13.6; 27.4)	
Number of household members				
• <5	487	70	14.9 (11.4; 17.8)	0.231
• ≥ 5	565	99	18.0 (14.5; 20.9)	
Demographic area				
• Rural	444	56	12.2 (9.7; 16.0)	
• Urban	608	113	19.1 (15.6; 21.9)	0.006

[1]Cut-off for having suspected CMD was a score of ≥6 points out of 20.
[2]All prevalence and population proportions of CMD were estimated using weighted data.
[3]Differences between proportions of adolescent with suspected CMD were tested by chi-square/ Fisher exact.

Based on eigenvalues, difference, proportion, and cumulative variance, we decided to extract 6 components for the entire sample which explained 45.5% of the CMD variance in the sample (Supplementary Table 4.4). It was considered reasonable to retain all components with eigenvalues greater than 1. Rotation (orthogonal) was used to maximize the variance captured by the first component, so that the selected components could explain maximum variance in the data set (S2 Fig). Each symptom of CMD was given a score for each component. In Table 4.2, we show the most important factor loadings of each of the six components. For clarity, we do not display small loadings (absolute value smaller than 3). The first component was characterized most strongly by parental education, and, although to a lesser extent, also by paternal occupation and living area (Table 4.2). It represents socio-economic and demographic determinants. The second component was representative of unhealthy food consumption which was characterized most prominently by salty food and high-fat food, and less so by soft drink consumption. The third component represented health and lifestyle factors, including haemoglobin concentration, smoking status, and asthma. The factor asthma was most prominent among the three.

Table 4.2. Results of PCA of selected characteristics among Indonesian girls aged 15-19 years old (Riskesdas 2018)

Items	Comp. 1	Comp. 2	Comp. 3	Comp. 4	Comp. 5	Comp. 6
Haemoglobin			0.325		0.370	
Age At Menarche				-0.586		
BMI z-score				0.574		
Occupation						
Iron Supplementation						0.658
Smoking status			0.410		-0.397	
Respiratory infection				-0.396		
Asthma			0.516			
Salty food consumption		0.605				
High fat food consumption		0.637				
Soft drink consumption		0.304				-0.446
Paternal education	0.585					
Maternal education	0.581					
Paternal occupation	0.349					
Maternal occupation					0.458	0.312
Number of household members					-0.561	
Living area (rural-urban)	0.412					
Variance proportion (%)	11.70	7.37	6.98	6.80	6.47	6.11
Cumulative (%)	45.44					

The last three components were composed of AAM (negative factor loading), BMI-for-age z-score, and respiratory tract infection (negative) (Component 4); health, socio-economic status, haemoglobin concentration, smoking status (negative), parental occupation, and number of household members (negative) (Component 5); and iron supplementation, soft drink consumption (negative), and maternal occupation (Component 6).

Principal Component Regression (PCR) was done using all components with CMD score as an outcome (Table 4.3). Based on this, only the first three components were significantly associated with CMD. Among these, component 3 had the strongest association with CMD score and explained the highest proportion of the variance in comparison to components 1 and 2. We did not find any significant associations between component 4, 5, or 6 and CMD. Several models were constructed including combinations of the principal components as explanatory factors to select the best model based on its goodness-of-fit. The analysis showed that the model only including component 3 had the best data fit (Supplementary Table 4.5).

Table 4.3. Results of principal component regression of six retained components

Component	β coefficient	(95% CI)	P-value	R^2
Component 1 • Paternal education • Maternal education • Paternal occupation • Living area	0.16	0.02; 0.30	0.022*	0.005
Component 2 • Salty food consumption • High fat consumption • Soft drink consumption	0.23	0.05; 0.40	0.016*	0.005
Component 3 • Haemoglobin • Smoking status • Asthma	1.74	1.59; 1.89	0.000*	0.337
Component 4 • Menarche • BMI z-score • Respiratory infection	0.16	-0.02; 0.34	0.091	0.003
Component 5 • Haemoglobin • Smoking status • Mother occupation • Number of household members	0.18	-0.07; 0.37	0.854	<0.001
Component 6 • Iron supplementation • Soft drink consumption • Maternal occupation	<0.01	-0.20; 0.19	0.975	<0.001

Additional analysis was employed for a more detailed picture of the interrelation between variables in component 3 (Table 4.4). Among the variables in Component 3, the interaction between asthma and smoking status was significant and strongly associated with CMD score, suggesting that teenagers who smoke while suffering from asthma have the largest risk for CMD. Haemoglobin concentration was positively associated with CMD in girls who had asthma or who smoked.

4

Table 4.4. Results of linear regression of asthma, smoking and Hb

Variables	**β coefficient**		
	Estimated Effect	**(95% CI)**	**P value**
Asthma (yes)	1.67	0.47; 2.87	0.006
Smoking (yes)	1.88	0.52; 3.24	0.007
Haemoglobin (g/dL)	0.05	-0.6; 0.18	0.330
Asthma (yes) and haemoglobin[1]	0.18	0.04; 0.32	0.016
Smoker (yes) and haemoglobin[2]	0.22	0.06; 0.37	0.008
Asthma (yes) and Smoker (no)[3]	1.32	0.09; 2.56	0.036
Asthma (no) and Smoker (yes)[4]	1.44	0.03; 2.86	0.046
Asthma (yes) and smoker (yes)[5]	7.17	2.53; 11.81	0.003

Notes:
[1]the estimated effect is the slope of haemoglobin for adolescents with asthma, relative to the slope of haemoglobin estimated for adolescents without asthma
[2]the estimated effect is the slope of haemoglobin for smokers, relative to the slope of haemoglobin estimated for non-smokers
[3]the estimated effect is relative to adolescents with asthma who do not smoke
[4]the estimated effect is relative to adolescents without asthma who do smoke
[5]the estimated effect is relative to adolescents who do not have asthma and who do not smoke

DISCUSSION

The current study aimed to determine the association between CMD and determinants of health among adolescent girls aged 15-19 years in Indonesia. The prevalence of mental health disorders was found to be 16.5%, which was higher than the prevalence reported for all 15 to 24 year olds of 10% [3]. This is consistent with the fact that prevalence of CMD among adolescent age groups in developing countries is growing [2]. Furthermore, the findings of this study imply that CMD occurs more often among adolescents who have parents with a higher socio-economic status and who are living in an urban environment, in addition to those having asthma. This study also suggests that AAM and anaemia were not linked to the occurrence of CMD.

We found that smoking status, asthma, salty food consumption, paternal education, and demographic area were associated with CMD in univariate analysis. This was in line with the PCA showing that having asthma, being a smoker, and having higher haemoglobin concentrations was the primary component to be associated with CMD score. A previous study showed that asthma caused complications including sleep difficulties, persistent coughing, and limitation of activity [30]. Furthermore, adolescents with asthma were twice as likely to exhibit anxiety symptoms in comparison to their healthy peers [31]. Perception of illness such as the feeling that asthma has a detrimental effect on one's life and emotions, and worry that it is difficult to control the disease is one of an individual's cognitive components that might be part of the pathway to explain why asthma may be related to anxiety symptoms [32]. The perception might also be linked to lower self-management and functional status, hospitalization, and increased medical cost [33].

Smoking has also been related to mental disorders previously. For instance, a cohort study in the US showed that adults with at least one psychiatric disorder in their life are three times more likely to be current smokers compared to those without such a disorder [34]. Another study showed that an association between depression and smoking was stronger among women as compared to men [35]. Higher smoking rates were also found specifically among adolescent girls living with mental disorders [36]. A question remains regarding the causality of this association since this cannot be disentangled in cross-sectional studies.

In the current study, anaemia was not independently associated with CMD, but haemoglobin concentration correlated positively in conjunction with asthma and smoking in explaining CMD score. The finding of higher haemoglobin among people with asthma is in line with another study [37]. Asthma may lead to increased binding of carbon monoxide to haemoglobin or to the formation of methaemoglobin by nitric oxide (NO), resulting in lower oxygen capacity and increasing NO concentration. This prevents oxygen to bind to haemoglobin and therefore leads to hypoxia, which can lead to increased haemoglobin concentration [38]. The longer hypoxia caused by breathing problems remains uncontrolled, the more likely that it will cause stress and anxiety in asthmatic patients. Although haemoglobin levels are not significantly different among adolescent smokers and non-smokers in this study, higher haemoglobin levels have been found in smokers compared to non-smokers because of the same hypoxia hypothesis [39].

Another component that we found to be related to CMD was consumption of salty food, high-fat food, and soft drinks. Unhealthy eating patterns including consumption of junk food and snacking behaviour have previously been associated with higher prevalence of mental disorders among adolescents [40]. Another study showed that westernized dietary patterns, such as diets characterized by high intake of saturated fat, processed meat and sodium, and low consumption of vegetables, were associated with depression and anxiety [41]. Also, high consumption of sugared beverages and sweet foods has been associated with several mental health problems [42]. A biological explanation for this could be that unhealthy diets low in micronutrients, such as magnesium, zinc, and folate, would be associated with depression and anxiety [43]. Another pathway could be a direct effect of unhealthy food on inflammatory parameters, oxidative stress, and the immune system which has a proven link with mental disorders [44]. A diet high in sugar was also found to be involved in neural pathways which impact low basal levels of dopamine, particularly in the nucleus accumbent. The consumption of sucrose triggers the mesocorticolimbic system in which morphological neural changes, emotional, and behavioural processing are impaired [45]. It might also be the other way around, however, that girls with CMD tend to consume unhealthy foods especially those with higher social economic status. However, a previous prospective study conducted among Australian adolescents did not support this reverse causality hypothesis [46]. Further prospective research would be needed to unravel the direction of the relationship between CMD and unhealthy food habits.

We also found that parents with a high level of education, a father with a secured job, and living in an urban area were components that were significantly associated with a higher CMD score. Although poverty, including unemployment, inferior housing, and low income have consistently been associated with increased prevalence of mental illness among adults, we found quite the opposite among these adolescent girls. This may be explained in various ways. Urbanicity is known as a rather independent risk factor of mental health problems among adolescents [47] with clear evidence of causality [48]. Adolescents who lived in urban areas were reported previously to have biological stress reactivity, expressed as the difference between cortisol concentration and heart rate during rest and during stress [49], and were more likely to have symptoms of depression, especially females [50]. In urban areas, greater psychosocial stress due to crowded environments and lack of social cohesion may also trigger the limbic system in the human brain negatively, expressed by higher neuronal glucocorticoid receptor expression and lower neuropeptide oxytocin. Furthermore, dysregulated systemic stress functioning, such as acute autonomic nervous system and hypothalamic-pituitary-adrenal axis reactivity and functioning measured by adolescents' heart rate and salivary cortisol level, was found among people who grew up in urban areas compared to rural areas [47].

In addition, higher socioeconomic status and living in an urban area may expose adolescents to less quality time with their parents which may make them more susceptible to mental health problems. Reversely, those with lower socio-economic status or living in rural areas may experience more social cohesion both within households as well as in the community [51]. Maintaining support, contact, everyday activities at home, and forming supportive peer relationships may lower the risk of CMD in adolescents [52]. A previous study conducted in a representative sample of Korean adolescents, showed that those who had a father with a better occupation, and a high work load were more likely to have depression and suicidal thoughts [53]. Moreover, the risk of mental health problems among Japanese children aged 4 – 12 years old increased when parents worked and returned home late or had irregular working hours [54]. Another study demonstrated that risk of adolescent depression was increased by less closeness and less time togetherness between parents and adolescents aged 13 and 14 years old [55]. The frequency of parent-child contact was found to be a protective factor against negative psychosocial outcomes among adolescents aged 10 – 15 years old [56].

Despite many findings stating that higher income reduces the risk of mental health problems as a consequence of financial stress and social well-being [57,58], our finding is in line with a previous study conducted in Indonesia that showed higher probability of depression among the high-income group of patients with psychiatrist-diagnosed clinical depression [59]. An alternative explanation could be that parents with higher education have higher expectations towards their children's achievements, and thereby put more pressure on them. However, the available dataset did not allow us to explore this or any of the other explanations described above, since no data were collected on covariates such as family income, family expenses, socio-cultural status and cohesion, adolescent's experience of violence and quality of their relationship with parents and peers. Follow-up studies will therefore be needed to further unravel this association.

This study was done with national representative data from Indonesia and included a comprehensive set of both social and health determinant factors. Self-reporting, as used in this survey, has previously been shown to be an effective method to evaluate certain subjective experiences such as depressive symptoms [60]. This study has some limitations. The analysis lacked covariates that could explain some of the associations found in more detail. Nevertheless, socioeconomic status was captured by parental education and occupation [24]. Furthermore, the cumulative variance of the PCA was low. Missing data analysis revealed a potential bias towards exclusion of cases that were more often member of a smaller household, lived in urban areas, had a highly educated father and a mother without education and tended to have CMD more often, which may have blunted some of the associations. Recall bias from self-reported CMD data might have led to misclassification. Lastly, the cross-sectional nature of the study prohibits causal inferences, and the time effect cannot be determined. Nevertheless, the findings provide valuable information for follow-up and policy decision making regarding adolescent mental health in Indonesia.

CONCLUSION

The strongest clustered associates of CMD among adolescent girls in Indonesia are asthma, smoking, and haemoglobin concentration, followed by consumption of unhealthy foods and higher socio-economic status. The causality of smoking and diet to CMD cannot be disentangled due to the cross-sectional study design. Anaemia and earlier age at menarche were not associated with CMD. This study implies that adolescent girls with asthma and smoking cigarettes, as well as those having higher parental education and secured occupation, have an increased risk of developing mental disorders.

ACKNOWLEDGEMENTS

The authors would like to thank the Director of National Institute of Health Research and Development, Ministry of Health, Republic of Indonesia, who permitted us to use the Indonesian National Basic Health (Riskesdas) data for this publication.

AUTHORS' CONTRIBUTION

All authors had an essential role in formulation of the research questions; MA wrote the first draft of the paper; MA and MJP analysed the data; all authors were involved in interpretation of the data and revision of the manuscript. All authors have read and approved the final paper.

COMPETING INTERESTS

The authors have declared that no competing interests exist

FINANCIAL DISCLOSURE STATEMENTS

This study was performed as part of obtaining a PhD degree for which MA received a scholarship from Lembaga Pengelola Dana Pendidikan (LPDP), Republic of Indonesia. LPDP had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

DATA AVAILABILITY STATEMENT

No data are available. Data cannot be shared publicly per agreement on data sharing between authors and the National Institute of Health Research and Development, Ministry of Health, Republic of Indonesia, to minimize participant risk and maximize privacy and confidentiality as much as possible. Data are available from the National Institute of Health Research and Development, Ministry of Health Republic of Indonesia (contact via labmandat.litbangkes@gmail.com) for researchers who meet the criteria for access to confidential data. All questionnaires of Riskesdas 2018 (household and individual questionnaire) are available online at https://labmandat.litbang.kemkes.go.id/riset-badan-litbangkes/menu-riskesnas/menu-riskesdas/426-rkd-2018.

REFERENCES

[1] World Health Organization. Depression and Other Common Mental Disorders: Global Health Estimate. 2017.
[2] Kieling C, Baker-Henningham H, Belfer M, Conti G, Ertem I, Omigbodun O, et al. Child and adolescent mental health worldwide: Evidence for action. Lancet 2011;378:1515–25. https://doi.org/10.1016/S0140-6736(11)60827-1.
[3] Kementerian Kesehatan Republik Indonesia. Laporan Nasional Riset Kesehatan Dasar 2018 (Report of Indonesian Basic Health Survey 2018). 2018.
[4] Korkmaz S, Yıldız S, Korucu T, Gundogan B, Sunbul ZE, Korkmaz H, et al. Frequency of anemia in chronic psychiatry patients. Neuropsychiatr Dis Treat 2015;11:2737–41. https://doi.org/10.2147/NDT.S91581.
[5] Lee YJ, Kim HB. Association between anaemia and adult depression: A systematic review and meta-analysis of observational studies. J Epidemiol Community Health 2020;74:565–72. https://doi.org/10.1136/jech-2020-213842.
[6] Kang SY, Kim HB, Sunwoo S. Association between anemia and maternal depression: A systematic review and meta-analysis. J Psychiatr Res 2020;122:88–96. https://doi.org/10.1016/j.jpsychires.2020.01.001.
[7] Azami M, Badfar G, Khalighi Z, Qasemi P, Shohani M, Soleymani A, et al. The association between anemia and postpartum depression: A systematic review and meta-analysis. Casp J Intern Med 2019;10:115–24. https://doi.org/10.22088/cjim.10.2.115.
[8] Bourre JM. Effects of nutrients (in food) on the structure and function of the nervous system: update on dietary requirements for brain. Part 1: micronutrients. J Nutr Health Aging 2006;10:377–85.
[9] Syed EU. Vitamin B12 Supplementation in Treating Major Depressive Disorder: A Randomized Controlled Trial. Open Neurol J 2013;7:44–8. https://doi.org/10.2174/1874205x01307010044.
[10] World Health Organization. Prevention of iron deficiency anaemia in adolescents role of weekly iron and folic acid supplementation 2011:50.
[11] Chen MH, Su TP, Chen YS, Hsu JW, Huang KL, Chang WH, et al. Association between psychiatric disorders and iron deficiency anemia among children and adolescents: A nationwide population-based study. BMC Psychiatry 2013;13:1–8. https://doi.org/10.1186/1471-244X-13-161.
[12] Carod-Artal FJ. Social determinants of mental health. Glob Ment Heal Prev Promot 2017:33–46. https://doi.org/10.1007/978-3-319-59123-0_4.
[13] Rose J, Roman N, Mwaba K, Ismail K. The relationship between parenting and internalizing behaviours of children: a systematic review. Early Child Dev Care 2018;188:1468–86. https://doi.org/10.1080/03004430.2016.1269762.
[14] Wallach EE, Moschos S, Chan JL, Mantzoros CS, D S. Leptin and reproduction : a review. Fertil Steril 2002;77:433–44. https://doi.org/10.1016/S0015-0282(01)03010-2.
[15] Manchishi SM, Cui RJ, Zou XH, Cheng ZQ, Li B jin. Effect of caloric restriction on depression. J Cell Mol Med 2018;22:2528–35. https://doi.org/10.1111/jcmm.13418.
[16] Felton J, Cole DA, Tilghman-Osborne C, Maxwell MA. The relation of weight change to depressive symptoms in adolescence. Dev Psychopathol 2010;22:205–16. https://doi.org/10.1017/S0954579409990356.

[17] Silva SA, Silva SU, Ronca DB, Gonçalves VSS, Dutra ES, Carvalho KMB. Common mental disorders prevalence in adolescents: A systematic review and metaanalyses. PLoS One 2020;15:1–19. https://doi.org/10.1371/journal.pone.0232007.

[18] Joinson C, Heron J, Lewis G, Croudace T, Araya R. Timing of menarche and depressive symptoms in adolescent girls from a UK cohort. Br J Psychiatry 2011;198:17–23. https://doi.org/10.1192/bjp.bp.110.080861.

[19] Whittle S, Yücel M, Lorenzetti V, Byrne ML, Simmons JG, Wood SJ, et al. Pituitary volume mediates the relationship between pubertal timing and depressive symptoms during adolescence. Psychoneuroendocrinology 2012;37:881–91. https://doi.org/10.1016/j.psyneuen.2011.10.004.

[20] Miller S, Shanahan L, Angold A, Maughan B, Copeland W, Costello EJ. Outcomes of Early Pubertal Timing in Young Women: A Prospective Population-Based Study. Am J Psychiatry 2010;167:1218–25. https://doi.org/10.1176/appi.ajp.2010.09081190.

[21] Mendle J, Turkheimer E, Emery RE. Detrimental Psychological Outcomes Associated with Early Pubertal Timing in Adolescent Girls. Dev Rev 2010;27:3921–32. https://doi.org/10.1039/b800799c.O.

[22] Hamilton JL, Hamlat EJ, Stange JP, Abramson LY, Alloy LB. Pubertal timing and vulnerabilities to depression in early adolescence: Differential pathways to depressive symptoms by sex. J Adolesc 2014;37:165–74. https://doi.org/10.1016/j.adolescence.2013.11.010.

[23] Stubbs ML. Cultural perceptions and practices around menarche and adolescent menstruation in the United States. Ann N Y Acad Sci 2008;1135:58–66. https://doi.org/10.1196/annals.1429.008.

[24] Dany F, Dewi RM, Tjandrarini DH, Pradono J, Delima D, Sariadji K, et al. Urban-rural distinction of potential determinants for prediabetes in Indonesian population aged ≥15 years: A cross-sectional analysis of Indonesian Basic Health Research 2018 among normoglycemic and prediabetic individuals. BMC Public Health 2020;20:1–9. https://doi.org/10.1186/s12889-020-09592-7.

[25] WHO. SRQ-20 user's guide.pdf 1994.

[26] Hartono IG. Psychiatric Morbidity among Patients Attending the Bangetayu Community Health Centre in Indonesia. Bul Penelit Kesehat 1996;24.

[27] Azam M, Sulistiana R, Fibriana AI, Savitri S, Aljunid SM. Prevalence of mental health disorders among elderly diabetics and associated risk factors in Indonesia. Int J Environ Res Public Health 2021;18:1–9. https://doi.org/10.3390/ijerph181910301.

[28] World Health Organization (WHO). State of Health Inequality Indonesia. 2017.

[29] Idaiani S, Raharni, Isfandari S. The Mental Emotional Disorder Pattern: Study of National Basic Health Research 2007, 2013, and 2018 2020;22:522–5. https://doi.org/10.2991/ahsr.k.200215.100.

[30] Guill MF. Asthma update: Epidemiology and pathophysiology. Pediatr Rev 2004;25:299–305. https://doi.org/10.1542/pir.25-9-299.

[31] Ross CJM, Davis TMA, Hogg DY. Screening and Assessing Adolescent Asthmatics for Anxiety Disorders. Clin Nurs Res 2007;16:5–24. https://doi.org/10.1177/1054773806295235.

[32] McGrady ME, Cotton S, Rosenthal SL, Roberts YH, Britto M, Yi MS. Anxiety and asthma symptoms in urban adolescents with asthma: The mediating role of illness perceptions. J Clin Psychol Med Settings 2010;17:349–56. https://doi.org/10.1007/s10880-010-9214-3.

[33] Katon WJ, Richardson L, Lozano P, McCauley E. The relationship of asthma and anxiety disorders. Psychosom Med 2004;66:349–55. https://doi.org/10.1097/01.psy.0000126202.89941.ea.

[34] Smith PH, Mazure CM, McKee SA. Smoking and mental illness in the US population. Tob Control 2014;23:e147–53. https://doi.org/10.1136/tobaccocontrol-2013-051466.

[35] Husky MM, Mazure CM, Paliwal P, McKee SA. Gender differences in the comorbidity of smoking behavior and major depression. Drug Alcohol Depend 2008;93:176–9. https://doi.org/10.1016/j.drugalcdep.2007.07.015.

[36] Lawrence D, Kisely S. Inequalities in healthcare provision for people with severe mental illness. J Psychopharmacol 2010;24:61–8. https://doi.org/10.1177/1359786810382058.

[37] Nasim F, Ashraf M, Ahmad S. Hematological and Biochemical Profile of Patients Suffering from Non-Atopic Asthma. IMedPub Journals 2017;2:1–10.

[38] Naples R, Laskowski D, McCarthy K, Mattox E, Comhair SAA, Erzurum SC. Carboxyhemoglobin and Methemoglobin in Asthma. Lung 2015;193:183–7. https://doi.org/10.1007/s00408-015-9686-x.

[39] Anandha Lakshmi S, Lakshmanan A, Ganesh Kumar P, Saravanan A. Effect of intensity of cigarette smoking on haematological and lipid parameters. J Clin Diagnostic Res 2014;8:11–3. https://doi.org/10.7860/JCDR/2014/9545.4612.

[40] Oellingrath IM, Svendsen M V., Hestetun I. Eating patterns and mental health problems in early adolescence - A cross-sectional study of 12-13-year-old Norwegian schoolchildren. Public Health Nutr 2013;17:2554–62. https://doi.org/10.1017/S1368980013002747.

[41] Howard AL, Robinson M, Smith GJ, Ambrosini GL, Piek JP, Oddy WH. ADHD is associated with a “Western” dietary pattern in adolescents. J Atten Disord 2011;15:403–11. https://doi.org/10.1177/1087054710365990.

[42] Øverby N, Høigaard R. Diet and behavioral problems at school in Norwegian adolescents. Food Nutr Res 2012;56:1–6. https://doi.org/10.3402/fnr.v56i0.17231.

[43] Jacka FN, Pasco JA, Williams LJ, Meyer BJ, Digger R, Berk M. Dietary intake of fish and PUFA, and clinical depressive and anxiety disorders in women. Br J Nutr 2013;109:2059–66. https://doi.org/10.1017/S0007114512004102.

[44] Bakunina N, Pariante CM, Zunszain PA. Immune mechanisms linked to depression via oxidative stress and neuroprogression. Immunology 2015;144:365–73. https://doi.org/10.1111/imm.12443.

[45] Jacques A, Chaaya N, Beecher K, Ali SA, Belmer A, Bartlett S. The impact of sugar consumption on stress driven, emotional and addictive behaviors. Neurosci Biobehav Rev 2019;103:178–99. https://doi.org/10.1016/j.neubiorev.2019.05.021.

[46] Jacka FN, Kremer PJ, Berk M, de Silva-Sanigorski AM, Moodie M, Leslie ER, et al. A prospective study of diet quality and mental health in adolescents. PLoS One 2011;6:1–7. https://doi.org/10.1371/journal.pone.0024805.

[47] Evans BE, Huizink AC, Greaves-Lord K, Tulen JHM, Roelofs K, van der Ende J. Urbanicity, biological stress system functioning and mental health in adolescents. PLoS One 2020;15:1–24. https://doi.org/10.1371/journal.pone.0228659.

[48] Van Os J, Kenis G, Rutten BPF. The environment and schizophrenia. Nature 2010;468:203–12. https://doi.org/10.1038/nature09563.

[49] Evans BE, Greaves-Lord K, Euser AS, Tulen JHM, Franken IHA, Huizink AC. Determinants of Physiological and Perceived Physiological Stress Reactivity in Children and Adolescents. PLoS One 2013;8.

[50] Galliher RV, Rostosky SS, Hughes HK. School belonging, self-esteem, and depressive symptoms in adolescents: An examination of sex, sexual attraction status, and urbanicity. J Youth Adolesc 2004;33:235–45. https://doi.org/10.1023/B:JOYO.0000025322.11510.9d.

[51] Mulyati M, Martiastuti K. the Relationship Between Family Function and Adolescent Autonomy in the Rural and Urban Area. J Fam Sci 2019;3:15. https://doi.org/10.29244/jfs.3.1.15-29.

[52] Williams LR, Anthony EK. A Model of Positive Family and Peer Relationships on Adolescent Functioning. J Child Fam Stud 2015;24:658–67. https://doi.org/10.1007/s10826-013-9876-1.

[53] Kim SH, Kim JS, Yoo HY, Ryu E. Parental Occupational Status and Suicidal Ideation in Adolescent: Cross-Sectional Secondary Data Analysis. J Pediatr Nurs 2019;45:e57–63. https://doi.org/10.1016/j.pedn.2019.01.005.

[54] Kizuki M, Ochi M, Isumi A, Kato T, Fujiwara T. Parental time of returning home from work and child mental health among first-year primary school students in Japan: Result from A-CHILD study. Front Pediatr 2018;6.

[55] Han WJ, Miller DP. Parental work schedules and adolescent depression. Heal Sociol Rev 2009;18:36–49. https://doi.org/10.5172/hesr.18.1.36.

[56] Elgar FJ, Mills RSL, McGrath PJ, Waschbusch DA, Brownridge DA. Maternal and paternal depressive symptoms and child maladjustment: The mediating role of parental behavior. J Abnorm Child Psychol 2007;35:943–55. https://doi.org/10.1007/s10802-007-9145-0.

[57] Zimmerman FJ, Katon W. Socioeconomic status, depression disparities, and financial strain: What lies behind the income-depression relationship? Health Econ 2005;14:1197–215. https://doi.org/10.1002/hec.1011.

[58] Christiani Y, Byles J, Tavener M, Dugdale P. Socioeconomic related inequality in depression among young and middle-adult women in Indonesia's major cities. J Affect Disord 2015;182:76–81. https://doi.org/10.1016/j.jad.2015.04.042.

[59] Mumang AA, Liaury K, Syamsuddin S, Maria IL, Tanra AJ, Ishida T, et al. Socio-economic-demographic determinants of depression in Indonesia: A hospital-based study. PLoS One 2020;15:1–15.

[60] https://doi.org/10.1371/journal.pone.0244108.Haeffel GJ, Howard GS. Self-Report : Psychology ' s Four-Letter Word. Am J Psychol 2016;123:181–8.

Supplementary Table 4.1. Variables: definition, unit, classification, score, survey question and descriptive analysis

Variable	Description of variables/ definition	Question/ measurement	Unit	Answering options	Classification
Adolescent variables					
CMD	CMD refers to anxiety and depression which impacts mood or feelings of affected adolescents	Individual 20-item questionnaire: *'In the past 2 weeks, have you experienced/felt any of the following symptoms?'*	Total score (0-20)	1: No, score = 0 2: Yes, score = 1	0: Total score <6: No CMD 1: Total score ≥ 6 CMD
Anaemia	Anaemia is a condition in which the number of red blood cells or haemoglobin concentration is lower than normal	Hemocue +201	Haemoglobin (g/dL)	-	0: Haemoglobin ≥12 g/dL: no anaemia 1: Haemoglobin <12 g/dL: anaemia
Age at Menarche (AAM)	AAM is the age when menarche or first menstruation occurs	Individual questionnaire: *'How old were you when you had the first menstruation?'*	Years of age	-	1: ≤11 years old 2: 12-14 years old 3: 15 – 17 years old 4: ≥ 18 years old
Nutritional status	Nutritional status is adolescent's weight status indicated by BMI-for age-z-score	Height (cm) and weight (kg)	BMI-for-age Z-score	-	1: ≤ -3SD (Severe thinness) 2: >-3SD ≤ -2SD (Thinness) 3: >-2SD < 1SD (Normal) 4: >1 SD to ≤2 SD (Overweight) 5: >2 SD (Obese)
Adolescent's Occupation	Occupation refers to activities in which adolescents engage when pursuing their pleasure on a daily basis	Individual questionnaire: *'What is your occupation?'*		1. No work 2. School 3. Civil servant, army, police, governmental organization 4. Non-governmental organization 5. Entrepreneur 6. Farmer 7. Fisherman 8. Driver/ housekeeper 9. Other	1: Unemployed (if 1) 2: Student (if 2) 3: Work (paid or unpaid) (if 3-9)

4

Supplementary Table 4.1. Continued

Variable	Description of variables/ definition	Question/ measurement	Unit	Answering options	Classification
Iron supplementation	Iron supplementation refers to the number of iron supplements that are consumed by adolescents to treat and prevent iron deficiency and anaemia, either received from a government program or bought	Individual questionnaire: *'Have you received / bought an iron supplement in the past 12 months?'*		1. Yes 2. No	0: Not supplemented (if 2) 1: Supplemented (if 1)
Smoking Status	Smoking status is a recoded variable based on a question about cigarette smoking	Individual questionnaire: *'Do you smoke?'*		1. Yes, every day 2. Yes, sometimes 3. No	0: Not smoking (if 3) 1: Smoking (if 1, 2)
Diagnosed diseases	Diagnosed diseases refer to all diseases that have been diagnosed by a medical doctor	Individual questionnaire: *'Have you been diagnosed with (disease) by a medical doctor?'*		1. Yes 2. No	1: Never been diagnosed (if 2) 2: Have been diagnosed (if 1)
Unhealthy food consumption	Unhealthy food consumption refers to consumption of salty food, high-fat food, and soft drink	Food frequency questionnaire: *'In the past month, how many times did you consume (food)?'*	Frequency of consumption	1. > 1 time per day 2. 1 time per day 3. 3 – 6 times per week 4. 1 – 2 times per week 5. < 1 time per month 6. Never	1: Low (if 4, 5, 6) 2: Moderate (if 3) 3: High (if 1, 2)
Household variables					
Parental education	Parental education is defined as the highest education level of parents attained	Household questionnaire: *'What is your (father/ mother) last education'*		1. Never attended school 2. Elementary school (not completed) 3. Elementary school (completed) 4. Middle school (completed) 5. Senior high school (completed) 6. Diploma (completed) 7. University (completed)	1: No education (if 1, 2) 2: Elementary school (if 3,4) 3: Senior high school (if 5) 4: Diploma or higher (if 6,7)

Supplementary Table 4.1. Continued

Variable	Description of variables/ definition	Question/ measurement	Unit	Answering options	Classification
Parental occupation	Parental occupation is defined as activities in which parents engage when pursuing their pleasure on a daily basis to have income	Household questionnaire: *'What is your (father/ mother) occupation?'*		1. No work 2. School 3. Civil servant, army, police, governmental organization 4. Non-governmental organization 5. Entrepreneur 6. Farmer 7. Fisher 8. Driver/ housekeeper 9. Other	1: Unemployed (if 1, 2) 2: Unsecured job (if 5, 6, 7, 9) 3: Secured job (if 3, 4, 8)
Number of household members	Number of household members is defined as the number of people living in the same building, not considering the household registration	Household questionnaire: *'How many people live in this house/ building (not based on household)?'*	Total number of people		1: ≤ 5 people 2: > 5 people
Demographic area	Demographic area is defined as the classification of the living area based on the percentage of agricultural households, and the presence/ access to facilities, as determined by Indonesia's Bureau of Statistics	Assessed by data collectors based on area criteria		1. Urban area 2. Rural area	1: Rural (if 2) 2: Urban (if 1)

4

Supplementary Table 4.2. Comparison of variables between all cases, complete cases and excluded cases of Indonesian girls aged 15-19 years old from RISKESDAS (2018)

	All cases		Complete cases		P-valuea	Excluded cases		P-valueb
	N	Value	N	Value		N	Value	
AAM, mean years ± SD	1,274	13.04 ± 1.29	1,052	13.01 ± 1.27	0.574	222	13.00 ± 1.09	0.664
CMD, %	1,268	16.9 (14.9; 19.1)	1,052	16.9 (14.9; 19.1)	0.599	216	21.8 (15.8; 26.7)	0.100
Anaemia, %	1,274	27.1 (24.7; 29.7)	1,052	27.3 (24.5; 29.9)	0.912	222	26.1 (20.5; 32.5)	0.784
Urban, %	1,274	59.1 (56.4; 61.8)	1,052	57.8 (54.8; (60.8)	0.496	222	73.9 (67.6; 79.6)	<0.001
Household size <5 members, %	1,274	49.0 (46.3; 51.8)	1,052	46·3 (43.3; 49.4)	0.194	222	62.6 (55·; 68.9)	0.000
Paternal education: university, %	1,274	6.7 (5.4; 8.4)	1,052	6.7 (5.3; 8.4)	0.619	167	8.0 (3.0; 16.6)	0.020
Maternal education: no education, %	1,219	4.7 (3.5; 5.9)	1,052	3.7 (2.6; 4.9)	0.239	167	10.8 (6.1; 15.6)	<0.001

[1]Cut-off for having suspected CMD was a score of ≥6 points out of 20

[2]All prevalence and population proportions were estimated using weighted data

[3]Differences between proportions were tested by a two-sample test of proportions

[a] Prevalence comparison between completed dataset of the variables and final dataset (1,052)

[b] Prevalence comparison between excluded and included data

Supplementary Table 4.3. Subdivision of CMD symptoms among girls aged 15-19 years old from Riskesdas Data 2018

Symptoms	Overall n (%)
Depressive/anxious (Yes)	
01. Feel nervous, tense, or worried	189 (17·8)
02. Easily frightened	161 (15·1)
03. Feel unhappy	83 (7·8)
04. Cry more than usual	86 (8·4)
Somatic symptoms (Yes)	
05. Often have headaches	354 (32·6)
06. Sleep badly	246 (24·4)
07. Uncomfortable feeling in the stomach	161 (15·1)
08. Poor digestion	109 11·2)
09. Poor appetite	217 (20·8)
10. Hands shake	111 (10·8)
Reduced vital energy (Yes)	
11. Easily tired	192 (19·3)
12. Difficult to make decisions	162 (15·4)
13. Difficult to enjoy your daily activities	66 (6·3)
14. Daily work suffering	41 (4·1)
15. Feel tired all the time	92 (9·1)
16. Trouble thinking clearly	106 (10·2)
Depressive thoughts (Yes)	
17. Unable to play a useful part	36 (3·6)
18. Lost interest in things	65 (6·1)
19. Thoughts of ending your life	10 (1·0)
20. Feel that you are worthless person	52 (5·2)

4

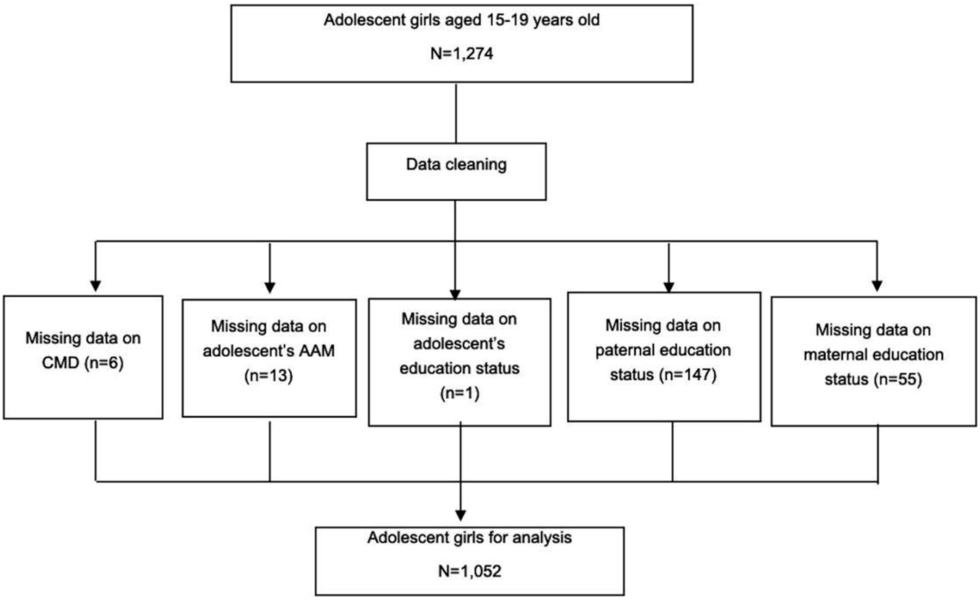
Supplementary Table 4.4. Eigen values of principal component in CMD

Items	Eigenvalue	Difference	Proportion	Cumulative
Component 1	2·2301	0·8407	0·1239	0·1239
Component 2	1·3894	0·1770	0·0772	0·2011
Component 3	1·2124	0·0392	0·0674	0·2684
Component 4	1·1732	0·0510	0·0652	0·333
Component 5	1·1222	0·0706	0·0623	0·3960
Component 6	1·0516	0·0582	0·0584	0·4544
Component 7	0·9934	0·0070	0·0552	0·5096
Component 8	0·9864	0·0109	0·0548	0·5644
Component 9	0·9756	0·0342	0·0542	0·6186
Component 10	0·9413	0·0121	0·0523	0·6709
Component 11	0·9292	0·0345	0·0516	0·7225
Component 12	0·8948	0·0363	0·0497	0·7722
Component 13	0·8585	0·0398	0·0477	0·8199
Component 14	0·8187	0·0299	0·0455	0·8654
Component 15	0·7888	0·0984	0·0438	0·9092
Component 16	0·6905	0·0814	0·0384	0·9476
Component 17	0·6092	0·2743	0·0338	0·9814
Component 18	0·3349	.	0·0186	1·0000

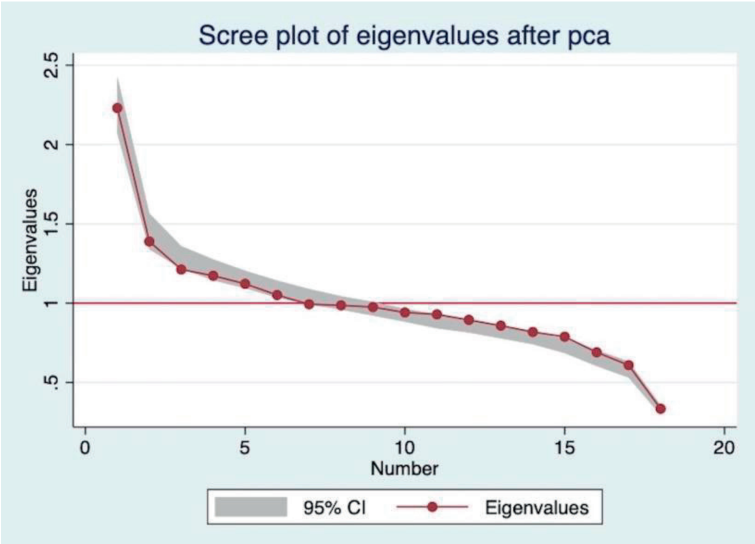
Supplementary Table 4.5. Model fit of principal component regression

Component	Criterion of fit				
	F	RMSE	AIC	BIC	R^2
Model 1 (CMD: β0+β3pc3)	532·9*	2·727	5,108·7	5,118·7	0·337
Model 2 (CMD: β0+β3pc3+β2pc2)	267·8*	2·742	5,108·7	5,123·6	0·335
Model 3 (CMD: β0+β3pc3+β2pc1)	267·3*	2·746	5,109·4	5,124·3	0·335
Model 4 (CMD: β0+β3pc3+β2pc+β1pc1)	179·1*	2·741	5,109·3	5,129·3	0·336

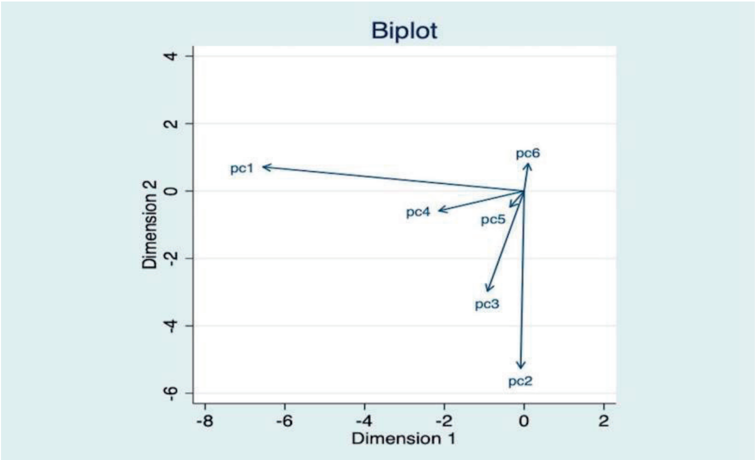
*Significant association (p<0·05)



Supplementary figure 4.1. Data cleaning process a)



b)



Supplementary figure 4.2. a). Scree plot of eigenvalues after PCA, b). Biplot of PCA

Chapter 5

Sleep quality, depression, and the risk of anaemia in adolescents aged 10-19 years during one year of the COVID-19 pandemic in Indonesia: a latent class analysis

Muhammad Asrullah, Ahmad Watsiq Maula, Sandra Olivia Frans, Shita Listya Dewi, Monique L'Hoir, Edith JM Feskens, Alida Melse-Boonstra

Submitted for publication

ABSTRACT

Sleep quality and depression are known to be associated with anaemia in adults, but studies are limited among children and adolescents. The present study aimed to determine the association between sleep quality, depression, and haemoglobin concentration in Indonesian adolescents aged 10 to 19 years old. Data of 452 adolescents, aged 10 to 19 years old, were collected across all subdistricts in Gunungkidul district, Yogyakarta province, Indonesia in 2021 (baseline) and 2022 (follow-up). Sleep quality was assessed using The Pittsburgh Sleep Quality Index (PSQI), and adolescent's depressive-anxiety disorder was assessed by the Kessler-10 Psychological Distress Scale (K10). Latent Class Analysis (LCA) was employed to identify and characterise the adolescents based on sleep quality and depression scoring patterns. Multiple linear regression was applied to identify associations between class membership and haemoglobin concentration at baseline, and follow-up with adjustments for baseline haemoglobin concentration, sex, age, pubertal status, alcohol consumption, smoking status, and household income. The overall prevalence of anaemia was 21% at baseline and 29% at follow-up, with girls being more affected than boys. LCA yielded 5 classes of sleep quality and depression. We did not find an association between class membership and haemoglobin concentration at baseline. However, in comparison to class A, membership of class B (moderate-to-good sleep quality and low risk of depression, with some tiredness) predicted a reduction of 0.43 g/dL (95%CI: -0.79; -0.07), whereas membership of class C (moderate sleep quality and moderate risk of depression) predicted a reduction of 0.49 g/dL (95%CI: -0.94; -0.04) in haemoglobin concentration at one year follow-up. In conclusion, compromised sleep quality and symptoms of depression can lead to lower haemoglobin concentration over time. Mental health and sleep quality should therefore be considered in intervention programs that address anaemia.

Keywords: sleep quality, depression, adolescence, haemoglobin concentration, Indonesia

INTRODUCTION

Anaemia is a global public health issue impacting an estimated 1.62 billion people worldwide [1]. Adolescents, especially girls, are vulnerable for anaemia, due to rapid physical growth and pubertal development. In Indonesia, the prevalence of anaemia in adolescents aged 5-14 years and 15-24 years was 26.4% and 32% in 2018, respectively, and seems to have increased since 2013 when it was found to be 17.9% in adolescents aged 13-18 years [2]. Anaemia can have a variety of physical, cognitive, and emotional consequences, and is therefore an important target for intervention in adolescents [6]. Importantly, anaemia is consistently reported to be related to depression and other mental disorders [3–5]. Mental disorders are among the most important causes of illness and disability in youth [6], and are increasing worldwide. The aetiology of mental health disorders is multi-factorial. Tiredness and apathy, which are common features of depression, can also be the consequence of anaemia, or of poor sleep quality. At the same time, each of these conditions may be capable to trigger the other.

Anaemia is the consequence of a low haemoglobin concentration, most commonly due to iron deficiency, which hampers the transport of oxygen throughout the body. Apart from fatigue and poor physical fitness, this may also lead to moodiness, isolation, feelings of failure, or even depression when left untreated [7]. On the other hand, poor mental health and depression can be hypothesized to lead to less self-care and poorer dietary choices, leading to nutritional deficiencies [8]. Similarly, depression and poor sleep quality can induce each other [9]; short sleep duration is a known cause of mood changes and of having difficulty to manage unpleasant emotions [10]. In a study among 528 Indonesian adolescents, aged 13 to 16 years old, it was shown that those with low depression scores experienced a better sleep quality [11]. Depressive symptoms were more strongly associated with sleep problems in adolescents than in younger children [12]. Also anaemia has repeatedly been linked to changes in sleep patterns in infants [13], in children [14], and in adults [15–17]. This may be due to the crucial role of iron in the metabolism of monoamines in the brain, which play a role in sleep physiology [18]. Based on current knowledge, however, it is unclear if anaemia is a cause, a consequence, or an epiphenomenon of depression and poor sleep quality.

During the COVID-19 pandemic, studies have demonstrated elevated levels of mental health problems worldwide, especially among adolescents. For instance, a study among students in Indonesia showed that 10.6% had emotional problems, and 38.1% experienced peer relationship problems during the early phases of the pandemic [19]. The pandemic has also made an impact on the sleep quality of adolescents, as evidenced in a number of studies [20–23]. In addition, the prevalence of anaemia can be expected to have increased, due to temporary stagnation of health service delivery through schools and other channels, such as nutrition education and iron-folic acid (IFA) supplementation programs, as well as due to loss of livelihoods and food security.

In this study, we aimed to assess the longitudinal association between sleep quality and symptoms of depression with anaemia in Indonesian adolescents aged 10 to 19 years, living in Gunungkidul, Yogyakarta province, against the backdrop of school closures, social distancing, and hygiene measures due to the COVID-19 pandemic.

MATERIAL AND METHODS

Study Design and Data Collection

Data of an envisaged number of 576 adolescents (equal numbers of boys and girls) aged 10-19 years were collected across all subdistricts of Gunungkidul district, Yogyakarta province, Indonesia. The required sample size was calculated with the assumption that the prevalence of anaemia among all adolescents in Gunungkidul was the same as found earlier for Yogyakarta province (23%) [24]. A multistage sampling strategy with probability proportionate to size was employed. The survey was conducted in 9 subdistricts and 18 villages across the district. To produce representative data, a listing survey was performed by visiting all villages and households with adolescents for a total of 9,942 adolescents available for random inclusion. However, the data were collected only in rural areas and do not represent any urban areas. More detailed information regarding the sampling strategy is explained in Chapter 1.

The first round of data collection (baseline) was conducted from May to August 2021 and was completed just before strict lockdowns were implemented due to the outbreak of the delta variant of the coronavirus**.** We collected follow-up data in the period May-July 2022. In Indonesia, schools had been closed due to the COVID-19 pandemic from March 2020 until April 2022. Twelve data collectors were involved in this study, who received a two-day online and a two-day offline training to ensure that the same quality standards were applied by all data collectors. The same data collectors were hired and re-trained for the follow-up. Data collectors visited all selected adolescents in their home with permission letters of the head of each subdistrict, village, and sub-village leader. Two software programs for mobile data collection were employed, the ODK Collect (Get ODK Inc.) and the Offline Surveys (LimeSurvey GmbH) android-based application. If a problem was encountered either online or offline, data collectors used a paper-based questionnaire and processed the data the same day into the online database.

Study Variables

All variables were assessed both at baseline and follow-up. For the present analysis haemoglobin concentration at follow-up was the outcome variable, and measurements at baseline were considered as determinants or confounders.

Assessment of anaemia, sleep quality, and depression

Haemoglobin data were collected from all adolescents who were willing to have their finger prick blood taken, using HemoCue 201+ (HemoCue AB, Ängelholm, Sweden). After correction of haemoglobin concentrations for altitude and smoking [25], anaemia was classified as haemoglobin <11.5 g/dL for adolescents aged 10-11 years old, <12 g/dL for those aged 12-14 years old and for girls aged 15 years and older, and <13 g/dL for boys aged 15 years old and older.

Sleep quality was assessed using The Pittsburgh Sleep Quality Index (PSQI) which is a self-reported questionnaire that evaluates sleep quality and disruptions over a one-month period (Supplementary Table 1). Subjective sleep quality, sleep latency, sleep length, habitual sleep performance, sleep disturbances, use of sleeping medication, and daytime dysfunction are among the 19 items which together form seven “component” ratings that each weighted equally on a 0–3-point scale, with increasing scores indicating worse sleep quality. The PSQI has been validated for adolescents in the Indonesian setting with high reliability and validity (Cronbach's alpha of 0.72 and total-item correlations of 0.36–0.56) [11].

The Kessler-10 Psychological Distress Scale (K10) was used to measure non-specific psychological distress in the anxiety-depression spectrum, i.e., levels of nervousness, agitation, psychological fatigue, and depression in the past four weeks. It has been translated and validated in Bahasa Indonesia (all the scales had Cronbach's alpha >0.8, with sensitivity of 85.7% and specificity of 74.7%). The K10 comprises of 10 questions that have strong psychometric properties by which psychiatric cases and non-psychiatric cases can be discriminated (Supplementary Table 1). The cut-off $\geq$ 18 was used to determine the prevalence of depression among adolescent boys and girls [26].

Assessment of potential covariates

A broad range of potential covariates was assessed, both at the individual and at the household level. At individual level, age of adolescents was recorded and classified into 10 - $\leq$ 13y, >13 - $\leq$ 16 y, >16 - $\leq$ 18 y and >18 - 19 y. Occupation of adolescents was classified as “student”, “work”, and “unemployed”. Physical activity was measured with the Physical Activity Questionnaire for all adolescents (PAQ-A), which asks for participation in different types of activities and sports (activity checklist), efforts during physical education classes, and activity during lunch, after school, in the evening and in the weekend during the past 7 days [27].

Weight and height were measured to assess nutritional status. Anthropometric measurements were mostly taken in the respondents' home straight after the interviews, to minimize response bias. Adolescent height was measured to the nearest 0.1 cm using a stadiometer (Kenko Stadiometer 250, China). Weight was measured without shoes and other accessories and recorded to the nearest 0.1 kg using a flat digital weighing scale (GEA EB1622, Indonesia), placed on a flat surface. Height and weight were measured and recorded twice, with an acceptable difference of 0.2 cm and 0.1 kg. All equipment was calibrated by the Certified Health Laboratory and Calibration Unit, Yogyakarta.

Presence of eating disorders was assessed using the EAT-26 questionnaire, based on 26 items, which has been used among the Indonesian population previously [28]. Body image perception and self-image perception were assessed using the Figure Rating Scale (FRS) [29], as also used in an earlier Indonesian study among adolescent girls and boys [30]. The FRS is gender-specific, with a scale that ranges from 1 (thinnest) to 9 (largest). Food consumption was assessed by asking consumption of 10 food groups during the last 24 hours, as part of the Minimum Dietary Diversity for Women (MDD-W): starchy staples, dark-green leafy vegetables, vitamin A-rich fruits and vegetables, other vegetables, other fruits, flesh and organ meat, eggs, fish, legumes/nuts/seeds, and milk products [31]. Dietary diversity score (DDS) was assessed using the total count out of the 10 food groups. We also assessed the consumption of risk foods, referring to the consumption of salty food, high-fat food, and soft drinks, which was classified as low if adolescents consumed such foods only 1-2 times a week, moderate if they consumed them 3-6 times a week, and high if they consumed them every day. Smoking status and alcohol consumption were assessed using questions on history of cigarette smoking and alcohol consumption on a daily and weekly basis.

Pubertal stage was assessed by the Picture-Based Interview about Puberty (PBIP) [32,33]. The 5-stage PBIP was employed as a self-administered questionnaire, which means that the respondents had to select the best-matching picture which represented their stage of pubertal development by themselves. Adolescents were classified into pre-pubertal (stage 1), early pubertal (stage 2 or 3), and late pubertal (stage 4 or 5). Self-aspiration for higher education was collected using questions from the Young Lives Study (https://www.younglives.org).

At the household level, parental education was defined as the highest education level attained by parents. In addition, parental occupation was assessed, defined as the daily activities in which parents engage to generate income. Household size was assessed as the total number of individuals who lived in the same house building, without considering the household registration. This number is therefore not limited to one household only, because it is possible in Indonesia to have more than one households in the same house building. Household total income was defined as the total income from all family members for food and non-food expenses and classified as less than Rp 3.000.000 (low), between Rp 3.000.000 and Rp 5.000.000 (moderate), and more than Rp 5.000.000 (high). Finally, household food access before and during the pandemic was assessed using an adapted version of HFIAS (Household Food Insecurity Access Scale)[34]. Questions were asked on purchasing behaviour of 10 food groups before the pandemic (6 months before) and after the pandemic (within 6 months). For each time point, each food item was scored 1 when frequently purchased (total scores=10). The sum provided the basis for categorizing the food insecurity status of households by dividing all scores to tertiles (3 categories: high, moderate, and low). A more detailed explanation of all the variables can be found in Supplementary Table 2.

Statistical analysis

All questionnaires and results were checked for completeness and consistency of responses. Descriptive statistics, adjusted for sampling weights calculated based on sex and age group per village, were used to produce prevalence characteristics of the study participants. Subsequently, latent classes of sleep and depressive symptoms were constructed using the bias-adjusted 3-step approach, and linear regression analysis was used to assess associations between the resulting classes and Hb at baseline and follow-up [35].

A latent class model was built, with cluster combinations for sleep and depression. Indicator variables were the 7 components of the sleep quality scale and the 10 components of the depression scale, entered as ordinal-fixed variables, indicating scores 0-3 for each sleep quality item and scores 0-4 for each depression item. Models with 1-7 classes were tested and compared based on their Bayesian Information Criteria (BIC), Akaike's Information Criteria (AIC), the number of parameters (Npar), and Bivariate Residual (BVR) values, as recommended [36]. Wald-test was applied to check the significance of the variables to the latent class formation. After deciding on the optimal number of classes, the next step was to check the assumption of local independence, with the BVR as an indicator for the model fit. A BVR higher than 3.84 indicates that there is a residual association left and this should preferably be adjusted for [36,37]. For BVRs that exceeded this value, direct effects were adjusted for one by one, starting with the largest direct effect until there was no residual association left. The individuals were then classified into the latent classes. Thereafter the relationship between the latent classes and anaemia at baseline and at follow-up was investigated using linear regression analysis. For this purpose six basic hierarchical models were applied, to include adolescent level, dietary-related factors, lifestyle-related factors, and household-related factors, which were identified a priori based on previous literature [3–5].

RESULTS

General characteristics

Complete data on a total of 576 adolescents (288 boys and 288 girls) were collected at baseline, and of 452 adolescents (222 boys and 230 girls) at follow-up. Characteristics of adolescents that were lost to follow-up (21%) did not differ from the original sample (Supplementary Table 5.3). The overall prevalence of anaemia was 21% at baseline and 29% at follow-up, with girls being more affected than boys (31% vs. 9% at baseline, and 42% vs. 15% at follow-up, respectively). The average AAM in adolescent girls was 12.5 years (SD: 1.2). In addition, mental health problems occurred in approximately 28.3% of adolescent boys and girls at baseline, with more prevalent among girls (35.3%) than boys (21.2%).

LCA analysis yielded five classes of sleep quality and depression (Supplementary Table 5.4): Class A (48.3%), with good sleep quality and low risk of depression; Class B (22%), with moderate-to-good sleep quality and low risk of depression, but with some tiredness; Class C (17%), with moderate sleep quality and moderate risk of depression; Class D (8%), with moderate sleep quality and high risk of depression; and Class E (4.7%), with poor sleep quality and high risk of depression (see Figure 5.1. a and b). The characteristics of adolescents in each of the five classes can be seen in Table 5.1.

Table 5.1. Characteristics of the adolescents (N=452) based on latent classes of sleep quality and depression

Characteristics	Latent class, n (%)1					
	Class A	Class B	Class C	Class D	Class E	P-value
	N=203 (48.3%)	N=119 (22%)	N=64 (17%)	N=44 (8.0%)	N=22 (4.7%)	
Adolescent characteristics						
Sex						<0.001
Boys, n (%)	122 (60.1)	58 (48.7)	19 (26.7)	21 (47.7)	2 (9.1)	
Girls, n (%)	81 (39.9)	61 (51.3)	45 (70.3)	23 (52.27)	20 (90.9)	
Age, y (mean ± SD)	13.6 ± 2.6	14.7 ± 2.6	15.3 ± 2.1	13.3 ± 2.2	15.2 ± 1.8	<0.001
Age group						<0.001
10 - ≤ 13 y	75 (37.0)	28 (23.5)	6 (9.4)	19 (43.2)	2 (9.2)	
>13 - ≤ 16 y	75 (37.0)	43 (36.1)	25 (39.1)	16 (36.4)	10 (45.4)	
>16 - ≤ 18 y	44 (21.6)	39 (32.8)	31 (48.4)	9 (20.4)	10 (45.4)	
>18 - 19 y	9 (4.4)	9 (7.6)	2 (3.1)	0 (0)	0 (0)	
Adolescent occupation, n (%)						0.242
Unemployed	17 (8.4)	14 (11.8)	6 (9.4)	1 (2.3)	0 (0)	
Student	181 (89.1)	99 (83.2)	57 (89.1)	43 (97.7)	21 (95.5)	
Work	5 (2.5)	6 (5.0)	1 (1.5)	0 (0)	1 (4.5)	
Physical activity, n (%)						0.517
Low	64 (31.5)	44 (37.0)	22 (34.4)	10 (22.7)	10 (45.5)	
Moderate	81 (39.9)	46 (38.6)	29 (45.3)	18 (40.9)	7 (31.8)	
High	58 (28.5)	29 (24.4)	13 (20.3)	16 (36.4)	5 (22.7)	

Table 5.1. Continued

Characteristics	Latent class, n (%)1					
	Class A	Class B	Class C	Class D	Class E	P-value
	N=203 (48.3%)	N=119 (22%)	N=64 (17%)	N=44 (8.0%)	N=22 (4.7%)	
Nutritional status (BMI z-score), n (%)						0.812
Severely thin	3 (1.5)	4 (3.4)	1 (1.6)	0 (0)	0 (0)	
Thin	18 (9.0)	13 (10.9)	4 (6.3)	5 (11.6)	3 (13.6)	
Normal	128 (63.7)	79 (66.4)	49 (76.5)	28 (65.2)	16 (72.7)	
Overweight	32 1(5.9)	16 (13.4)	7 (10.9)	5 (11.6)	2 (9.1)	
Obese	20 (9.9)	7 (5.9)	3 (4.7)	5 (11.6)	1 (4.5)	
Anaemia at baseline (yes), n (%)	45 (22.2)	29 (24.4)	24 (37.5)	7 (15.9)	6 (27.3)	0.082
Haemoglobin at baseline (mean ± SD)	13.3 ± 1.8	13.1 ± 1.6	12.8 ± 1.7	12.8 ± 1.5	12.6 ± 1.7	0.248
Anaemia at follow-up (yes), n (%)	52 (25.6)	41 (34.5)	29 (45.3)	15 (34.1)	10 (45.5)	0.025
Haemoglobin at follow-up (mean ± SD)	13.2 ± 1.8	12.7 ± 1.7	12.4 ± 2.0	12.7 ± 1.7	12.3 ±1.6	<0.001
Eating disorder (yes), n (%)	5 (2.5)	4 (3.4)	2 (3.12)	2 (3.12)	1 (4.6)	0.944
Diet diversity (Inadequate), n (%)	15 (7.4)	7 (5.9)	2 (3.1)	3 (6.8)	2 (9.1)	0.772
Diet diversity scores, (mean ± SD)	8.5 ± 2.4	8.7 ± 2.0	8.9 ± 1.6	8.6 ± 2.2	8.3 ± 2.7	0.790
Risk consumption						0.448
High	157 (77.4)	85 (71.4)	44 (68.7)	35 (79.5)	17 (72.3)	
Moderate	24 (11.8)	15 (12.6)	6 (9.4)	6 (13.6)	2 (9.1)	
Low	22 (10.8)	19 (16.0)	14 (21.9)	3 (6.8)	3 (13.6)	
Smoking Status (yes), n (%)	29 (14.3)	28 (23.5)	11 (17.2)	2 (4.6)	4 (18.2)	0.046
Alcohol consumption (yes), n (%)	2 (1.0)	4 (3.4)	2 (3.1)	0 (0.0)	2 (9.1)	0.085
Pubertal status (based on PBIP), n (%)						<0.001
Pre-pubertal	59 (29.1)	18 (15.1)	4 (6.2)	14 (31.8)	2 (9.1)	
Early pubertal	115 (56.6)	81 (68.1)	41 (64.1)	23 (52.3)	15 (68.2)	
Late pubertal	229 (14.3)	20 (16.8)	19 (29.7)	7 (15.9)	5 (22.7)	
Self-aspiration for higher education, n (%)	82 (42.4)	55 (46.2)	32 (50.0)	27 (61.4)	14 (63.6)	0.013
Household characteristic						
Paternal education, n (%)						0.436
No education	17 (8.4)	11 (9.2)	5 (7.8)	1 (2.3)	1 (4.5)	
Elementary school	121 (59.9)	78 (65.5)	35 (54.7)	28 (65.1)	9 (40.9)	
Senior high school	57 (28.2)	25 (21.0)	20 (31.2)	13 (30.2)	10 (45.5)	
University	7 (3.5)	5 (4.3)	4 (6.2)	1 (2.3)	2 (9.1)	
Maternal education, n (%)						0.175
No education	18 (9.1)	10 (8.4)	6 (9.4)	1 (2.3)	1 (4.8)	
Elementary school	129 (65.5)	76 (64.4)	39 (60.9)	31 (72.1)	10 (47.6)	
Senior high school	40 (20.3)	27 (22.8)	15 (23.4)	8 (18.6)	5 (23.8)	
University	10 (5.1)	5 (4.2)	4 (6.3)	3 (7.0)	5 (23.8)	
Paternal occupation, n (%)						<0.001
Unemployed	0 (0)	0 (0)	0 (0)	0 (0)	1 (4.8)	
Unsecured job	89 (45.6)	60 (52.6)	23 (39.7)	18 (42.9)	5 (23.8)	
Secured Job	106 (54.4)	54 (47.4)	35 (60.3)	24 (57.1)	15 (71.4)	
Maternal occupation, n (%)						0.594
Unemployed	70 (36.5)	36 (34.3)	22 (40.0)	13 (30.9)	5 (23.8)	
Unsecured job	95 (49.5)	48 (45.7)	24 (43.6)	24 (5.2)	10 (47.6)	
Secured job	27 (14.0)	21 (20.0)	9 (16.4)	5 (11.9)	6 (28.6)	

Table 5.1. Continued

Characteristics	Latent class, n (%)1					
	Class A	**Class B**	**Class C**	**Class D**	**Class E**	**P-value**
	N=203 (48.3%)	**N=119 (22%)**	**N=64 (17%)**	**N=44 (8.0%)**	**N=22 (4.7%)**	
Number of household members > 5 people, n (%)	43 (21.2)	24 (20.2)	16 (25)	9 (20.5)	3 (13.6)	0.845
Household income, n (%)						0.016
Low	169 (83.3)	101 (84.9)	53 (82.8)	37 (84.1)	15 (68.2)	
Moderate	31 (15.3)	15 (12.6)	8 (12.5)	5 (11.4)	3 (13.6)	
High	3 (1.4)	3 (2.5)	3 (4.7)	2 (4.6)	4 (18.2)	
Household food access at baseline, n (%)						
Before pandemic						0.271
High	59 (39.1)	41 (40.6)	14 (25.9)	15 (40.5)	3 (17.6)	
Moderate	56 (37.1)	36 (35.6)	23 (42.6)	9 (24.3)	7 (41.2)	
Low	36 (23.8)	24 (23.8)	17 (31.5)	13 (35.2)	7 (41.2)	
After pandemic						0.148
High	77 (51.3)	46 (44.7)	27 (52.9)	18 (51.4)	5 (29.4)	
Moderate	48 (32.0)	41 (39.8)	14 (27.5)	6 (17.1)	7 (41.2)	
Low	25 (16.7)	16 (15.5)	10 (19.6)	11 (31.5)	5 (29.4)	

[1] **Class A**: Good sleep quality and low risk of depression; **Class B**: Moderate-to-good sleep quality and low risk of depression, with some tiredness; **Class C**: Moderate sleep quality and moderate risk of depression; **Class D**: Moderate sleep quality and high risk of depression; **Class E**: Poor sleep quality and high risk of depression.

Adolescents in Class A comprised mostly boys (60%), aged <16 years (74%), who were more likely to be pre-pubertal (29%) and non-anaemic (baseline, 78%; follow- up, 74%). Adolescents in Class B were more often (severely) thin (14%), and more likely to smoke (23.5%). Class C included mostly girls (70%), aged ≥16 years (49%), who were more likely to be anaemic (baseline, 38%; follow-up, 45%), and to be in their late pubertal stage (30%). Adolescents in Class D were mostly aged <16 years (80%), more often pre-pubertal (32%), overweight or obese (23%), and non-anaemic (baseline, 84%; follow-up, 66%). Lastly, adolescents in Class E were almost only girls (91%), and more often aged ≥16 years (45%), were more likely to be thin (14%) and to have low physical activity (46%), were more likely to have anaemia at follow-up (46%), to engage in alcohol drinking (9%) and smoking (18%), and to live in smaller households (86% ≤ 5 people) with higher educated parents.

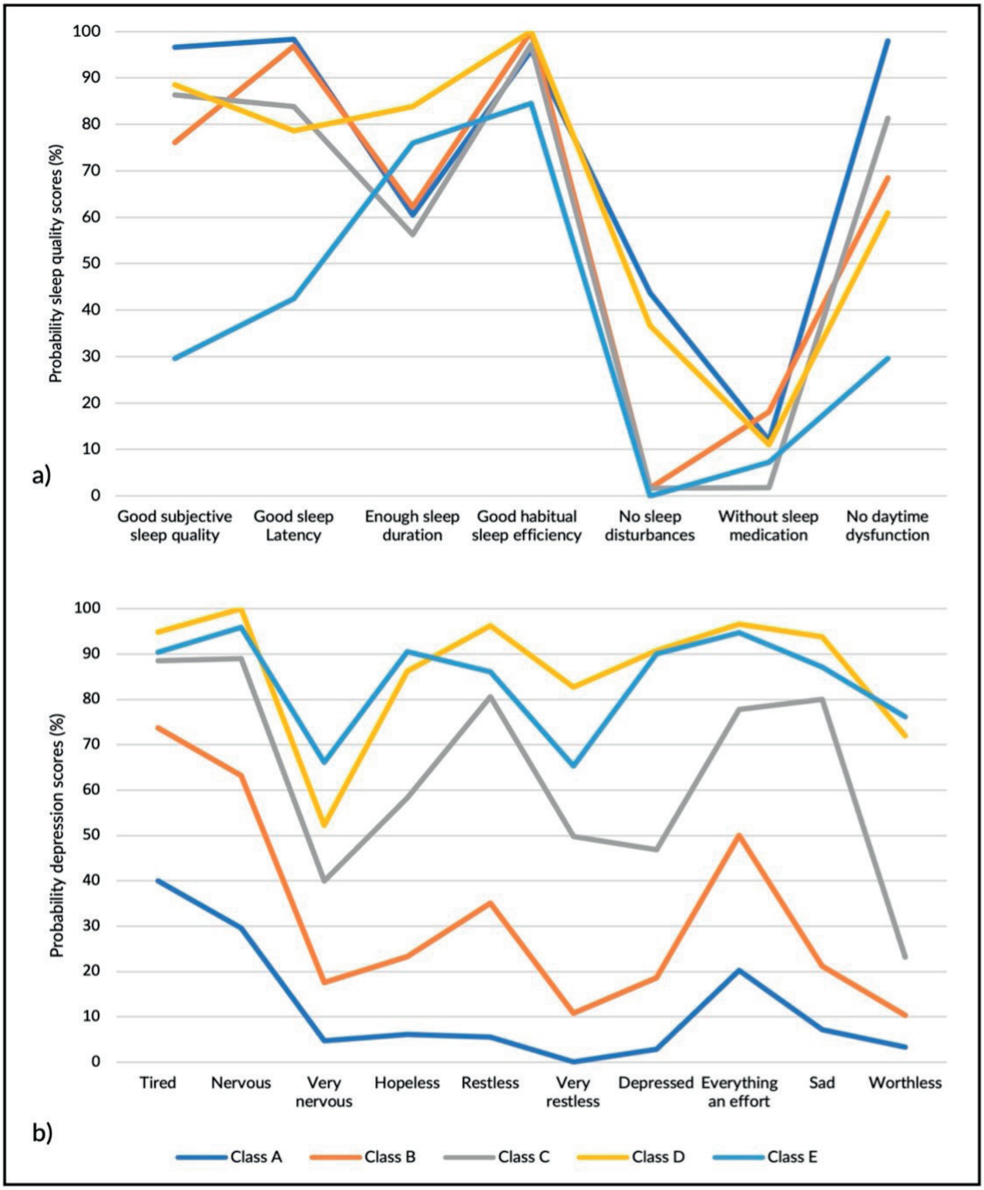


Figure 5.1. a) Probability of sleep quality scores among latent classes A-E; and b) Probability of depression scores among latent classes A-E. Class A: (48.3%), with good sleep quality and low risk of depression; Class B (22%), with moderate-to-good sleep quality and low risk of depression, but with some tiredness; Class C (17%), with moderate sleep quality and moderate risk of depression; Class D (8%), with moderate sleep quality and high risk of depression; and Class E (4.7%), with poor sleep quality and high risk of depression.

In regression analyses, no association was found between class membership of sleep quality and depression with haemoglobin concentration at baseline in crude and adjusted models (Table 5.2). However, we found inverse associations between baseline membership of classes B, C and E, and haemoglobin concentration at follow-up (Table 5.3). These associations largely remained after adjusting for haemoglobin at baseline, sex, pubertal status, alcohol consumption, smoking status, and household income (Table 5.3, model 7). We found adolescent sex to be a strong determinant of the association between class membership and haemoglobin concentration at follow-up (Model 2), indicating that being a girl blunted the association. Meanwhile, after additionally adjusting for age and pubertal status (model 3 and 4), the associations became somewhat stronger again. The final model (model 7) showed that, in comparison to class A, membership of class B (moderate-to-good sleep quality and low risk of depression, with some tiredness) predicted a reduction of 0.43 g/dL (95%CI: -0.79; -0.07), whereas membership of class C (moderate sleep quality and moderate risk of depression) predicted a reduction of 0.49 g/dL (95%CI: -0.94; -0.04) in haemoglobin concentration at one year follow-up.

Table 5.2. Linear regression analysis of sleep quality index and depression with baseline haemoglobin concentration (N=452)

Statistical model	Haemoglobin (g/dL) at baseline												
	Class A (N= 203)	Class B (N= 119)			Class C (N= 64)			Class D (N= 44)			Class E (N= 22)		
		β	SE	(95% CI)	β	SE	(95% CI)	β	SE	(95% CI)	β	SE	(95% CI)
Model 1 (crude)	Ref.	-0.13	0.20	-0.53; 0.26	-0.42	0.25	-0.91; 0.08	-0.36	0.29	-0.94; 0.20	-0.66	0.39	-1.44; 0.11
Model 2	Ref.	0.03	0.19	-0.60; 0.34	0.03	0.24	-0.41; 0.50	-0.19	0.26	-0.71; 0.34	0.09	0.37	-0.64; 0.82
Model 3	Ref.	-0.07	0.24	-0.60; 0.34	-0.13	0.24	-0.60; 0.34	-0.15	0.26	-0.68; 0.36	-0.05	0.37	-0.78; 0.67
Model 4	Ref.	-0.03	0.18	-0.41; 0.34	-0.09	0.24	-0.56; 0.38	-0.17	0.27	-0.70; 0.3	-0.01	0.37	-0.73; 0.72
Model 5	Ref.	-0.11	0.18	-0.47; 0.27	-0.16	0.24	-0.66; 0.39	-0.14	0.27	-0.68; 0.38	-0.13	0.37	-0.87; 0.60
Model 6	Ref.	-0.10	0.19	-0.48; 0.27	-0.14	0.24	-0.61; 0.33	-0.13	0.26	-0.66; 0.39	-0.06	0.38	-0.81; 0.69

Note: Class A: good sleep quality and low risk of depression; Class B: moderate-to-good sleep quality and low risk of depression, with some tiredness; Class C: moderate sleep quality and moderate risk of depression; Class D: moderate sleep quality and high risk of depression; Class E: poor sleep quality and high risk of depression.

Model 1: crude model; R squared: 0.0120

Model 2: adjusted for sex; R squared: 0.1713

Model 3: adjusted for sex and age; R squared: 0.1897

Model 4: adjusted for sex and pubertal status; R squared: 0.1865

Model 5: model 4, additionally adjusted for alcohol use and smoking; R squared: 0.2006

Model 6: model 5, additionally adjusted for household income; R squared: 0.2021

Table 3. Linear regression analysis of sleep quality index and depression with haemoglobin concentration at one year follow-up (N=452)

Statistical model	Haemoglobin (g/dL) at follow-up												
	Class A (N= 203)	Class B (N= 119)			Class C (N= 64)			Class D (N= 44)			Class E (N= 22)		
		β	SE	(95% CI)	β	SE	(95% CI)	β	SE	(95% CI)	β	SE	(95% CI)
Model 1 (crude)	Ref.	**-0.50**	0.21	-0.92; -0.08	**-0.83**	0.27	-1.35; -0.32	-0.46	0.30	-1.06; 0.14	**-0.87**	0.36	-1.69; -0.06
Model 2	Ref.	**-0.44**	0.19	-0.81; -0.07	**-0.63**	0.23	-1.09; -0.17	-0.28	0.30	-0.81; 0.26	**-0.54**	0.36	-1.26; -0.18
Model 3	Ref.	-0.32	0.18	-0.66; 0.04	-0.32	0.23	-0.76; 0.12	0.18	0.26	-0.68; 0.33	-0.02	0.36	-0.72; 0.68
Model 4	Ref.	**-0.36**	0.18	-0.72; -0.01	-0.40	0.23	-0.85; 0.04	0.16	0.25	-0.67; 0.33	-0.09	0.35	-0.79; 0.60
Model 5	Ref.	**-0.38**	0.18	-0.74; -0.03	-0.42	0.23	-0.87; 0.03	-0.17	0.26	-0.67; 0.33	-0.11	0.36	-0.80; 0.60
Model 6	Ref.	**-0.42**	0.18	-0.77; -0.06	**-0.47**	0.23	-0.91; 0.16	-0.16	0.25	-0.67; 0.34	-0.25	0.35	-0.96; 0.45
Model 7	Ref.	**-0.43**	0.18	-0.79; -0.07	**-0.49**	0.23	-0.94; -0.04	-0.18	0.25	-0.67; 0.33	-0.35	0.36	-1.07; 0.36

Note: Class A: good sleep quality and low risk of depression; Class B: moderate-to-good sleep quality and low risk of depression, with some tiredness; Class C: moderate sleep quality and moderate risk of depression; Class D: moderate sleep quality and high risk of depression; Class E: poor sleep quality and high risk of depression.

Model 1: crude model; R squared: 0.0313

Model 2: adjusted for haemoglobin at baseline; R squared: 0.2490

Model 3: adjusted for haemoglobin at baseline and sex; R squared: 0.3277

Model 4: adjusted for haemoglobin at baseline, sex, and age; R squared: 0.3314

Model 5: model 3, additionally adjusted for pubertal status; R squared: 0.3379

Model 6: model 4, additionally adjusted for alcohol use and smoking; R squared: 0.3499

Model 7: model 5, additionally adjusted for household income; R squared: 0.3542

DISCUSSION

In this analysis, we examined the association between sleep quality-depression classification and haemoglobin concentration at baseline (2021) and at one year follow-up (2022) in Indonesian adolescents. We found that the prevalence of anaemia had increased by 8 percent points (from 21% to 29%) over the course of one year, with girls more likely to be anaemic than boys. Furthermore, we did not find an association between sleep quality-depression class membership and haemoglobin concentrations at baseline. However, after controlling for baseline haemoglobin concentration and other covariates, and relative to those with good sleep quality and low risk of depression, class membership predicted a reduction of 0.43 g/dL (95%CI: -0.79; -0.07) and 0.49 g/dL (95%CI: 0.94; -0.04) in haemoglobin concentration at follow-up for those with moderate-to-good sleep quality and low risk of depression, with some tiredness (class B), and for those with moderate sleep quality and moderate risk of depression (class C), respectively.

Our findings are not in line with a previous 8-year prospective cohort study among 2,920 adults in the Netherlands, which did not show an independent association between depression, including sleep symptoms, and haemoglobin or anaemia status [38]. However, another prospective study of similar duration among 84,791 Chinese people indicated that both short as well as long sleep duration at night were associated with increased risk of anaemia [39]. A longitudinal study of 6,465 men and women aged 50–99 years, found that short sleep duration and sleep disturbances were associated with lower haemoglobin levels, with a stronger association between disturbed sleep and anaemia in men (OR: 1.73, C.I. 1.13—2.65) compared to women (OR: 1.59, C.I. 1.02—2.46) [17]. In contrast, high-school girls in Finland were found to be more likely to have anaemia and insomnia-related depression than boys [40]. Since most of these studies have been conducted in adults, the association between sleep, depression and haemoglobin concentration among adolescents remains to be further investigated.

The underlying mechanism of how poor sleep quality and depression reduce haemoglobin concentration is still unclear. A potential biological mechanism could be a shared gene: the MEIS1 gene, known to be associated with anaemia, was also found to be associated with sleep disturbances [41]. Another potential mechanism could be the altered blood flow in the brain, which is a symptom of sleep disturbance, but is also associated with anaemia [17,42]. The potential mechanism could also be explained through poor dietary intake. Sleep patterns and depression are linked to altered appetite, and low haemoglobin and other micronutrient concentrations could be a consequence of the dietary changes [43]. A previous observational study showed that adolescents who slept 3h or more during daytime reported greater caloric intake and food cravings [44]. Furthermore, chronic stress may affect the mesolimbic dopaminergic system and other brain regions which may shift food preferences towards hyperpalatable “comfort” (e.g., high-fat, high sugar) food [45]. However, a previous study with one year follow-up showed that sleep disturbances at baseline did not necessarily have impact on poorer clinical outcomes including anaemia, but did have impact on depressive symptoms and overall physical functioning [46], which we did not consider in the present study.

We constructed latent classes as a combination of sleep quality and depression, because poor sleep quality is known to be one of the key symptoms of mental health problems in adolescents [47], which makes it difficult to disentangle these two constructs. In adolescents a reduced quantity and quality of sleep has been reported to increase the risk of having mental health problems by three-fold [48]. A cross-sectional study among 1,111 young adults (aged 18–25 years) from New Zealand and the United States showed that sleep quality was the strongest predictor of depressive symptoms and well-being, followed by sleep quantity and less physical activity [49]. In addition, a longitudinal study in 4,951 adolescents in the USA showed that sleep disturbances predicted future mental health problems, particularly depression [50]. A study including 2,018 Indonesian adolescents (10 to 24-year age) showed that 54.1% experienced varying degrees of psychological distress during the COVID-19 pandemic, while better sleep quality was found to be protective [51]. In our study population we observed 5 underlying classes based on various combination of sleep quality and depressive symptoms.

The increase in prevalence of anaemia from baseline to follow-up could be due to several factors. For instance, COVID-19 measures taken by the government may have limited the availability of nutritious foods due to food chain disruptions, a decline in nutrient-rich food consumption due to loss of income, and stagnating implementation of micronutrient supplementation programs [52]. For instance, the IFA supplementation program in Indonesia was replaced by providing education about anaemia through online media during the pandemic [54], which may not have been as effective. Surprisingly, we found that access to food was better during the pandemic (Table 1), but this does not necessarily mean that this equals access to nutritious food. Government assistance, consisting of the provision of cash money or foods (typically rice, noodles and oil) during the pandemic, has helped to protect households against food insecurity [53]. However, this is not a guarantee for the purchase and consumption of nutritious food. Nevertheless, during the pandemic, people shifted their ideas about goods and foods considered to be essential, such as from animal food sources (such as fish) towards eggs, oranges and hand sanitizer [53].

In our study, girls were overrepresented in classes C and E, which represent two of the more problematic sleep-depression clusters. Anaemia was also more prevalent in both of these classes, at baseline as well as at follow-up. In addition, these classes tended to represent adolescents at a later pubertal stage. A previous study found that differences in risk of sleep disturbances emerged in association with onset of menses in adolescent girls [55]. Furthermore, risk of anaemia is higher in older girls due to the exposure time to menses. Among girls, a significant increase in sleeping problems with advanced pubertal development score has been reported, which was not found among boys [56]. A study among children and adolescents aged 0-18 years old using polysomnography found that sleep parameters including sleep disturbances differed greatly between Tanner stages in both boys and girls [57].

The current study was conducted longitudinally, at two time points one year apart, which enables us to draw inferences regarding the direction of causality between sleep quality, depression, and the occurrence of anaemia. Another strength of the current study is that classification by LCA better discriminates between groups of individuals with common features, in this case similarity in patterns of sleep quality and depression scores, as compared to commonly used categorical diagnostic constructs. However, we also acknowledge some limitations: the number of adolescents in group D and E were relatively small, which may have limited the power to detect associations. In addition, there may be residual confounding from factors that were not considered in the analysis, such as extensive information on dietary intake, morbidity, and inflammation [58]. Self-reported sleep quality and depression can be biased, although the questionnaires had been adapted, translated, and validated for adolescents in the Indonesian setting. A longer prospective study would be warranted to further explore the longitudinal relationship between sleep quality, depression, and risk of anaemia in adolescents.

CONCLUSION

Our study showed that, in comparison to adolescents with good sleep quality and low risk of depression, those with moderate-to-good sleep quality and low-to-moderate risk of depression had a 0.43-0.49 g/dL lower haemoglobin concentration. Therefore, mental health and sleep quality should be taken into account in anaemia intervention programs.

ACKNOWLEDGEMENTS

The authors would like to thank the team of the Centre for Health Policy and Management (CHPM) UGM for their support in the data collection, as well as all data collectors, adolescents, and parents who participate in the study.

CONTRIBUTORS

All authors had an essential role in formulation of the research questions; MA wrote the first draft of the paper and analysed the data; all authors were involved in interpretation of the data and revision of the manuscript. All authors have read and approved the final paper.

FUNDING

This study was performed as part of obtaining a PhD degree for which MA received a scholarship from the Indonesian Endowment Fund for Education (LPDP), Republic of Indonesia. This work was implemented as a part of the Ten2Twenty Project with funding support from the Neys van Hoogstraten Foundation, the Netherlands for this study in Indonesia. LPDP and Neys van Hoogstraten Foundation had no role in the design and writing process of this article.

CONFLICT OF INTERESTS

All authors stated no conflict of interest.

ETHICS APPROVAL

The study proposal and protocols have been approved by the ethical committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada (UGM). The first ethical approval was granted in 2020 (Letter number: KE/FK/0039/EC/2020), but due to COVID-19 pandemic the study was postponed to 2021 with granted ethical approval in 2021 (Letter number: KE/FK/0009/EC/2021). The study was also permitted by a local permit of the District Level office (Letter number: 070/00189) and by the District Health Office (DHO). Before conducting the interviews, all participants and their parents/guardians were given an information sheet and consent form to be signed.

DATA AND QUESTIONNAIRES AVAILABILITY STATEMENT

No data are not yet available. After finalizing data cleaning, anonymized data can be made available in a repository under a CC BY licence.

REFERENCES

[1] McLean E, Cogswell M, Egli I, Wojdyla D, De Benoist B. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993-2005. Public Health Nutr 2009;12:444–54. https://doi.org/10.1017/S1368980008002401.

[2] Kementerian Kesehatan Republik Indonesia. Laporan Nasional Riset Kesehatan Dasar 2018 (Report of Indonesian Basic Health Survey 2018). 2018.

[3] Lee YJ, Kim HB. Association between anaemia and adult depression: A systematic review and meta-analysis of observational studies. J Epidemiol Community Health 2020;74:565–72. https://doi.org/10.1136/jech-2020-213842.

[4] Kang SY, Kim HB, Sunwoo S. Association between anemia and maternal depression: A systematic review and meta-analysis. J Psychiatr Res 2020;122:88–96. https://doi.org/10.1016/j.jpsychires.2020.01.001.

[5] Azami M, Badfar G, Khalighi Z, Qasemi P, Shohani M, Soleymani A, et al. The association between anemia and postpartum depression: A systematic review and meta-analysis. Casp J Intern Med 2019;10:115–24. https://doi.org/10.22088/cjim.10.2.115.

[6] Abbafati C, Abbas KM, Abbasi-Kangevari M, Abd-Allah F, Abdelalim A, Abdollahi M, et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020;396:1223–49. https://doi.org/10.1016/S0140-6736(20)30752-2.

[7] Lee HS, Chao HH, Huang WT, Chen SCC, Yang HY. Psychiatric disorders risk in patients with iron deficiency anemia and association with iron supplementation medications: A nationwide database analysis. BMC Psychiatry 2020;20:1–9. https://doi.org/10.1186/s12888-020-02621-0.

[8] Schweren LJS, Larsson H, Vinke PC, Li L, Kvalvik LG, Arias-Vasquez A, et al. Diet quality, stress and common mental health problems: A cohort study of 121,008 adults. Clin Nutr 2021;40:901–6. https://doi.org/10.1016/j.clnu.2020.06.016.

[9] Oh CM, Kim HY, Na HK, Cho KH, Chu MK. The effect of anxiety and depression on sleep quality of individuals with high risk for insomnia: A population-based study. Front Neurol 2019;10:1–8. https://doi.org/10.3389/fneur.2019.00849.

[10] Baum KT, Desai A, Field J, Miller LE, Rausch J, Beebe DW. Sleep restriction worsens mood and emotion regulation in adolescents. J Child Psychol Psychiatry Allied Discip 2014;55:180–90. https://doi.org/10.1111/jcpp.12125.

[11] Setyowati A, Chung MH. Validity and reliability of the Indonesian version of the Pittsburgh Sleep Quality Index in adolescents. Int J Nurs Pract 2021;27:1–7. https://doi.org/10.1111/ijn.12856.

[12] Alfano CA, Zakem AH, Costa NM, Taylor LK, Weems CF. Sleep problems and their relation to cognitive factors, anxiety, and depressive symptoms in children and adolescents. Depress Anxiety 2009;26:503–12. https://doi.org/10.1002/da.20443.

[13] Algarín C, Peirano P, Garrido M, Pizarro F, Lozoff B. Iron deficiency anemia in infancy: Long-lasting effects on auditory and visual system functioning. Pediatr Res 2003;53:217–23. https://doi.org/10.1203/01.PDR.0000047657.23156.55.

[14] Uebergang LK, Arnup SJ, Hiscock H, Care E, Quach J. Sleep problems in the first year of elementary school: The role of sleep hygiene, gender and socioeconomic status. Sleep Heal 2017;3:142–7. https://doi.org/10.1016/j.sleh.2017.02.006.

[15] Kim W-H, Kim B-S, Kim S-K, Chang S-M, Lee D-W, Cho M-J, et al. Prevalence of insomnia and associated factors in a community sample of elderly individuals in South Korea. Int Psychogeriatrics 2013;25:1729–37. https://doi.org/10.1017/S1041610213000677.
[16] Chen-Edinboro LP, Murray-Kolb LE, Simonsick EM, Ferrucci L, Allen R, Payne ME, et al. Association between Non-Iron-Deficient Anemia and Insomnia Symptoms in Community-Dwelling Older Adults: The Baltimore Longitudinal Study of Aging. Journals Gerontol - Ser A Biol Sci Med Sci 2018;73:380–5. https://doi.org/10.1093/gerona/glw332.
[17] Jackowska M, Kumari M, Steptoe A. Sleep and biomarkers in the english longitudinal study of ageing: Associations with C-reactive protein, fibrinogen, dehydroepiandrosterone sulfate and hemoglobin. Psychoneuroendocrinology 2013;38:1484–93. https://doi.org/10.1016/j.psyneuen.2012.12.015.
[18] Ferreira A, Neves P, Gozzelino R. Multilevel impacts of iron in the brain: The cross talk between neurophysiological mechanisms, cognition, and social behavior. Pharmaceuticals 2019;12:1–26. https://doi.org/10.3390/ph12030126.
[19] Wiguna T, Anindyajati G, Kaligis F, Ismail RI, Minayati K, Hanafi E, et al. Brief Research Report on Adolescent Mental Well-Being and School Closures During the COVID-19 Pandemic in Indonesia. Front Psychiatry 2020;11:1–9. https://doi.org/10.3389/fpsyt.2020.598756.
[20] Genta FD, Neto GBR, Sunfeld JPV, Porto JF, Xavier AD, Moreno CRC, et al. COVID-19 pandemic impact on sleep habits, chronotype, and health-related quality of life among high school students: A longitudinal study. J Clin Sleep Med 2021;17:1371–7. https://doi.org/10.5664/jcsm.9196.
[21] Zhai X, Zeng J, Eshak ES, Zhang Y, Yang M, Di L, et al. The influencing factors of sleep quality among Chinese junior and senior high school adolescents during the COVID-19 pandemic. J Trop Pediatr 2021;67:1–14. https://doi.org/10.1093/tropej/fmab069.
[22] Meherali S, Punjani N, Louie-Poon S, Rahim KA, Das JK, Salam RA, et al. Mental health of children and adolescents amidst covid-19 and past pandemics: A rapid systematic review. Int J Environ Res Public Health 2021;18. https://doi.org/10.3390/ijerph18073432.
[23] Wang W, Guo Y, Du X, Li W, Wu R, Guo L, et al. Associations Between Poor Sleep Quality, Anxiety Symptoms, and Depressive Symptoms Among Chinese Adolescents Before and During COVID-19: A Longitudinal Study. Front Psychiatry 2022;12:1–10. https://doi.org/10.3389/fpsyt.2021.786640.
[24] Kementerian Kesehatan Republik Indonesia. Riskesdas dalam Angka Indonesia Tahun 2013. Lap Nas 2013 2013:1. https://doi.org/10.3406/arch.1977.1322.
[25] World Health Organization. Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity. Miner Nutr Inf Syst World Heal Organ 2013:1–6. https://doi.org/2011.
[26] Tran TD, Kaligis F, Wiguna T, Willenberg L, Nguyen HTM, Luchters S, et al. Screening for depressive and anxiety disorders among adolescents in Indonesia: Formal validation of the centre for epidemiologic studies depression scale – revised and the Kessler psychological distress scale. J Affect Disord 2019;246:189–94. https://doi.org/10.1016/j.jad.2018.12.042.
[27] Kowalski K, Crocker P, Donen R. The Physical Activity Questionnaire for Older Children (PAQ-C) and Adolescents (PAQ-A) Manual Examining the Physical Self in Adolescent Girls Over Time: Further Evidence Against the Hierarchical Model 2004.
[28] Sulistyan A, Huriyati E, Hastuti J. Distorsi citra tubuh, perilaku makan, dan fad diets pada remaja putri di Yogyakarta. J Gizi Klin Indones 2016;12:99. https://doi.org/10.22146/ijcn.22644.

[29] Stunkard AJ, Sørensen T, Schulsinger F. Use of the Danish Adoption Register for the study of obesity and thinness. Res Publ Assoc Res Nerv Ment Dis 1983;60:115–20.

[30] Sari AFP, Poncorini Pamungkasari E, Lanti Retno Dewi Y. Body Image Satisfaction and Its Association with Physical Activity and Body Mass Index among Health Students from Surakarta, Indonesia 2020:784–8. https://doi.org/10.5220/0009905807840788.

[31] FAO, USAID. Minimum Dietary Diversity for Women: A Guide for Measurement. 2016.

[32] Carskadon & Christine. A self-administered Rating Scale for Pubertal Development. J Adolesc Heal 1993;14:190–5.

[33] Shirtcliff EA, Dahl RE, SD P. Pubertal Development: Correspondence Between Hormonal and Physical Development. Child Dev 2009;80:327–37.

[34] Coates J, Swindale a, Bilinsky P. Household Food Insecurity Access Scale (HFIAS) for measurement of food access: indicator guide. Washington, DC Food Nutr Tech … 2007:Version 3.

[35] Bakk Z, Tekle FB, Vermunt JK. Estimating the Association between Latent Class Membership and External Variables Using Bias-adjusted Three-step Approaches. vol. 43. 2013. https://doi.org/10.1177/0081175012470644.

[36] Vermunt JK, Magidson J. Technical Guide for Latent GOLD Choice 5.1: Basic, Advanced and Syntax 2016:167.

[37] Van Kollenburg GH, Mulder J, Vermunt JK. Assessing model fit in latent class analysis when asymptotics do not hold. Methodology 2015;11:65–79. https://doi.org/10.1027/1614-2241/a000093.

[38] Lever-van Milligen BA, Vogelzangs N, Smit JH, Penninx BWJH. Hemoglobin levels in persons with depressive and/or anxiety disorders. J Psychosom Res 2014;76:317–21. https://doi.org/10.1016/j.jpsychores.2014.01.004.

[39] Liu X, Song Q, Hu W, Han X, Gan J, Zheng X, et al. Night Sleep Duration and Risk of Incident Anemia in a Chinese Population: A Prospective Cohort Study. Sci Rep 2018;8:1–7. https://doi.org/10.1038/s41598-018-22407-5.

[40] Langvik E, Saksvik-Lehouillier I, Kennair LEO, Sørengaard TA, Bendixen M. Gender differences in factors associated with symptoms of depression among high school students: an examination of the direct and indirect effects of insomnia symptoms and physical activity. Heal Psychol Behav Med 2019;7:179–92. https://doi.org/10.1080/21642850.2019.1615926.

[41] Hammerschlag AR, Stringer S, De Leeuw CA, Sniekers S, Taskesen E, Watanabe K, et al. Genome-wide association analysis of insomnia complaints identifies risk genes and genetic overlap with psychiatric and metabolic traits. Nat Genet 2017;49:1584–92. https://doi.org/10.1038/ng.3888.

[42] Spira AP, Gonzalez CE, Venkatraman VK, Wu MN, Pacheco J, Simonsick EM, et al. Sleep duration and subsequent cortical thinning in cognitively normal older adults. Sleep 2016;39:1121–8. https://doi.org/10.5665/sleep.5768.

[43] Yau YHC, Potenza MN. Stress and eating behaviors. Minerva Endocrinol 2013;38:255–67.

[44] Landis AM, Parker KP, Dunbar SB. Sleep, hunger, satiety, food cravings, and caloric intake in adolescents. J Nurs Scholarsh 2009;41:115–23. https://doi.org/10.1111/j.1547-5069.2009.01262.x.

[45] Pecoraro N, Reyes F, Gomez F, Bhargava A, Dallman MF. Chronic stress promotes palatable feeding, which reduces signs of stress: feedforward and feedback effects of chronic stress. Endocrinology 2004;145:3754–62. https://doi.org/10.1210/en.2004-0305.

[46] Urrila AS, Karlsson L, Kiviruusu O, Pankakoski M, Pelkonen M, Strandholm T, et al. Sleep complaints in adolescent depression: One year naturalistic follow-up study. BMC Psychiatry 2014;14:1–9. https://doi.org/10.1186/s12888-014-0283-y.

[47] Wesselhoeft R, Heiervang ER, Kragh-Sørensen P, Juul Sørensen M, Bilenberg N. Major depressive disorder and subthreshold depression in prepubertal children from the Danish National Birth Cohort. Compr Psychiatry 2016;70:65–76. https://doi.org/10.1016/j.comppsych.2016.06.012.

[48] Roberts RE, Duong HT. The prospective association between sleep deprivation and depression among adolescents. Sleep 2014;37:239–44. https://doi.org/10.5665/sleep.3388.

[49] Wickham SR, Amarasekara NA, Bartonicek A, Conner TS. The Big Three Health Behaviors and Mental Health and Well-Being Among Young Adults: A Cross-Sectional Investigation of Sleep, Exercise, and Diet. Front Psychol 2020;11:1–10. https://doi.org/10.3389/fpsyg.2020.579205.

[50] Goldstone A, Javitz HS, Claudatos SA, Buysse DJ, Hasler BP, de Zambotti M, et al. Sleep Disturbance Predicts Depression Symptoms in Early Adolescence: Initial Findings From the Adolescent Brain Cognitive Development Study. J Adolesc Heal 2020;66:567–74. https://doi.org/10.1016/j.jadohealth.2019.12.005.

[51] Angelina S, Kurniawan A, Agung FH, Halim DA, Wijovi F, Jodhinata C, et al. Adolescents' mental health status and influential factors amid the Coronavirus Disease pandemic. Clin Epidemiol Glob Heal 2021;12:100903. https://doi.org/10.1016/j.cegh.2021.100903.

[52] Osendarp S. COVID-19 and anemia. Micronutr Forum 2020.

[53] Indonesian Ministry of Finance;, Smeru Research Institute;, Prospera;, Unicef; The Social and Economic Impact of COVID-19 on Households in Indonesia: A Second Round of Surveys in 2022 2022.

[54] Soewondo P, Sakti GMK, Irawati DO, Pujisubekti R, Rahmayanti NM, Sumartono AHI, et al. Capturing adjustment and innovation of nutrition services program during COVID-19 Pandemic: Case Study at 8 cities/districts in Indonesia. Strateg Purch Prim Heal Care 2020:1–21.

[55] Johnson EO, Roth T, Schultz L, Breslau N. Epidemiology of DSM-IV Insomnia in Adolescence: Lifetime Prevalence, Chronicity, and an Emergent Gender Difference. Pediatrics 2006;117:e247–56. https://doi.org/10.1542/peds.2004-2629.

[56] Knutson KL. The association between pubertal status and sleep duration and quality among a nationally representative sample of U. S. Adolescents. Am J Hum Biol 2005;17:418–24. https://doi.org/https://doi.org/10.1002/ajhb.20405.

[57] Scholle S, Beyer U, Bernhard M, Eichholz S, Erler T, Graneß P, et al. Normative values of polysomnographic parameters in childhood and adolescence: Quantitative sleep parameters. Sleep Med 2011;12:542–9. https://doi.org/10.1016/j.sleep.2010.11.011.

[58] Neumann SN, Li JJ, Yuan XD, Chen SH, Ma CR, Murray-Kolb LE, et al. Anemia and insomnia: a cross-sectional study and meta-analysis. Chin Med J (Engl) 2021;134:675–81. https://doi.org/10.1097/CM9.0000000000001306.

Supplementary Table 5.1 PSQI and K10 questionnaires

Instructions: The following questions relate to your usual sleep habits during the past month only, Your answers should indicate the most accurate reply for the majority of days and nights in the past month, Please answer all questions, During the past month, *Petunjuk: Pertanyaan-pertanyaan berikut ini berkaitan dengan kebiasaan tidur Anda yang biasa selama sebulan terakhir, Jawaban Anda sebaiknya mewakili tidur sebagian besar siang dan malam dalam sebulan terakhir, Mohon jawab semua pertanyaan, Selama sebulan terakhir,*
1. When have you usually gone to bed? *Kapan biasanya Anda tidur?* 2. How long (in minutes) has it taken you to fall asleep each night? *Berapa lama (dalam menit) Anda biasanya butuhkan untuk tertidur setiap malam?* 3. When have you usually gotten up in the morning? *Kapan biasanya Anda bangun di pagi hari?* 4. How many hours of actual sleep do you get at night? (This may be different than the number of hours you spend in bed) *Berapa jam Anda tidur di malam hari? (Ini mungkin berbeda dari jumlah jam yang Anda habiskan di tempat tidur)* 5. During the past month, how often have you had trouble sleeping because you,,, *Selama sebulan terakhir, seberapa sering Anda sulit tidur karena ,,,* *Answer:* **Not during the past month** *Tidak selama sebulan terakhir,* **Less than once a week (1)** *Kurang dari sekali seminggu (1)*; **Once or twice a week (2);** *Sekali atau dua kali seminggu (2)* **Three or more times week (3)** *Tiga kali atau lebih dalam seminggu (3)*
a. Cannot get to sleep within 30 minutes *Tidak bisa tidur dalam 30 menit*
b. Wake up in the middle of the night or early morning *Bangun di tengah malam atau dini hari*
c. Have to get up to use the bathroom *Harus bangun untuk ke kamar mandi*
d. Cannot breathe comfortably *Tidak bisa bernapas dengan nyaman*
e. Cough or snore loudly *Merasa terlalu dingin*
f. Feel too cold *Merasa terlalu dingin*
g. Feel too hot *Merasa terlalu panas*
h. Have bad dreams *Mimpi buruk*
i. Have pain *Sakit*
j. Other reason(s), please describe, including how often you have had trouble sleeping because of this reason(s): *Alasan lain, harap jelaskan, termasuk seberapa sering Anda sulit tidur karena alasan ini: ,,,,,,,,,,,,,, ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,*
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep? *Selama sebulan terakhir, seberapa sering Anda minum obat (dengan resep atau beli sendiri untuk membuat Anda tidur?*
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity? *Selama sebulan terakhir, seberapa sering Anda mengalami kesulitan untuk tetap terjaga saat mengemudi, makan, atau melakukan aktivitas sosial?*
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done? *Selama sebulan terakhir, seberapa besar masalah yang Anda alami dalam mempertahankan antusiasme untuk menyelesaikan sesuatu?*
9. During the past month, how would you rate your sleep quality overall? *Selama sebulan terakhir, bagaimana Anda menilai kualitas tidur Anda secara keseluruhan?*

The Kessler Psychological Distress Scale English and Bahasa Version (K10)

Anxiety and depression checklist (K10) These questions relate to how you've been feeling over the past four weeks, Give an answer to each question that best reflects your thoughts, feelings and behaviour, **None of the time, A little of the time, Some of the time, Most of the time, or All of the time** *Berikut adalah pertanyaan-pertanyaan mengenai bagaimana Anda merasakan berbagai situasi di bawah ini dalam kurun waktu 4 minggu terakhir, Pilih jawaban yang paling tepat untuk menggambarkan seberapa sering kamu mengalaminya dengan memberikan tanda: Tidak pernah, jarang, kadang-kadangm sering, atau selalu*
About *tentang*:
1. how often did you feel tired for no good reason? *kira-kira seberapa sering Anda merasa lelah tanpa alasan yang jelas?*
2. how often did you feel nervous? *kira-kira seberapa sering anda merasa gugup?*
3. About how often did you feel so nervous that nothing could calm you down? *kira-kira seberapa sering anda merasa gugup sehingga tidak ada yang dapat menenangkan diri anda?*
4. About how often did you feel hopeless? *kira-kira seberapa sering anda merasa putus asa?*
5. About how often did you feel restless or fidgety? *kira-kira seberapa sering anda merasa gelisah atau tidak nyaman?*
6. About how often did you feel so restless you could not sit still? *Kira-kira seberapa sering Anda merasa sangat gelisah sehingga tidak dapat duduk tenang?*
7. About how often did you feel depressed? *kira-kira seberapa sering anda merasa depresi/sedih?*
8. About how often did you feel that everything was an effort? *kira-kira seberapa sering anda merasa bahwa segala sesuatu memerlukan usaha berat?*
9. About how often did you feel so sad that nothing could cheer you up? *kira-kira seberapa sering anda merasa sangat sedih dan tidak ada yang dapat membuat anda ceria?*
10. About how often did you feel worthless? *kira-kira seberapa sering anda merasa tidak berarti?*

Supplementary Table 5.2. Variable definition, scores, and survey question

Socioeconomic and characteristic

Variable	Definition	Question/measurement	Answering options	Classification/ analysis
Adolescent variables				
Adolescent's Occupation	Occupation refers to activities in which adolescents engage when pursuing their pleasure daily	Scale	10. No work 11. School 12. Civil servant, army, police, governmental organization 13. Non-governmental organization 14. Entrepreneur 15. Farmer 16. Fisherman 17. Driver/ housekeeper Other	1: Unemployed (if 1) 2: Student (if 2) 3: Work (paid or unpaid) (if 3-9)
Smoking Status	Smoking status is a recoded variable based on a question about cigarette smoking	Smoking status	1: Yes 2: No	1: Yes 0: No
Alcohol consumption	Alcohol consumption refers to frequency of consumption of alcohol on daily and weekly basis	Alcohol consumption in the past month	1: Yes 2: No	1: Yes 0: No
		Total days of alcohol consumption in the past month	…, Days	Continuous data (number of days)
Nutritional status	Nutritional status is adolescent's weight status indicated by BMI-for age-z-score	Height (cm) and weight (kg) to calculate BMI-for-age Z-score	Scale	1: < -3SD (Severe thinness) 2: ≥ -3 SD ≤ -2 SD (Thinness) 3: >-2 SD to ≤1 SD (Normal) 4: >1 SD to ≤2 SD (Overweight) 5: >2 SD (Obese)
Physical activity	Physical activity is any bodily movement resulting in energy expenditure, reported by recall of the individual's movement	PAQ- A		

Supplementary Table 5.2. Socioeconomic and characteristic Continued

Variable	Definition	Question/measurement	Answering options	Classification/ analysis
Anaemia	Anaemia is a condition in which the number of red blood cells or haemoglobin concentration is lower than normal	Hemocue / Haemoglobin (g/dL)	Based on measurement using Hemocue, Hb is in g/dL	3 new variables: **1. Anaemia and non-anaemia** Age 10-11 years: No-anaemia: 11,5 or higher Anaemia: lower than 11,5 Age 12-4 years No-anaemia: 12 or higher Anaemia: lower than 12 Girls age 15 years or above No-anaemia: 12 or higher Anaemia: lower than 12 Boys age 15 years or above No-anaemia: 13 or higher Anaemia: lower than 13 **2. Anaemia classification** Age 10-11 years: No-anaemia: 11,5 or higher Mild anaemia: 11-11,4 Moderate anaemia: 8-10,9 Severe anaemia: lower than 8 Age 12-4 years No-anaemia: 12 or higher Mild anaemia: 11-11,9 Moderate anaemia: 8-10,9 Severe anaemia: lower than 8 Girls aged 15 years or above No-anaemia: 12 or higher Mild anaemia: 11-11,9 Moderate anaemia: 8-10,9 Severe anaemia: lower than 8 Boys aged 15 years or above No-anaemia: 13 or higher Mild anaemia: 11-12,9l Moderate anaemia: 8-10,9 Severe anaemia: lower than 8 **3. Continuous data Hb**

Supplementary Table 5.2. Socioeconomic and characteristic Continued

Variable	Definition	Question/measurement	Answering options	Classification/ analysis
Anaemia (altitude adjustment)	Anaemia level with taking into account of altitude (Hb correction)	Hemocue / Haemoglobin (g/dL)	Based on measurement using Hemocue, Hb is in g/dL	***Hb correction = −0,032 (altitude × 0,0032808) + 0,022 (altitude × 0,0032808)²*** The classification is the same the previous one,
Household variables				
Parental education	Parental education is defined as the highest education level of parents attained	Household questionnaire: *'What is your (father/ mother) highest? last education'*	8. Never attended school 9. Elementary school (not completed) 10. Elementary school (completed) 11. Middle school (completed) 12. Senior high school (completed) 13. Diploma (completed) 14. University (completed)	1: No education (if 1, 2) 2: Elementary school (if 3,4) 3: Senior high school (if 5) 4: Diploma or higher (if 6,7)
Parental occupation	Parental occupation is defined as activities in which parents engage on a daily basis to have income	Household questionnaire: *'What is your (father/ mother) occupation?'*	10. No work 11. School 12. Civil servant, army, police, governmental organization 13. Non-governmental organization 14. Entrepreneur 15. Farmer 16. Fisher 17. Driver/ housekeeper Other	1: Unemployed (if 1, 2) 2: Unsecured job (if 5, 6, 7, 9) 3: Secured job (if 3, 4, 8)
Number of household members	Number of household members is defined as the number of people living in the same building, not considering the household registration	Household questionnaire*: 'How many people live in this house/ building (not based on household)?'*	Total number of people	1: ≤ 5 people 2: > 5 people

5

Supplementary Table 5.2. Socioeconomic and characteristic Continued

Variable	Definition	Question/measurement	Answering options	Classification/ analysis
Wealth index	Wealth index measured by ownership of the goods and expenses for food and non-food, using 10 items of questionnaire and classified using on Central Bureau of Statistics (BPS) Indonesia	BPS questionnaire	Scoring from 0-10	1: Poor Household 2: Not a poor household
Household income	All income from all family members for food and non-food expenses	Household questionnaire:	1. < Rp 1,000,000 2. Rp 1,000,000 - Rp 3,000,000 3. Rp 3,000,000 - Rp 5,000,000 4. Rp 5,000,000 - Rp 7,000,000 5. > Rp 7,000,000	Total Household income: 1. < Rp 3,000,000 2. Rp 3,000,000 - Rp 5,000,000 3. > Rp 5,000,000
Household insurance	Insurance ownership of household either given by government, self-payment/ out of pocket, or both	Household questionnaire: *Type of family health insurance*	1. National Health Insurance (BPJS)-full covered by government 2. National Health Insurance (BPJS)-self payment 3. Jamkesos 4. Jamkesda	1. Government insurance 2. Private insurance 3. Combination
Access to health care services	Accessibility of health care services based on respondent's knowledge	Household questionnaire: *Do household members know of the nearest hospital / Puskesmas / Pustu / Posyandu?* *How long it takes to reach the facility?*	1. In the city 2. In closest city 3. Nothing 4. Do not know	1: Accessible 2: Not accessible
Demographic area	Demographic area was divided into rural and urban, assessed using classification of Indonesia's Bureau of Statistics, which is based on population density, percentage of agricultural households, and presence/access to facilities	BPS Classification	1: Rural area 2: Urban area	1: Rural area 2: Urban area

Supplementary Table 5.2. Pubertal development and body image

Variable	Definition	Question/measurement	Answering options	Classification
Pubertal development	Puberty is broadly defined as the time at which a child develops secondary sexual characteristics and reproductive function,	The Self-Rating Scale for Pubertal Development	Boys and girls (5 questions) 1: has not yet begun 2: has barely started 3: is definitely underway 4: seems completed 0: I don't know Especially for girls' question about menarche: 4: Yes 1: No	**Boys:** Prepubertal = 3 Early Pubertal = 4 or 5 (no 3-point responses) Mid-pubertal = 6, 7, or 8 (no 4-points) Late pubertal = 9-11 Post-pubertal = 12 **Girls:** Prepubertal = 2 and no menarche Early Puberty = 3 and no menarche Mid-pubertal = > 3 and no menarche Late Puberty = <= 7 and menarche Post-pubertal = 8 and menarche,
		Self-reported picture	**Pubic Hair Scale (both males and females)** Stage 1, Stage 2, Stage 3, Stage 4, Stage 5 **Female Breast Development Scale** Stage 1, Stage 2, Stage 3, Stage 4, Stage 5 **Male External Genitalia Scale** Stage 1, Stage 2, Stage 3, Stage 4, Stage 5	**3 generate variables in each development indicators** ***A (Classification I)*** 1: pre-pubertal (stage 1) 2: early pubertal (stages 2–3) 3: late pubertal (stages 4–5) ***B (Classification II)*** 1: pre pubertal (stage 1) 2: Pubertal (stage 4-5) ***C, Continuous data***

Supplementary Table 5.2. Mental health and well-being

Variable	Definition	Question/measurement	Answering options	Classification
Anxiety and depression	Measurement of distress based on questions about anxiety and depressive symptoms that a person has experienced in the most recent 4-week period,	K-10: the simple checklist asks you to reflect on your feelings over the past four weeks, ***Note:*** The maximum score is 50 indicating severe distress, the minimum score is 10 indicating no distress, Questions 3 and 6 are not asked if the preceding question was 'none of the time' in which case questions 3 and 6 would automatically receive a score of one,	1: All of the time 2: most of the time 3: some of the time 4: a little of the time 5: none of the time ***Note:*** The maximum score is 50 indicating severe distress, the minimum score is 10 indicating no distress, Questions 3 and 6 are not asked if the preceding question was 'none of the time' in which case questions 3 and 6 would automatically receive a score of one,	**Total Score** ***Scoring:*** 1: All of the time, score 5 2: most of the time, score 4 3: some of the time, score 3 4: a little of the time, score 2 5: none of the time, score 1 ***Note:*** The maximum score is 50 indicating severe distress, the minimum score is 10 indicating no distress, Questions 3 and 6 are not asked if the preceding question was 'none of the time' in which case questions 3 and 6 would automatically receive a score of one,
Eating disorders	An eating disorder is a mental disorder defined by abnormal eating habits that negatively affect a person's physical and/or mental health	EAT-26 questionnaire with 26 items of questions	1: Always 2: Usually 3: Often 4: Sometimes 5: Rarely 6: Never	**Classification:** 0: No (total score<20) 1: have eating disorder (total score>20) **Continues data (Total score)** ***Note:*** For all the items, except no 26, for each of the answer assign the score as following: Always =3 Usually =2 Often =1, Sometimes =0 Rarely =0 Never =0 For item no 26 assign the score as following: Always =0 Usually =0 Often =0 Sometimes =1 Rarely =2 Never =3

Supplementary Table 5.2. Mental health and well-being Continued

Variable	Definition	Question/measurement	Answering options	Classification
Sleep quality index	a self-report questionnaire that assesses sleep quality over a 1-month time interval,	The Pittsburgh Sleep Quality Index (PSQI)	**Question C22-C24:** 1: Not during the past month (0) 2: Less than once a week (1) 3: Once or twice a week (2) 4: Three or more times a week (3) **Questions C25:** 1: Very good 2: Fairly good 3: Fairly bad 4: Very bad	**Question C22-C24:** 1: Not during the past month (score 0) 2: Less than once a week (score 1) 3: Once or twice a week (score 2) 4: Three or more times a week (score 3) **Question C25:** 1: Very good, score 0 2: Fairly good, score 1 3: Fairly bad, score 2 4: Very bad, score 3 **Total Scoring** *Component 1:* #C25 Score *Component 2:* #C19 Score (<15min (0), 16-30min (1), 31-60 min (2), >60min (3)) + #C21a Score (if sum is equal 0=0; 1-2=1; 3-4=2; 5-6=3) *Component 3:* #C20 Score (>7(0), 6-7 (1), 5-6 (2), <5 (3) *Component 4:* (total # of hours asleep) / (total # of hours in bed) x 100 >85%=0, 75%-84%=1, 65%-74%=2, <65%=3 *Component 5:* # sum of scores C21b to 5j (0=0; 1-9=1; 10-18=2; 19-27=3) *Component 6:* #6 Score *Component 7:* #C23 Score + #8C24 score (0=0; 1-2=1; 3-4=2; 5-6=3) ***Total score: Add the seven component scores together*** ***Classification:*** 0: normal sleep (if total score<5) 1: poor sleep (if total score equal or higher than 5)

5

Supplementary Table 5.2. Food consumption

Variable	Definition	Question/measurement	Answering options	Classification
Risk consumption	Unhealthy food consumption refers to consumption of salty food, high-fat food, and soft drinks		1. >1x /day 2. 1x /day 3. 3 – 6x /week 4. 1 – 2x /week 5. <3x /month 6. Never 7. Not answered	**Continuous data (total score)** Selected answer (score =1) Unselected answer (score =0)
Food consumption before and after pandemic	Frequently Foods consumed before and during the quarantine/pandemic	DDS/scale	Yes: 1 No: 0	Tertiles of the each frequently consumed food before pandemic (6 months before), and during Pandemic (within 6 months)
Diet Diversity Score	Total score of several food groups consumed during the las 24 hours	MMD-W Foods consumed will be assigned into 10 different food groups - Starchy staples - Dark green leafy vegetables - Vitamin A-rich fruits, tubers & vegetables - Other vegetables - Other fruits - Flesh and organ meats - Eggs - Fish - Legumes, nuts, seeds - Milk products Reference: Minimum Dietary Diversity for Women, A guide to measurement FAO, 2016 https://www.mdpi.com/2072-6643/12/8/2230/htm	**Starcy staples:** - Rice, cassava, potato, sweet potato, bread **Dark-green leafy vegetables**: - Spinach, daun kacang panjang (lembayung), daun ubi **Vitamin A-rich fruits & vegetables** - Carrot, red guava, orange-sweet potato, papaya (ripe), mango (ripe) **Other vegetables** - Cucumber, cauliflower, green beans, bitter melon etc **Other fruits** - Banana, orange, **Flesh and organ meat**: - Chicken, beef, pigeon, duck, liver, **Eggs** - Chicken, duck, quail eggs **Fish** - Seafoods, prawn, gurameh and other fish **Legumes, nuts, seeds** - Tahu, tempe, mung bean, adzuki bean, kidney bean, **Milk products:** - Milk, cheese, yoghurt, peanuts	1. Identify each food consumed by adolescent and assigned into food group 1 – 10 2. Score 1: if they consumed at least 1 food item of each food group, at least 1 tablespoon of foods 3. Sum the food groups consumed by the adolescent **DDS < 5: inadequate DD** **DDS $\geq$ 5: adequate DD**

Supplementary Table 5.3. Characteristics comparison of exclude and included data from analysis[1]

Characteristics	Excluded case N= 124	Included Cases N=452	P-value[1]
Adolescent characteristics			
Sex			
• Boys	64 (51.6)	222 (49.1)	0.724
• Girls	60 (48.4)	230 (50.9)	0.730
Age group			
• 10 - ≤ 13y	19 (15.3)	130 (28.8)	0.216
• >13 - ≤ 16 y	28 (22.6)	169 (37.4)	0.129-1
• >16 - ≤ 18 y	61 (49.2)	133 (29.4)	0.057
• >18 - 19 y	16 (12.9)	20 (4.4)	0.355
Adolescent occupation			
• Unemployed	32 (25.8)	38 (8.4)	0.059
• Student	84 (67.7)	401 (88.7)	0.001
• Work	8 (6.5)	13 (2.9)	0.692
Physical activity			
• Low	37 (29.8)	150 (33.2)	0.692
• Moderate	53 (42.7)	(181 (40.0)	0.724
• High	34 (27.5)	121 (26.8)	0.935
Nutritional status (BMI z-score)			
• Severely thin	3 (2.4)	8 (1.8)	0.949
• Thin	9 (7.3)	43 (9.6)	0.828
• Normal	92 (74.2)	300 (66.8)	0.181
• Overweight	11 (8.8)	62 (13.8)	0.189
• Obese	9 (7.3)	36 (8.0)	0.944
Disabilities			
• None	51 (41.2)	198 (43.8)	0.738
• Low	41 (33.0)	107 (23.7)	0.250
• Moderate	252 (20.2)	121 (26.8)	0.152
• Severe/Very Severe	7 (5.6)	26 (5.7)	0.991
Household characteristic			
Paternal education			
• No education	10 (8.3)	35 (7.8)	0.958
• Elementary school	75 (60.2)	271 (60.2)	1.000
• Senior high school	35 (28.2)	125 (27.8)	0.962
• University	4 (3.3)	19 (4.2)	0.933
Maternal education			
• No education	9 (7.3)	36 (8.1)	0.936
• Elementary school	91 (73.4)	285 (64.3)	0.109
• Senior high school	18 (14.5)	95 (21.4)	0.504
• University	6 (4.8)	27 (6.1)	0.902
Paternal occupation			

Supplementary Table 5.3. Continued

Characteristics	Excluded case N= 124	Included Cases N=452	P-value[1]
• Unemployed	6 (4.8)	1 (0.2)	0.830
• Unsecured job	64 (51.6)	195 (45.4)	0.388
• Secured Job	54 (43.6)	234 (54.4)	0.152
Maternal occupation			
• Unemployed	41 (33.1)	146 (35.2)	0.802
• Unsecured job	58 (46.8)	201 (48.4)	0.829
• Secured job	25 (20.1)	68 (16.4)	0.676
Number of household members > 5 people	23 (18.6)	95 (21.0)	0.798
Household income			
• Low	102 (82.3)	375 (82.9)	0.886
• Moderate	16 (12.9)	62 (13.8)	0.925
• High	6 (4.8)	15 (3.3)	0.869

[1]Values are n (%) for categorical data. P values were generated using a two-sample test of proportion.

Supplementary Table 5.4. LCA cluster models' fit and simplicity statistics

		LL	BIC	AIC	Npar	L^2	df	p-value	Max,BVR
Model1	1-Cluster	-6540,95	13436,83	13197,9	58	7780,115	397	1,7e-1350	43,3921
Model2	2-Cluster	-5868,88	12453,75	11971,77	117	6435,984	338	1,3e-1111	13,9479
Model3	3-Cluster	-5695,85	12468,73	11743,7	176	6089,915	279	8,4e-1079	4,2782
Model4	4-Cluster	-5593,67	12625,42	11657,35	235	5885,563	220	4,5e-1077	4,3315
Model5	5-Cluster	-5522,99	12845,1	11633,97	294	5744,191	161	2,6e-1091	4,1527
Model 6	6-Cluster	-5467,25	13094,67	11640,5	353	5632,712	102	3,6e-1116	4,3726
Model 7	7-Cluster	-5428,14	13377,49	11680,27	412	5554,488	43	1,0e-1155	3,4612
Model 5+ direct effects*	5-Cluster	-5499,74	12853,69	11605,49	303	5697,702	152	1,5e-1088	3,495

*Direct effects from component of sleep duration (component 3) and sleep medication (component 6). Bold values designated the selected model with the best balance between model fit and model simplicity based on Bayesian information Criterion (BIC) and Akaike Information Criterion (AIC), The lower BIC and AIC, the better the balance

5

Chapter 6

General Discussion

As described in **Chapter 1**, the main objective of this thesis was to better understand the connections between pubertal development, anaemia, and nutritional status in relation to physical, mental, and cognitive health of Indonesian adolescents. We first identified the trend of Age at Menarche (AAM) over time and its association with obesity and noncommunicable diseases (NCD) among women. Next, we evaluated to what extent cognitive function during adolescence is associated with Hb concentrations of their mothers while being *in utero.* Further, we assessed the associations between anaemia and mental health outcomes by exploring potential aetiologic factors as determinants of Common Mental Disorders (CMD) in adolescent girls, and, finally, determined associations between sleep quality, depression, and haemoglobin concentration in adolescent boys and girls. The findings of the thesis are summarized in Table 6.1.

AAM IS ASSOCIATED WITH OVERWEIGHT/OBESITY, BUT NOT WITH NCDS

In **Chapter 2**, we found that AAM has significantly declined over time, from 14.4 years of age in the 1940s to 13.4 in the 1990s. This finding is in line with a systematic review on the time trend of age at menarche in Indonesia, which showed a decline from 14.4 years to 13.6 years since 1970 [1]. Compared to other Asian countries the mean AAM of our population was somewhat lower. For instance, in China an average AAM of 14.7 years was found for those born after 1959 [2], and AAM amounted to 16.2 years in women born before 1950. However, like in Indonesia, the average AAM has declined in China to approximately 13.2 years for women born in the period 1975-1985 [3]. Both in developed and developing countries, declining AAM has been associated with factors such as economic development, wealth, access to health facilities, and food intake. This decline varies within a population based on the local context [4].

In our study population, AAM was significantly inversely associated with BMI and body weight at later age, but not with height, nor with NCD. This is in line with a large systematic review, which showed a higher BMI in adult women with earlier compared to later start of menarche (<12 vs ≥12 years) of 0.34 kg/m^2 (95% confidence interval: 0.33–0.34) [5].

6

Methodological considerations

In **Chapter 2**, the retrospective recall of NCDs and AAM might not have been completely accurate, although the respondents of IFLS were generally healthy and able to remember their health history. Moreover, self-reported AAM collected by a personal interview, which was the method used in IFLS, has been shown to be consistent with AAM up till 30 years earlier in a retrospective follow-up study [6], as well as in a study with repeated interviews of menstrual history in the period of 1985-1993 [7]. However, since data on AAM were only collected from married women (**Chapter 2)**, the analysis may have selectively excluded unmarried women, or those who were not willing to participate or who had already passed away. This validity threat is inherent to the longitudinal design and cannot be avoided. Nevertheless, the number of missing data was relatively small, and therefore we do not expect that this potential bias has greatly influenced the outcome of our study.

Implications of the link between early menarche and adolescent health trajectories

The decrease in AAM can be expected to have some health consequences for Indonesian women. Early age at menarche has been shown to be a predictor of physical, nutritional, and reproductive health outcomes, even at adolescent age, which has implications for the adolescent girl's healthy transition from childhood into young adulthood [8,9]. Unintended pregnancy and its additional risks such as ectopic pregnancy, miscarriage, low birth weight, and preterm birth, as well as overweight/obesity have all been associated with early menarche [10–12]. Given that weight increase after menarche is accelerated, BMI could be a mediating factor in the relationship between early menarche and unfavourable health outcomes [13]. However, because obesity and overweight often begin in childhood and have been shown to initiate puberty at earlier age, BMI during childhood could still be one of the confounders that need to be considered when investigating the association.

Although in our study AAM was not shown to be associated with NCDs later in life, chances are high that such an association will be observed in the Indonesian context in the future. After all, the prevalence of obesity among Indonesian women is increasing rapidly, while AAM is still declining. This means that the prevalence of NCDs in Indonesia may not yet be at its highest point, which may have weakened any associations. The incidence of NCDs is still much lower in Indonesia compared to other countries, such as for example in Mexico [14], China [2], and Korea [15]. Besides, several other studies have clearly shown that AAM can be a risk factor for diseases such as breast cancer [16], and type 2 diabetes [17] later in life.

NON-ANAEMIC MOTHERS PRESERVE BETTER COGNITIVE FUNCTION IN STUNTED OFFSPRING

In **Chapter 3,** the association between maternal Hb concentration and her offspring's cognitive function at age 10-14 years is described. We showed that adolescents who were stunted, anaemic, or living in a rural area had a significantly lower cognitive score than their counterparts who were not stunted or anaemic, or who were living in an urban area. The effect of maternal Hb concentration on cognitive function of her offspring was modified by stunting status of the child.

Others have shown that stunted children have a higher risk of being anaemic [18,19]. Moreover, along with other risk factors such as poverty and poor home environments, stunting has been associated with lower cognitive functioning at school age and during adulthood [20]. As adolescents in the present study were born during the economic crisis between 1997 and 1999, their parents' economic status may have been affected. Our finding is in line with previous studies in Indonesia, which found a stronger and more consistent association of adolescents' cognitive scores with socioenvironmental risk factors, including stunting, than with biomedical factors [21]. However, it should be noted that stunting in adolescents is multi-causal and can be the result of a combination of poor nutrition, environmental stress, and morbidity, starting from the foetal period to later in life [22]. There may also be unmeasured confounding in **Chapter 3**, e.g., by ignoring exposures that impact both maternal nutritional status and child development, such as for example dietary intake. Furthermore, gestational age at the time point of Hb testing was not assessed, which is of importance as timing of anaemia may affect foetal development [23].

Methodological considerations

The longitudinal design of the study described in **Chapter 3** enabled us to draw conclusions about potential causal relationships between maternal anaemia and their offspring's cognitive function. Our findings showed that being non-anaemic during pregnancy may result in a brighter child when the child is stunted. However, some residual confounding may have been present as in every observational study. In fact, to exclude competing explaining factors, additional information on other potential confounders would be needed, i.e. gestational age at time of maternal Hb measurement, and on determinants of childhood stunting [24]. Cognitive function was assessed using the Raven's Progressive Matrices (RPM). This is a standardized method to measure non-verbal cognitive ability that has previously been used in Indonesia [25] and is not biased by educational background or by cultural or linguistic deficiencies [26]. However, the results for cognition cannot be directly compared to those obtained with other tools. Finally, altitude and smoking status were not taken into account to correct Hb concentration, while WHO suggested to consider those variables for Hb adjustment [27].

Implications of the role of maternal anaemia in cognitive functioning of adolescents

As showed in **Chapter 3**, the high prevalence of maternal anaemia (49%) and of adolescent stunting (32%) is a continued concern, considering that each stunted child who has been exposed to anaemia *in utero* runs the risk of long-term developmental backlog. The co-occurrence poses a greater threat to offspring's cognitive function than maternal anaemia only. Given the fact that stunting status was shown to be a mediating factor in the association, the effect of maternal anaemia may further reduce mental capacity, delay motor development, cause poor educational attainment, and reduce economic productivity [28,29].

Since adolescent anaemia and stunting can have common underlying causes, early life interventions, i.e. during pregnancy, may be more effective to simultaneously address all forms of malnutrition [30]. It is worthwhile to intervene in the critical developmental period of the first 1000 days of life, during which the body is more vulnerable to both nutritional and non-nutritional threats [31]. Existing guidelines recommend the adoption of comprehensive and multi-sectoral prevention strategies to overcome malnutrition in children and adolescents [32]. Thus, our findings support the need to scale up interventions, such as those aimed at preventing anaemia and stunting, within the window of opportunity that is defined by pregnancy and the first two years of life.

DETERMINANTS OF MENTAL HEALTH IN INDONESIAN ADOLESCENT GIRLS

We explored national representative data gathered in 2018, and the results are presented in **Chapter 4**. We found that the prevalence of CMD among adolescent girls of 15-19 years old was 16.5%. This was higher than the reported national prevalence of 10% among people aged 15 years or older in 2018 [33]. Previous studies indicated that the prevalence of CMD among adolescents in developing countries is increasing [34]. Compared to other countries in the area, the prevalence of mental health problems in Indonesia observed our study was higher than in Malaysia, with 11.1% reported for Malaysian children aged 5-15 years assessed by a validated Strengths and Difficulties Questionnaire in National Health and Morbidity Survey in 2015 [35]. In Thailand, 15% of adolescents aged 13-17 years developed DSM-IV mental disorders in the period of 2015-2016 based on a national survey in 18 provinces [36]. However, different time, age group and tools might hamper these prevalence comparisons.

In Chapter 4 we investigated whether anaemia was associated with CMD, but this did not seem to be the case. This result was not conform our prior expectation, as iron and vitamin $B_{12,}$, both important in red blood cell formation, are also known to be involved in processes affecting mental disorders [37]. In addition, we found that CMD occurs more often among adolescents who have parents with a higher socio-economic status and who are living in an urban environment, and in those having asthma. Furthermore, higher CMD scores were associated with a high level of the adolescent's education and better paternal occupation. Previous studies have shown that adolescents, especially girls, who lived in an urban area more often reported to have stress symptoms during non-working time [38], and were more likely to have symptoms of depression [39]. Furthermore, living in an urban area and having a better socio-economic status seems to affect psychosocial stress, possibly due to reduced social interaction despite more crowded environments, less quality time with parents, and higher parental expectations of academic achievements such as grades [40–42].

The strongest clustered determinants of CMD among adolescent girls in Indonesia were asthma, smoking, and higher haemoglobin concentration. This result is in line with a previous study that showed an association between smoking and depression, which was stronger among women compared to men [43]. In addition, higher smoking rates were also found specifically among adolescent girls living with mental disorders [44]. However, the causality of this pathway remains open, and reverse causality cannot be excluded due to the cross-sectional study design. Adolescents found to have a higher risk for CMD were those with asthma who also had higher haemoglobin levels which is in line with a previous study [45].This can be explained by asthma preventing oxygen to bind to haemoglobin, therefore leading to hypoxia, which increases haemoglobin concentration [46]. Adolescents with asthma were found to have a number of complications that may influence their mental well-being, including sleep difficulties, persistent coughing, and limitations in physical activity [47], and had a higher risk of anxiety symptoms in comparison to their healthy peers [48]. However, the size of the cluster was rather small, hence for public health practice it is also important to consider the second cluster found to be at risk of CMD, namely adolescents with higher SES.

Methodological considerations

In **Chapter 4**, the cross-sectional nature of the study prohibits clear causal inferences, as the time effect of exposure on outcomes cannot be determined. Furthermore, missing data, especially on AAM and parental occupation, may have caused some bias. Exclusion of adolescents who were more often member of a smaller household, lived in urban areas, had a highly educated father and a mother without education, and tended to have CMD more often, may have blunted some of the associations. However, the number of these cases was rather small (~13% of the original sample) and we expect the impact to be small. Similar to Chapter 3, due to unavailability of the data, altitude and smoking status could not be taken into account to correct Hb concentrations, although it is known that Hb concentrations increase with altitude and smoking as an adaptive response to lower blood oxygen saturation and oxygen carrying capacity [27]. The data unavailability may have influenced the Hb concentrations in our study.

6

We acknowledge that non-differential recall bias from self-reported CMD data might have led to underestimating the associations. CMD, including depressive symptoms, anxiety, and psychosomatic complaints, were measured with the SRQ-20. The SRQ-20 has been found to detect probable cases of common mental disorders with reasonable accuracy and has been used in the National Survey, the questionnaire has been translated in Bahasa, and was validated. Since the tool consisted of 20 questions, adolescents may have taken a little longer than the time reserved for completing the questionnaire, which may have caused errors because of the time pressure. For the data analysis, we determined CMD prevalence using the established standard criteria of the SRQ-20. However, the use of categorical diagnostic constructs can possibly be a source of misclassification because of the latent factors underlying CMD. In addition, the analysis in **Chapter 4** lacked some important covariates, such as adolescents' experience of violence and quality of their relationship with parents and peers. Such data may have helped to explain some of the associations in more detail. Nevertheless, socioeconomic status was captured sufficiently, by parental education and occupation [49].

Implications of mental health problems on adolescent health trajectories

Mental health problems can affect children and young adults throughout their life. Adolescents who experience mental health issues may have a difficult time when adjusting to adult life. They may, for instance, experience problems in adulthood, such as completing education, getting a job, and avoiding illegal and health risk behaviours [50]. Previous studies reported that early adult functioning was significantly influenced by both a complex adolescence period and current mental health status. For instance, current and former mental health problems were strongly related to adult functioning in Dutch adults, even if the symptoms decreased over adolescence [51]. Several studies indicated that having any type of mental disorder during adolescent age predicts adverse outcomes related to health behaviour, social functioning, and financial issues [52–54]. This is supported by the finding that onset of depression at younger age is linked to significant functional impairment and a higher burden of illness than onset at later age [55].

ANAEMIA, SLEEP QUALITY, AND DEPRESSION IN INDONESIAN ADOLESCENTS

Latent Class Analysis yielded 5 underlying latent classes of sleep quality and depression (described in **Chapter 5**). We found that 48.3% of the adolescents in our study could be classified as having good sleep quality and low risk of depression (class A); 22%, a good to moderate sleep quality and low risk of depression, but with some tiredness (class B); 17% with moderate sleep quality and moderate risk of depression (class C); 8% with moderate sleep quality and high risk of depression (class D); and 4.7% with poor sleep quality and high risk of depression (class E). The latter, class E, consisted of almost only girls (91%), were more often aged ≥16 years (45%), and were more likely to be thin (14%), to have low physical activity (46%), to engage in alcohol drinking (9%) and smoking (18%), to live in smaller households (86% ≤ 5 people) with higher educated parents, and were more likely to have anaemia at follow-up (46%), compared to the other classes. These findings support our finding in Chapter 4, i.e., that a higher socio-economic status of the household is a determinant of CMD.

Class membership, in particular for classes B and C, significantly predicted haemoglobin concentration at one-year follow-up, after adjusting for Hb at baseline. In addition, among girls but not in boys, a significant increase in sleeping problems with advanced pubertal development score has been reported [56]. Furthermore, the higher risk of sleep disturbances, depression, and anaemia has been shown to coincide with the onset of menses in adolescent girls [57]. Nevertheless, also other behavioural determinants can potentially be associated with an increased risk of sleep problems and depression, such as inconsistent bed routines and gadget screen device use [58].

Methodological considerations

Taking the disadvantages of the measurement tools described in Chapter 3 into consideration, in **Chapter 5** mental health disorders in adolescents were assessed using the K10 scale, which focuses on psychometric properties and can discriminate psychiatric cases from non-psychiatric, healthy cases. The tool has been used in Indonesia, translated in Bahasa, validated among adolescents, and only required a short time to administer during the field data collection. We used LCA analysis in **Chapter 5** to identify subgroups of sleep quality and depression. As sleep quality and depression consist of latent indicators, LCA helps to identify subgroups of adolescents who share common characteristics of sleep quality and depression by grouping them by similar scoring patterns [59].

To overcome the limitation of using non-adjusted haemoglobin concentration in previous chapters, haemoglobin concentration in **Chapter 5** was adjusted for altitude and smoking status as these additional data were collected in this longitudinal study. We acknowledge that Hb cannot be interpreted as a direct measure of iron deficiency, so therefore it would also have been worthwhile to take iron status indicators into consideration, such as serum ferritin (SF), transferrin saturation, and soluble transferrin receptor (sTfR). A full longitudinal analyses, e.g., investigating changes in Hb related to changes in sleep/ depression, was not possible due to delays in data cleaning, but are scheduled for later.

Implications of the relationship between sleep quality-depression and anaemia on adolescent health development

Sleep and depression gained more attention, especially during the COVID-19 pandemic. It is not a novel finding that one of the most typical signs of depression in adolescence is a chronic lack of sleep or a severe sleep disorder [60]. A meta-analysis, in which 150,000 participants were followed for a period of three months to 34 years, showed that those who had sleep issues had a two times higher risk of developing a depression

[61]. Furthermore, based on a study that looked at data of adolescents who were tracked from the age of 15 to 24 years, those who reported poor sleep at the age of 15 but did not yet experience depression or anxiety at that time, were more likely to deal with this problem at the age of 17, 21, or 24 than their peers [62]. At crucial life stages, having a depression combined with sleep disruption is linked to an increased risk of suicide [63]. Particularly, adolescents who sleep on average less than six hours are three times as likely to consider suicide than those who sleep for eight hours [64]. Lack of sleep increases the propensity to withdraw from friends and family, a lack of ambition, and an increase in irritability. These can all have an impact on a person's social relationships and thus the risk for depression [65]. Clinical evidence concerning treatment, shows that treating insomnia in people, including adolescents who already have depressive symptoms, not only improves their sleep but also reduces the symptoms of depression [66].

The finding from this thesis concerning the association between sleep quality-depression and low Hb potentially has important public health implications. Sleep and depression are found as risk factors of anaemia in adolescents; thus, the prevention and treatment of anaemia can be focused on promoting sleep and preventing depression, which may reduce the risk to develop anaemia at the same time. Furthermore, anaemia prevention programs should always consider evaluating sleep quality and depression in anaemic adolescents.

INTEGRATION OF RESEARCH FINDINGS ON HEALTH INDICATORS

In our study, AAM was assessed in **chapters 2, 4, and 5** using a similar recall question: "*how old were you (in years) at your first menstruation?*" In **chapter 2**, based on IFLS data, we found a decline in AAM of one year between women born in 1940s-1990s, from 14.4 (SD:2.1) to 13.4 (SD:1.5) years of age. In **chapter 4**, based on data from the National Basic Health Survey, girls born between 2003-2008 reported their AAM to be 13.1 years (SD:1.3), while in **chapter 5**, based on newly collected data in one district, girls born between 2006-2011 reported it to be 12.5 years (SD:1.2). These findings indicate that AAM in Indonesia may still be declining.

Regarding the prevalence of anaemia, **chapter 3** (IFLS data) showed that 22.2% of adolescents aged 10-14 years were anaemic in 2015, with girls being more affected (30.4%) than boys (14%). Furthermore, 27.3% of adolescent girls aged 15-19 years were found to be anaemic in 2018 (**chapter 4**). In both of these studies no adjustment of Hb concentration for altitude and smoking status was possible, and the age ranges differ from the definition of adolescents by WHO (age 10-19 years). Nevertheless, findings from the primary data collection in one district as described in **chapter 5** show that the prevalence of anaemia in adolescents aged 10-19 years old was in the same range of 20-30%, namely 21% in 2021 and 29% in 2022. In addition, girls were found to be more affected by anaemia than boys (31% vs. 9% at baseline, and 42% vs. 15% at follow-up, respectively). Our studies indicate that anaemia among adolescent girls is not declining in Indonesia and may even have increased during the COVID-19 pandemic.

Chapter 3 showed that 32% of adolescents were stunted, 7.7% were overweight, and 5.3% were obese, but none of them were thin. Different results were found in **chapter 4**, in which 26.6% of adolescents were thin, 6.2% were overweight, and 20.2% were obese. Differences between surveys, age groups, sampling size, sampling frame, and time points may have caused these discrepancies. These factors were considered in **chapter 5**, and findings show that the prevalence of adolescents, aged 10-19 years in the study area, who were thin was 11.7%, overweight was 14.1%, and obese 8.4%.

With regard to mental health, 16.8% of adolescent girls aged 15-19 years were found to have mental health problems, as assessed by SRQ-20 questionnaire in 2018 (cut-off ≥6) (**chapter 4**). In contrast, mental health problems as assessed by K10 questionnaire (cut-off ≥18) occurred in approximately 28.3% of adolescent boys and girls in 2021 (**chapter 5**). Mental health problems were more prevalent in girls compared to boys, with 35.3% and 21.2%, respectively. When combined, classes D and E represented 12.7% of adolescents with poor-to-moderate sleep quality and high risk of depression. Discrepancies between these findings may be attributed to differences in methodologies, sampling, living area, and time period of data collection.

GENERAL CONCLUSION AND IMPLICATIONS FOR FUTURE RESEARCH

General conclusion

In the introduction of this thesis three specific research questions were formulated:

1. To identify the time trend of AAM and its association with obesity and NCD among women from diverse socio-economic groups, living areas, and regions in Indonesia;
2. To evaluate the relationship between intra-uterine maternal Hb concentration and cognitive function of their offspring at adolescent age;
3. To assess associations between pubertal development, anaemia, and mental health outcomes.

The studies in this thesis show that AAM declined over decades from 14.4 years in the 1940s to 13.4 years in the 1990s, and that women with earlier AAM had a higher BMI and body weight later in life. AAM was not independently associated with any of the NCD outcomes and mental health problems. Maternal Hb concentration was associated with lower cognition in their adolescent offspring, when modified by adolescent stunting status. Considering mental health, adolescent girls with asthma and smoking cigarettes, as well as those having parents with higher education and secured occupation, are at increased risk of developing mental disorders. Furthermore, severity of sleep quality and depression was not associated with haemoglobin concentrations at baseline but did predict lower concentrations at one-year follow-up.

Existing policy on adolescent anaemia and mental health in Indonesia

In recent decades, the Indonesian government has shown political commitment to address malnutrition and made numerous efforts to do so. Although there have been modest improvements, Indonesia is still not on track to reach the global nutrition targets [67]. Currently, there is no set of regulations aimed at the health needs of adolescents, particularly not regarding the prevention of anaemia nor the promotion of mental health. Despite efforts of the Ministry of Health to promote adolescent health in a broader sense, most of the initiatives so far have centred on reproductive health concerns.

Regarding anaemia prevention, no progress has been made towards achieving the target of reducing 50% anaemia among women of reproductive age (15 to 49 y) [67]. Weekly Iron Folic Acid supplementation (WIFS), a national program for preventing anaemia in adolescent girls, was introduced in 2016. However, it is still in its very early stage with poor coverage and compliance [68]. Since the high importance to promote adolescent health, much can still be achieved in this area and further policies should be developed and applied.

Our findings show that anaemia in adolescents is multidimensional. Non-nutritional aspects such as mental health problems, pubertal status, and poor sleep quality are important determinants which play crucial roles in increasing the anaemia prevalence in Indonesia. In addition, social-economic determinants, and factors such as parental education and occupation, living area, and smoking status also contribute to the association between anaemia and mental health. Comprehensive non-nutritional approaches to complement existing nutritional programs are needed to overcome anaemia and anaemia-related consequences in adolescents.

General recommendations

Based on the findings in this thesis, we recommend further research in the following areas:

1. With the prospect of increasing prevalence of anaemia, overweight-obesity, early puberty, and adolescent mental health issues in Indonesia:

a) Future national health surveys should clearly differentiate between adolescent age (10-19 years) and/or pubertal developmental stage to facilitate future comparisons and should include additional adolescence related topics such as pubertal status and sleep quality.

b) Longitudinal studies in which pubertal status and mental health are measured, are needed to unravel causal pathways and to provide evidence for tailored preventive programs.

2. Studies that focus on adolescents' anaemia in Indonesia should consider evaluating stunting status, sleep quality, and mental health indicators over continued time periods and in various geographic areas, with validated methodologies, and should start from an early stage of life.
3. Comprehensive measurements of puberty among adolescent girls in relation to anaemia, such as menstrual blood loss, are crucial to provide evidence about the effect of early puberty on anaemia and mental health development.

Learning from our findings from Indonesia and some other ASEAN countries [69] through national health survey data, to provide evidence-based policies which target both physical and mental health, is crucial. While ensuring the interventions' accessibility, acceptance, availability, and affordability, it is now the right time to prevent and treat adolescent anaemia with a multidisciplinary approach and to deliver interventions through appropriate delivery platforms.

Table 6.1 Summary of the results

Exposure and/or outcome of interest	Aim	Study design and population	Results	Chapter
Age at menarche (AAM) and risk of non-communicable diseases (NCD)	To determine the time trend of AAM in Indonesia, and its association with BMI and NCD prevalence at later age	Longitudinal study of 15,744 women aged 15-65 years from 5 waves of the Indonesian Family Life Survey (IFLS) conducted in the period 1993 to 2015	§ AAM has significantly declined with one year over time, from 14.4 years of age in the 1940s to 13.4 in the 1990s § AAM was significantly inversely associated with BMI and body weight, but not with height § AAM was not associated with NCD, i.e., hypertension, type 2 diabetes mellitus, liver diseases, asthma, chronic lung diseases, cardiovascular diseases, stroke, cancer, or arthritis	2
Maternal anaemia and cognitive function	To investigate the association between intra-uterine maternal haemoglobin (Hb) concentration and cognitive function of their offspring during adolescence	Cohort data of 363 paired pregnant mothers and their offspring at 10-14 years of age from the Indonesian Family Life Survey (IFLS) conducted in the period 1997 to 2014	§ Adolescents who were stunted, anaemic, or living in a rural area had a significantly lower cognitive score than their counterparts who were not stunted or anaemic, or who lived in an urban area § The association of maternal Hb concentration with cognitive function of their offspring was modified by stunting status	3
Anaemia and other determinants of Common Mental Disorders (CMD)	To determine the association between haemoglobin concentration and other determinants of CMD among adolescent girls in Indonesia	Cross-sectional study of 1,052 adolescent girls aged 15-19 years old from the Indonesian Basic Health Survey 2018	§ The prevalence of CMD among the study population was 16.5% § Anaemia and Age at AAM were not associated with CMD § The strongest clustered associates of CMD among adolescent girls in Indonesia were asthma, smoking status, and higher haemoglobin concentration	4
Sleep quality, depression, and Hb concentration	To determine the association between sleep quality, depression, and haemoglobin concentration in Indonesian adolescents aged 10 to 19 years ol.	Longitudinal study of 452 adolescent boys and girls aged 10-19 years in Gunungkidul district, Yogyakarta province, Indonesia, in the period 2021 (baseline) to 2022 (follow-up).	§ LCA yielded 5 differential classes (A-E) of sleep quality and depression combined § Compared to class A (good sleep quality and no depression), membership of classes B (moderate-to-good sleep quality and low risk of depression, with some tiredness), and C (moderate sleep quality and moderate risk of depression) predicted a lower Hb concentration at one-year follow-up, after adjusting for Hb concentration and other factors at baseline.	

REFERENCES

[1] Wahab A, Wilopo SA, Hakimi M, Ismail D. Declining age at menarche in Indonesia: A systematic review and meta-analysis. Int J Adolesc Med Health 2018:1–9. https://doi.org/10.1515/ijamh-2018-0021.

[2] Yang L, Li L, Millwood IY, Peters SAE, Chen Y, Guo Y, et al. Age at menarche and risk of major cardiovascular diseases: Evidence of birth cohort effects from a prospective study of 300,000 Chinese women. Int J Cardiol 2017;227:497–502. https://doi.org/10.1016/j.ijcard.2016.10.115.

[3] Chang CJ, Lai MM, Lin CC, Liu CS, Li TC, Li CI, et al. Age at menarche and its association with the metabolic syndrome in Taiwan. Obes Res Clin Pract 2016;10:S26–34. https://doi.org/10.1016/j.orcp.2015.10.003.

[4] McDowell MA, Brody DJ, Hughes JP. Has Age at Menarche Changed? Results from the National Health and Nutrition Examination Survey (NHANES) 1999-2004. J Adolesc Heal 2007;40:227–31. https://doi.org/10.1016/j.jadohealth.2006.10.002.

[5] Prentice P, Viner RM. Pubertal timing and adult obesity and cardiometabolic risk in women and men: A systematic review and meta-analysis. Int J Obes 2013;37:1036–43. https://doi.org/10.1038/ijo.2012.177.

[6] Must A, Phillips SM, Naumova EN, Blum M, Harris S, Dawson-Hughes B, et al. Recall of early menstrual history and menarcheal body size: After 30 years, how well do women remember? Am J Epidemiol 2002;155:672–9. https://doi.org/10.1093/aje/155.7.672.

[7] Bosetti C, Tavani A, Negri E, Trichopoulos D, La Vecchia C. Reliability of data on medical conditions, menstrual and reproductive history provided by hospital controls. J Clin Epidemiol 2001;54:902–6. https://doi.org/10.1016/S0895-4356(01)00362-6.

[8] Ibitoye M, Choi C, Tai H, Lee G, Sommer M. Early menarche: A systematic review of its effect on sexual and reproductive health in low- and middle-income countries. PLoS One 2017;12:1–24. https://doi.org/10.1371/journal.pone.0178884.

[9] Sommer M. Menarche: A missing indicator in population health from low-income countries. Public Health Rep 2013;128:399–401. https://doi.org/10.1177/003335491312800511.

[10] Harris MA, Prior JC, Koehoorn M. Age at Menarche in the Canadian Population: Secular Trends and Relationship to Adulthood BMI. J Adolesc Heal 2008;43:548–54. https://doi.org/10.1016/j.jadohealth.2008.07.017.

[11] Deng X, Li W, Luo Y, Liu S, Wen Y, Liu Q. Association between small fetuses and puberty timing: A systematic review and meta-analysis. Int J Environ Res Public Health 2017;14. https://doi.org/10.3390/ijerph14111377.

[12] Li H, Song L, Shen L, Liu B, Zheng X, Zhang L, et al. Age at menarche and prevalence of preterm birth: Results from the Healthy Baby Cohort study. Sci Rep 2017;7:1–7. https://doi.org/10.1038/s41598-017-12817-2.

[13] Yu EJ, Choe SA, Yun JW, Son M. Association of Early Menarche with Adolescent Health in the Setting of Rapidly Decreasing Age at Menarche. J Pediatr Adolesc Gynecol 2020;33:264–70. https://doi.org/10.1016/j.jpag.2019.12.006.

[14] Petersohn I, Zarate-Ortiz A, Cepeda-Lopez A, Melse-Boonstra A, Petersohn I, Zarate-Ortiz AG, et al. Time Trends in Age at Menarche and Related Non-Communicable Disease Risk during the 20th Century in Mexico. Nutrients 2019;11:394. https://doi.org/10.3390/nu11020394.

[15] Won JC, Hong JW, Noh JH, Kim D-J. Association Between Age at Menarche and Risk Factors for Cardiovascular Diseases in Korean Women. Medicine (Baltimore) 2016;95:e3580. https://doi.org/10.1097/md.0000000000003580.

[16] Burgess S, Thompson DJ, Rees JMB, Day FR, Perry JR, Ong KK. Dissecting causal pathways using mendelian randomization with summarized genetic data: Application to age at menarche and risk of breast cancer. Genetics 2017;207:481–7. https://doi.org/10.1534/genetics.117.300191.

[17] Lim JS, Lee HS, Kim EY, Yi KH, Hwang JS. Early menarche increases the risk of Type 2 diabetes in young and middle-aged Korean women. Diabet Med 2015;32:521–5. https://doi.org/https://doi.org/10.1111/dme.12653.

[18] Wang JY, Hu PJ, Luo DM, Dong B, Ma Y, Dai J, et al. Reducing Anemia Among School-Aged Children in China by Eliminating the Geographic Disparity and Ameliorating Stunting: Evidence From a National Survey. Front Pediatr 2020. https://doi.org/10.3389/fped.2020.00193.

[19] Rahman MS, Mushfiquee M, Masud MS, Howlader T. Association between malnutrition and anemia in under-five children and women of reproductive age: Evidence from Bangladesh demographic and Health Survey 2011. PLoS One 2019. https://doi.org/10.1371/journal.pone.0219170.

[20] Black MM, Walker SP, Fernald LCH, Andersen CT, DiGirolamo AM, Lu C, et al. Early childhood development coming of age: science through the life course. Lancet 2017;389:77–90. https://doi.org/10.1016/S0140-6736(16)31389-7.

[21] Prado EL, Sebayang SK, Apriatni M, Adawiyah SR, Hidayati N, Islamiyah A, et al. Maternal multiple micronutrient supplementation and other biomedical and socioenvironmental influences on children's cognition at age 9–12 years in Indonesia: follow-up of the SUMMIT randomised trial. Lancet Glob Heal 2017;5:e217–28. https://doi.org/10.1016/S2214-109X(16)30354-0.

[22] Christian P, Smith ER. Adolescent Undernutrition: Global Burden, Physiology, and Nutritional Risks. Ann Nutr Metab 2018. https://doi.org/10.1159/000488865.

[23] Kumar KJ, Asha N, Murthy DS, Sujatha MS, Manjunath VG. Maternal anemia in various trimesters and its effect on newborn weight and maturity: An observational study. Int J Prev Med 2013;4:193–9.

[24] Arjas E, Parner J. Causal reasoning from longitudinal data. vol. 31. 2004. https://doi.org/10.1111/j.1467-9469.2004.02-134.x.

[25] Sandjaja S, Poh BK, Rojroonwasinkul N, Le Nyugen BK, Budiman B, Ng LO, et al. Relationship between anthropometric indicators and cognitive performance in Southeast Asian school-aged children. Br J Nutr 2013;110. https://doi.org/10.1017/S0007114513002079.

[26] Motta RW, Joseph JM. Group Intelligence Tests. Woodhead Publishing Limited; 2000. https://doi.org/10.1016/b978-008043645-6/50084-7.

[27] World Health Organization. Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity. Miner Nutr Inf Syst World Heal Organ 2013:1–6. https://doi.org/2011.

[28] Balarajan Y, Ramakrishnan U, Özaltin E, Shankar AH, Subramanian S V. Anaemia in low-income and middle-income countries. Lancet 2011;378:2123–35. https://doi.org/10.1016/S0140-6736(10)62304-5.

[29] Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, De Onis M, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet 2013;382:427–51. https://doi.org/10.1016/S0140-6736(13)60937-X.

[30] Shekar M, Kakietek J, Eberwein JD, Walters D. An Investment Framework for Nutrition. Washington D.C: 2016. https://doi.org/10.1596/26282.

[31] Smith LC, Haddad L. Reducing Child Undernutrition: Past Drivers and Priorities for the Post-MDG Era. World Dev 2015;68:180–204. https://doi.org/10.1016/j.worlddev.2014.11.014.

[32] Reinhardt K, Fanzo J. Addressing Chronic Malnutrition through Multi-Sectoral, Sustainable Approaches: A Review of the Causes and Consequences. Front Nutr 2014;1:1–11. https://doi.org/10.3389/fnut.2014.00013.

[33] Kementerian Kesehatan Republik Indonesia. Laporan Nasional Riset Kesehatan Dasar 2018 (Report of Indonesian Basic Health Survey 2018). 2018.

[34] Kieling C, Baker-Henningham H, Belfer M, Conti G, Ertem I, Omigbodun O, et al. Child and adolescent mental health worldwide: Evidence for action. Lancet 2011;378:1515–25. https://doi.org/10.1016/S0140-6736(11)60827-1.

[35] Sahril N, Ahmad NA, Idris IB, Sooryanarayana R, Razak MAA. Factors associated with mental health problems among malaysian children: A large population-based study. Children 2021;8:1–12. https://doi.org/10.3390/children8020119.

[36] UNHCR. Strengthening Mental Health and Psychosocial Support in 2021 2021.

[37] Syed EU. Vitamin B12 Supplementation in Treating Major Depressive Disorder: A Randomized Controlled Trial. Open Neurol J 2013;7:44–8. https://doi.org/10.2174/1874205x01307010044.

[38] Evans BE, Greaves-Lord K, Euser AS, Tulen JHM, Franken IHA, Huizink AC. Determinants of Physiological and Perceived Physiological Stress Reactivity in Children and Adolescents. PLoS One 2013;8.

[39] Galliher RV, Rostosky SS, Hughes HK. School belonging, self-esteem, and depressive symptoms in adolescents: An examination of sex, sexual attraction status, and urbanicity. J Youth Adolesc 2004;33:235–45. https://doi.org/10.1023/B:JOYO.0000025322.11510.9d.

[40] Zimmerman FJ, Katon W. Socioeconomic status, depression disparities, and financial strain: What lies behind the income-depression relationship? Health Econ 2005;14:1197–215. https://doi.org/10.1002/hec.1011.

[41] Christiani Y, Byles J, Tavener M, Dugdale P. Socioeconomic related inequality in depression among young and middle-adult women in Indonesia's major cities. J Affect Disord 2015;182:76–81. https://doi.org/10.1016/j.jad.2015.04.042.

[42] Mumang AA, Liaury K, Syamsuddin S, Maria IL, Tanra AJ, Ishida T, et al. Socio-economic-demographic determinants of depression in Indonesia: A hospital-based study. PLoS One 2020;15:1–15. https://doi.org/10.1371/journal.pone.0244108.

[43] Husky MM, Mazure CM, Paliwal P, McKee SA. Gender differences in the comorbidity of smoking behavior and major depression. Drug Alcohol Depend 2008;93:176–9. https://doi.org/10.1016/j.drugalcdep.2007.07.015.

[44] Lawrence D, Kisely S. Inequalities in healthcare provision for people with severe mental illness. J Psychopharmacol 2010;24:61–8. https://doi.org/10.1177/1359786810382058.

[45] Nasim F, Ashraf M, Ahmad S. Hematological and Biochemical Profile of Patients Suffering from Non-Atopic Asthma. IMedPub Journals 2017;2:1–10.

[46] Naples R, Laskowski D, McCarthy K, Mattox E, Comhair SAA, Erzurum SC. Carboxyhemoglobin and Methemoglobin in Asthma. Lung 2015;193:183–7. https://doi.org/10.1007/s00408-015-9686-x.

[47] Guill MF. Asthma update: Epidemiology and pathophysiology. Pediatr Rev 2004;25:299–305. https://doi.org/10.1542/pir.25-9-299.

[48] Ross CJM, Davis TMA, Hogg DY. Screening and Assessing Adolescent Asthmatics for Anxiety Disorders. Clin Nurs Res 2007;16:5–24. https://doi.org/10.1177/1054773806295235.

[49] Dany F, Dewi RM, Tjandrarini DH, Pradono J, Delima D, Sariadji K, et al. Urban-rural distinction of potential determinants for prediabetes in Indonesian population aged ≥15 years: A cross-sectional analysis of Indonesian Basic Health Research 2018 among normoglycemic and

prediabetic individuals. BMC Public Health 2020;20:1–9. https://doi.org/10.1186/s12889-020-09592-7.

[50] Copeland WE, Wolke D, Shanahan L, Costello J. Adult functional outcomes of common childhood psychiatric problems a prospective, longitudinal study. JAMA Psychiatry 2015;72:892–9. https://doi.org/10.1001/jamapsychiatry.2015.0730.

[51] Oerlemans AM, Wardenaar KJ, Raven D, Hartman CA, Ormel J. The association of developmental trajectories of adolescent mental health with early-adult functioning. PLoS One 2020;15:1–20. https://doi.org/10.1371/journal.pone.0233648.

[52] Olino TM, Klein DN, Lewinsohn PM, Rohde P, Seeley JR. Latent trajectory classes of depressive and anxiety disorders from adolescence to adulthood: descriptions of classes and associations with risk factors. Compr Psychiatry 2010;51:224–35. https://doi.org/10.1016/j.comppsych.2009.07.002.

[53] Ormel J, Oerlemans AM, Raven D, Laceulle OM, Hartman CA, Veenstra R, et al. Functional outcomes of child and adolescent mental disorders. Current disorder most important but psychiatric history matters as well. Psychol Med 2017;47:1271–82. https://doi.org/DOI: 10.1017/S0033291716003445.

[54] Nivard MG, Lubke GH, Dolan C V, Evans DM, St. Pourcain B, Munafò MR, et al. Joint developmental trajectories of internalizing and externalizing disorders between childhood and adolescence. Dev Psychopathol 2017;29:919–28. https://doi.org/DOI: 10.1017/S0954579416000572.

[55] Zisook S, Lesser I, Stewart JW, Wisniewski SR, Balasubramani GK, Fava M, et al. Effect of age at onset on the course of major depressive disorder. Am J Psychiatry 2007;164:1539–46. https://doi.org/10.1176/appi.ajp.2007.06101757.

[56] Knutson KL. The association between pubertal status and sleep duration and quality among a nationally representative sample of U. S. Adolescents. Am J Hum Biol 2005;17:418–24. https://doi.org/https://doi.org/10.1002/ajhb.20405.

[57] Johnson EO, Roth T, Schultz L, Breslau N. Epidemiology of DSM-IV Insomnia in Adolescence: Lifetime Prevalence, Chronicity, and an Emergent Gender Difference. Pediatrics 2006;117:e247–56. https://doi.org/10.1542/peds.2004-2629.

[58] Richter SA, Ferraz-Rodrigues C, Schilling LB, Camargo NF, Nunes ML. Effects of the COVID-19 pandemic on sleep quality in children and adolescents: A systematic review and meta-analysis. J Sleep Res 2022. https://doi.org/10.1111/jsr.13720.

[59] Nielsen AM, Kent P, Hestbaek L, Vach W, Kongsted A. Identifying subgroups of patients using latent class analysis: should we use a single-stage or a two-stage approach? A methodological study using a cohort of patients with low back pain. BMC Musculoskelet Disord 2017;18:1–17. https://doi.org/10.1186/s12891-017-1411-x.

[60] Orchard F, Pass L, Marshall T, Reynolds S. Clinical characteristics of adolescents referred for treatment of depressive disorders. Child Adolesc Ment Health 2017;22:61–8. https://doi.org/https://doi.org/10.1111/camh.12178.

[61] Li L, Wu C, Gan Y, Qu X, Lu Z. Insomnia and the risk of depression: A meta-analysis of prospective cohort studies. BMC Psychiatry 2016;16. https://doi.org/10.1186/s12888-016-1075-3.

[62] Orchard F, Gregory AM, Gradisar M, Reynolds S. Self-reported sleep patterns and quality amongst adolescents: cross-sectional and prospective associations with anxiety and depression. J Child Psychol Psychiatry 2020;61:1126–37. https://doi.org/https://doi.org/10.1111/jcpp.13288.

[63] Goldstein TR, Bridge JA, Brent DA. Sleep Disturbance Preceding Completed Suicide in Adolescents. J Consult Clin Psychol 2008;76:84–91. https://doi.org/10.1037/0022-006X.76.1.84.

[64] Weaver MD, Barger LK, Malone SK, Anderson LS, Klerman EB. Dose-Dependent Associations between Sleep Duration and Unsafe Behaviors among US High School Students. JAMA Pediatr 2018;172:1187–9. https://doi.org/10.1001/jamapediatrics.2018.2777.

[65] Beattie L, Kyle SD, Espie CA, Biello SM. Social interactions, emotion and sleep: A systematic review and research agenda. Sleep Med Rev 2015;24:83–100. https://doi.org/10.1016/j.smrv.2014.12.005.

[66] Gee B, Orchard F, Clarke E, Joy A, Clarke T, Reynolds S. The effect of non-pharmacological sleep interventions on depression symptoms: A meta-analysis of randomised controlled trials. Sleep Med Rev 2019;43:118–28. https://doi.org/10.1016/j.smrv.2018.09.004.

[67] Development Initiatives. Global Nutrition Report 2019 Country Profiles: Indonesia. Bristol, UK: 2019.

[68] Shyam T, Roshita A, Rah J-H. Adolescent Nutrition Programme Aksi Bergizi: From District Pilot to National Scale-Up 2019:1–12.

[69] Sunuwar DR, Singh DR, Chaudhary NK, Pradhan PMS, Rai P, Tiwari K. Prevalence and factors associated with anemia among women of reproductive age in seven South and Southeast Asian countries: Evidence from nationally representative surveys. PLoS One 2020;15:1–17. https://doi.org/10.1371/journal.pone.0236449.

Summary

The main objective of this study is to comprehensively assess the association of adolescent anaemia with mental health disorders, with a focus on Indonesia. So far, limited research has been done to assess the prevalence of anaemia among adolescent in Indonesia and data on the relationship between anaemia and pubertal development indicators in Indonesia are scarce.

Chapter 2 addresses the time trend of age at menarche (AAM) in Indonesia and its association with BMI and non-communicable disease (NCD) prevalence at later age. We used data of 15,744 women aged 15-65 years from 5 waves of the Indonesian Family Life Survey (IFLS) conducted in the period 1993 to 2015. Multiple linear regression was applied to determine the association of AAM with BMI, and Poisson regression with robust variance for investigating the association of AAM with NCD prevalence. Models were adjusted for age, and effect modification by wealth status, living area, and region was investigated. We found that AAM has significantly declined over time, from 14.4 (SD:2.1) years of age in the 1940s to 13.4 (SD:1.5) in the 1990s. AAM was inversely associated with BMI (β: -0.30 kg/m^2, 95%CI: -0.37, -0.22) and body weight (β: -0.67 kg, 95%CI: -0.75, -0.54), but not with height. After adjustment for age, AAM was not associated with NCDs, i.e., hypertension, type 2 diabetes mellitus, liver diseases, asthma, chronic lung diseases, cardiovascular diseases, stroke, cancer, or arthritis. Including BMI in the models did not change these results. Further longitudinal research is needed to disentangle the direction of causality of the associations.

Chapter 3 investigated the association between intra-uterine maternal haemoglobin (Hb) concentration and cognitive function of their offspring during adolescence. We used longitudinal cohort data of 363 paired pregnant mothers and their offspring at 10-14 years of age from the Indonesia Family Life Survey (IFLS) conducted in 1997-2014. Multiple linear regression models with maternal Hb as exposure and cognitive function (Raven's Progressive Matrices test) as outcome were explored, with adjustments for maternal age, maternal height, and socioeconomic status. The weighted anaemia prevalence was found to be 49.3% in pregnant mothers and 22.2% in adolescents. The mean total cognitive score of adolescents was 12.4 points out of 17. Adolescents who were stunted, anaemic, or living in a rural area had a significantly lower cognitive score than their counterparts. In the adjusted model, maternal Hb was not associated with adolescent cognitive function (β: 0.14; 95%CI: -0.052 – 0.340). However, the effect of maternal Hb concentration on cognitive function of their offspring was modified by stunting status (β, stunted: 0.44; 95%CI: 0.05 – 0.82 and β, non-stunted: 0.01; 95%CI: -0.02 – 0.24, p-interaction 0.039). This study shows that adverse cognitive outcomes at adolescent age is likely to be multi-causal and may best be addressed by tackling pregnancy-related anaemia as well as warranting good nutrition for growth and development during childhood.

Chapter 4 reports on the association between haemoglobin concentration and other determinants of Common Mental Disorders (CMD) among adolescent girls in Indonesia. Data of 1,052 adolescent girls aged 15-19 years old from the Indonesian Basic Health Survey 2018 were analysed for this purpose. CMD was measured using the Self Reporting Questionnaire (SRQ-20). Principal Component Analysis of main determinants was applied and resulting principal components were investigated as risk factors for CMD. We found that the prevalence of CMD among the study population was 16.5%. Anaemia and AAM were not associated with CMD. The strongest clustered associates of CMD among adolescent girls in Indonesia were asthma, smoking status, and higher haemoglobin concentration (β: 1.74, 95%-CI: 1.59; 1.89). Our findings imply that adolescent girls who have asthma and smoke, as well as those having parents with higher education and secured occupation, are more likely to have mental disorders. Causal pathways need to be disentangled in future studies.

In **Chapter 5** an association between sleep quality, depression, and haemoglobin concentration was identified. Data of 452 adolescents aged 10 to 19 years old were collected across all subdistricts in Gunungkidul district, Yogyakarta province, Indonesia during 2021 (baseline) to 2022 (follow-up). Sleep quality was assessed using The Pittsburgh Sleep Quality Index (PSQI) and adolescent's depressive-anxiety disorder by the Kessler-10 Psychological Distress scale (K10) questionnaire. Latent Class Analysis (LCA) was used to identify and characterise the adolescents based on sleep quality and depression indicators. In the present study, 20.3% of all adolescents were anaemic at the baseline. LCA yielded 5 classes of sleep quality and depression. We did not find an association between classes and adolescent haemoglobin at baseline. However, in comparison to class A (describe A), membership of class B (moderate-to-good sleep quality and low risk of depression, with some tiredness) predicted a Hb reduction of 0.43 g/dL (95%CI: -0.79; -0.07), whereas membership of class C (moderate sleep quality and moderate risk of depression) predicted a Hb reduction of 0.49 g/dL (95%CI: 0.94; -0.04) at one year follow-up. Mental health and sleep quality should therefore be considered in intervention programs that address anaemia.

Chapter 6 summarized the main findings and integrates them to fill part of the research gaps identified in the introductory chapter. Based on our findings, this chapter highlights the needs to improve Indonesian adolescent health through further data-driven policies and future research in area of pubertal status, mental health, and sleep quality. Since no progress has been made towards achieving the target of reducing anaemia among women of reproductive age in Indonesia, a multidiscipline approach and deliver intervention through appropriate delivery platform to prevent and treat adolescent anaemia is crucial, while ensuring the accessibility, acceptance, availability, and affordability of the intervention.

Acknowledgements

ACKNOWLEDGEMENTS

Firstly, I want to start by rewarding myself for all the hard work, difficult times, and patience to come to this stage. Everything was not smooth, but the way you kept running is an amazing achievement you should be proud of.

My most profound appreciation goes to my PhD supervisors Alida Melse-Boonstra and Monique L'Hoir, and my promotor Edith JM Feskens, for their time, effort, and understanding in helping me succeed in my study. Their vast wisdom and wealth of experience have inspired me throughout my studies. My appreciation also goes to the examining committee for their time to give me constructive feedback on my thesis.

I would like to express my gratitude to everyone in the chair group Global Nutrition, and friends in the Netherlands and in Indonesia whom I could not mention one by one. Thanks to their generosity and encouragement, my time spent studying and living in the Netherlands and in Indonesia has been truly rewarding.

I am also thankful to LPDP, Indonesian Ministry of Finance for providing me with the scholarship that allowed me to complete this PhD. The same gratitude goes to colleagues at CHPM UGM, Neys van Hoogstraten foundation, and stakeholders in Yogyakarta for their contributions in my study. My special thanks to all data collectors, parents, and adolescents who participated in the Indonesian adolescent health project.

Last but certainly not least, I would like to thank my parents, my wife, my brother and sisters, and all family in Indonesia and the Netherlands. It would have been impossible to finish my studies without their unwavering support over the past four years. *Mama, papa, dan saudara-saudaraku, terima kasih atas semua doa dan dukungannya. Pencapaian ini saya tujukan untuk kalian semua*.

To conclude, adolescence is always a comma, not a full stop. The same goes to my life journey and the research on adolescents!

About the Author

Muhammad Asrullah was born on the 25th of February 1991 in Kendari, Southeast Sulawesi province, in the middle part of Indonesia. After his secondary education, he was admitted into Hasanuddin University, located in South Sulawesi in 2008, where he successfully graduated in 2012 (4-years BSc in Nutrition), with 3 years scholarship from the Ministry of Education through the PPA scholarship scheme.

During his bachelor, he was active as laboratory assistant and participated in national and local surveys as a research assistant. He continued working as a lecture assistant for a year in the Nutrition Department at the same university after his graduation. In 2013 Asrullah was admitted to Universitas Gadjah Mada (UGM) in Yogyakarta to the MPH in Nutrition, with a full BPPDN-scholarship of the Ministry of Higher Education. He started his career after his master program as a research assistant in the Centre for Health Policy and Management (CHPM) at Universitas Gadjah Mada in 2015. He was involved in several studies and surveys as researcher in 2017, which mainly focused on maternal and neonatal health in Indonesia, funded by several national and multinational institutions.

He was awarded the Indonesia Endowment Funds for Education (LPDP) scholarship from Indonesian Ministry of Finance for his PhD programme at Wageningen University, within the Ten2Twenty Research Programme starting in March 2019. His research focuses on adolescent nutrition in Indonesia, under the supervision of Prof. Dr Edith J.M. Feskens, Dr. Alida Melse-Boonstra, and Dr. Monique L'Hoir. Additionally, during the PhD training, he assisted MSc courses and supervised MSc thesis students. He has published several scientific articles in international journals. Currently, he is a researcher at CHPM. He can be contacted through his email: Muhammad.asrullah@mail.ugm.ac.id

LIST OF PUBLICATIONS

Referred Scientific Publications

Asrullah, M., L'Hoir, M., Feskens, E.J.M. Melse-Boonstra, A (2022) Trend in age at menarche and its association with body weight, body mass index and non-communicable disease prevalence in Indonesia: evidence from the Indonesian Family Life Survey (IFLS). BMC Public Health 22, 628 https://doi.org/10.1186/s12889-022-12995-3.

Asrullah, M., L'Hoir, M., Paulo M-J., Feskens, E.J.M., Melse-Boonstra, A (2022) Determinants of Common Mental Disorders (CMD) among adolescent girls aged 15-19 years in Indonesia: Analysis of the 2018 National Basic Health Survey Data. PLOS Glob Public Health 2(3): e0000232. https://doi.org/10.1371/journal.pgph.0000232.

Conferences

Asrullah, M., L'Hoir, M., Feskens, E.J.M. Melse-Boonstra, A. Maternal Haemoglobin and Cognitive Function: A Longitudinal Study from Maternal Haemoglobin to Adolescent in Indonesia. *Dutch Nutrition Science Day (NSD) 2021*; *Online; oral Presentation.*

Asrullah, M., L'Hoir, M., Feskens, E.J.M. Melse-Boonstra, A. Time trend of age at menarche and its link to nutritional status and non-communicable disease prevalence in Indonesia. *Wageningen PhD Symposium 2019*. *Oral presentation.*

Asrullah, M., L'Hoir, M., Feskens, E.J.M. Melse-Boonstra, A (2022). Dietary Patterns and Anaemia among Indonesian Adolescents Aged 15-19 years. *Micronutrient Forum 2020*; *Online; Poster presentation.*

Scientific Reports

Muhammad Asrullah, Sandra Olivia Frans, Faisal, Siti Nurfadillah, Hastrin Hositanisita, Ahmad Watsiq Maula, Monique L-Hoir, Edith JM Feskens, Alida Melse-Boonstra. The socio-economic, cultural, and biologic aetiology of anaemia and its association with mental health among 10-19-year-old adolescents in Yogyakarta Province, Indonesia. *Technical report of Indonesian Adolescent Health Study*, 2022.

OVERVIEW OF COMPLETED TRAINING ACTIVITIES

Completed Training and Supervision Plan[1]

Discipline specific courses	Organizing Institute	Year
Diagnosing health behaviour for global health programs	John Hopkins University	2019
Global adolescent health	University of Melbourne	2019
Global health policy	University of Tokyo	2019
Stable isotope method in nutrition research	VLAG Graduate School, WUR	2019
The production and use of food composition data in nutrition	VLAG Graduate School, WUR	2019
VLAG online lecture series	VLAG Graduate School, WUR	2020
Major depression in the population: a public health approach	John Hopkins University	2020
Able-minded -mental health and people with intellectual disability	The University of Quensland	2020

Discipline specific conferences and meeting	Organizing Institute	Year
Wageningen Indonesia Scientific Exposure (WISE) conference 2019	Wageningen University	2019
Dutch Nutrition Science Day (NSD) 2019	Nederlandse Academie voor Voedingswetenschappen	2019
Wageningen PhD Symposium 2019	Wageningen University	2019
Symposium of one health	Wageningen University	2019
Micronutrient Forum 2020	Micronutrient Forum	2020
Nutrition 2020	ASN	2020
ANH 2020 Academy week	ANH Academy	2020
Dutch Nutrition Science Day (NSD) 2021	Nederlandse Academie voor Voedingswetenschappen	2021
Dutch Nutrition Science Day (NSD) 2022	Nederlandse Academie voor Voedingswetenschappen	2022
International Congress of Nutrition 2022	IUNS-ICN	2022
General courses	**Organizing Institute**	**Year**
VLAG PhD week	VLAG Graduate School, WUR	2019
Research data management	WGS	2019
Big data analysis in life science	VLAG Graduate School, WUR	2019
Start to teach	ESD, WUR	2019
The Essentials of Scientific Writing & Presenting	Wageningen Graduate School	2019
Reviewing a scientific paper	Wageningen Graduate School	2022
Writing A Grant Proposal	Wageningen Graduate School	2022

Other activities	Organizing Institute	Year
Preparation of research proposal	HNH Global Nutrition	2019-2020
Writing a grant proposal for research	HNH Global Nutrition, CHPM UGM Indonesia	2020
Chair group meeting (biweekly meeting)	HNH Global Nutrition	2019-2022
PhD Paper clip and paper café	HNH Global Nutrition	2019-2022
Staf/MR4 Meeting	HNH Global Nutrition	2021-2022

[1]With the listed activity, the PhD candidate complied with 30 ECTS educational requirements of VLAG Graduate School, a Wageningen University and Research graduate school. One ECTS equals a study load of 28 hours

Colophon

The Indonesian Endowment Fund for Education (LPDP), Ministry of Finance, Republic of Indonesia is acknowledged for a doctoral scholarship to the author. The PhD work was implemented as part of the Ten2Twenty Project in HNH Global Nutrition. Ten2twenty project in Indonesia had funding support from the Neys van Hoogstraten Foundation, the Netherlands. The views expressed in this document cannot be taken to reflect the official opinions of the organization.

Cover Illustration: Muhammad Asrullah and M.P. Garry Hanantyo

Lay-out and printing: ProefschriftMaken | proefschriftmaken.nl