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LITERATURE REVIEW **Open Access**

Peran Insulin-like Growth Factor-1 dan Adiponektin dalam Hubungan antara Asupan, Aktifitas Fisik, dan Sindrom Metabolik pada Anak dan Remaja Melayuaustronesia: Protokol Resensi Sistematis

Role of Insulin-Like Growth Factor-1 and Adiponectin in The Association between Dietary Intake, Physical Activity, and Metabolic Syndrome in Malayaustronesia Children and Adolescent: A Systematic Review Protocol

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ABSTRAK

Latar Belakang: *Faktor risiko sindrom metabolik berkembang di masa kanak-kanak dan berlanjut sepanjang hidup, yang dapat menyebabkan mereka berisiko lebih tinggi terkena penyakit kardiovaskular dan kematian dini. Pola makan yang sehat dan aktif secara fisik diharapkan dapat mengubah risiko sindrom metabolik (MetS). Namun, pengamatan tersebut terutama dilakukan pada sampel orang dewasa dan mekanisme biologis yang menghubungkan faktor perilaku tersebut dan MetS pada anak-anak dan remaja masih perlu dieksplorasi. Orang Asia lebih mungkin tertular MetS dibandingkan orang kulit putih, namun studi pada anak-anak Melayu-Austronesia sangat minim.*
Tujuan: *Penelitian ini bertujuan untuk meninjau dan menilai secara komprehensif penelitian yang menjelaskan faktor biologis (insulin-like growth factor-1 dan adiponektin) yang mungkin mengaitkan hubungan antara faktor risiko tersebut dan MetS pada anak-anak Melayu-Austronesia.*
Metode: *Pencarian akan dilakukan di PubMed, Scopus, Web of Science, Google Scholar, dan database lokal Garuda (Garba Rujukan Digital, Bahasa Indonesia) dan Mycite (indeks kutipan Malaysia). Semua studi kohort prospektif yang menguji hubungan salah satu faktor perilaku (asupan makanan atau aktivitas fisik) dan salah satu faktor biologis (Faktor pertumbuhan seperti insulin atau adiponektin) dengan MetS atau komponennya pada anak-anak sehat dengan paparan dimulai dari usia 1 dan 12 tahun dan hasil mulai dari 1 tahun dua bulan sampai usia 18 tahun memenuhi syarat. Hanya literatur dalam bahasa Inggris dan bahasa lokal dari awal hingga 31 Desember 2023 yang memenuhi kriteria kelayakan yang akan disertakan. National Institute of Health tool untuk studi observasional akan digunakan untuk menilai kualitas studi yang disertakan. Resensi sistematis ini sudah teregistrasi pada PROSPERO dengan nomor CRD42023471481.*
Hasil: *Temuan ini mungkin menjelaskan bagaimana faktor biologis yang telah ditentukan sebelumnya berkaitan dengan faktor perilaku tersebut pada MetS pada anak-anak. Temuan ini juga akan dipublikasikan dalam jurnal peer-review.*
Kesimpulan: *Tinjauan ini menggunakan database yang relevan untuk mengoptimalkan pencarian studi yang memenuhi syarat. Studi yang memenuhi syarat akan diambil oleh lebih (empat) peneliti yang bekerja secara independen dengan template ekstraksi data yang telah ditentukan sebelumnya. Ada kemungkinan beberapa penelitian melaporkan temuan signifikan pada protein pengikat IGF-1*

dibandingkan total IGF-1 atau rasio molarnya yang akan menantang analisis statistik.

Kata kunci: *Aktifitas fisik, Adiponektin, Asupan makan, Insulin-like growth factor, Sindrom metabolik*

ABSTRACT

Background: Risk factors of metabolic syndromes develop in childhood and tacks across life, which may lead them to a higher risk of getting cardiovascular diseases and premature deaths. A healthy diet and being physically active are supposed to modify the risk of metabolic syndromes (MetS). However, those observations primarily work in adult samples and the biological mechanisms that link that behavioral factor and MetS in children and adolescents still need to be explored. Asian people are more likely to get MetS than their white counterparts, but study in Malay-Austronesia children is minimal.
Objectives: This study aims to comprehensively review and appraise studies that elucidate biological factors (insulin-like growth factor-1 and adiponectin) that possibly mediate the relationship between those risk factors and MetS in Malay-Austronesia children.
Methods: The search will be performed in PubMed, Scopus, Web of Science, Google Scholar, and local databases Garuda (Garba Rujukan Digital, Indonesian) and Mycite (Malaysian citation index). All prospective cohort studies that examine the association of one of the behavioral factors (dietary intakes OR physical activity) AND one of the biological factors (Insulin-like growth factor OR adiponectin) with MetS or its components in healthy children with the exposures start from the age of 1 and 12 years of age and outcomes begin from 1 year and two months until the age of 18 years old are eligible. Only literature in English and local languages from inception to 31 December 2023 that match eligibility criteria will be included. National Institute of Health tool for observational studies will be used to assess the quality of included studies. This work was registered to PROSPERO CRD42023471481.
Results: The findings may shed light on how the predefined biological factors mediate those behavioural factors on MetS in children. The findings will also be published in a peer-reviewed journal.
Conclusion: This review utilizes relevant databases to optimize the searching of eligible studies**.** Eligible studies will be extracted by more (four) researchers who work independently with a predefined data extraction template. There are possibility some studies report significant finding on IGF-1 binding protein instead of total IGF-1 or its molar ratio will challenge the statistical analysis.

Keywords: Adiponectin, Dietary intakes, Insulin-like growth factor-1, Physical activity, Metabolic syndrome

INTRODUCTION

Globally, the prevalence of metabolic syndrome (MetS) in children and adolescents has increased, with recent estimates ranging from 0.3 to 26.4%(Friend, Craig and Turner, 2013; Reisinger *et al.*, 2021). A slightly higher prevalence of MetS was observed in children and adolescents from low and middle-income countries, (Bitew *et al.*, 2020), which spanned from 3.2% to 29.9% (Grabia, Markiewicz-Żukowska and Socha, 2021). As a consequence, children with MetS are at an increased risk of CVDs(cardiovascular diseases) (Ler *et al.*, 2022) and premature death before 30 years of age (6) that result in low quality of human resources in a country. MetS is characterized by the coexistence of risk factors such as abdominal obesity, hyperlipidemia, elevated blood pressure, hyperglycaemia, and insulin resistance (IR)(Kassi *et al.*, 2011; Bovolini *et al.*, 2021).

A number of studies reported that MetS might be modified by certain behavioural factors such as risky dietary patterns (i.e. western diet, alcohol, skip breakfast)(Chen *et al.*, 2015; Gutiérrez-Solis, Datta Banik and Méndez-González, 2018; Fabiani, Naldini and Chiavarini, 2019; Jankowska *et al.*, 2021), lack of physical activity(Krishnamoorthy *et al.*, 2020), high BMI (body mass index) at a younger age(Ibrahim *et al.*, 2022), smoking(Kusuma *et al.*, 2019), and depression(Ghanei Gheshlagh,

Parizad and Sayehmiri, 2016). On the contrary, several unmodifiable factors are attributed to MetS in children, such as child sex, particularly male (Ambachew *et al.*, 2020; Krishnamoorthy *et al.*, 2020; Alamnia *et al.*, 2021; Jankowska *et al.*, 2021) , living in an urban area(Krishnamoorthy *et al.*, 2020) and parental factors such as educational level (Jankowska *et al.*, 2021), social class(Ibrahim *et al.*, 2022), history of MetS(Irakoze *et al.*, 2021). Compelling evidence revealed that risk factors of MetS develop in childhood and tacks across life (Grillo *et al.*, 2016; Koskinen *et al.*, 2017; Bernhardsen *et al.*, 2020; Irakoze *et al.*, 2021). Sudden pandemic COVID-19 exposures also deteriorate the prevalence of MetS in some countries due to extreme changes in society's behaviour to comply with the COVID-19 mitigation strategy (Stefan, Birkenfeld and Schulze, 2021)

Furthermore, MetS risk factors in children may vary across ethnicity and region (1,2), as shown by the Suriname Health Study, which reported that the prevalence of MetS is higher in Hindustan than in Amerindian and Javanese ethnic (Krishnadath *et al.*, 2016). Another study showed that Asian-American adults had a higher risk of getting MetS, whereas they appear to be slimmer than those Western (white) counterparts(Zhu *et al.*, 2021). This implies that particular ethnic may be more prone to getting MetS than others. The same findings are also observed regarding the region where the samples lived. Studies reported that the risk factors of MetS differed across countries (Scuteri *et al.*, 2015; Lear and Gasevic, 2019). A few studies examine several risk factors, and MetS in the Asian population (Sigit *et al.*, 2020; Thor, Yau and Ramadas, 2021), but studies in the Malay-Austronesia population are hardly found (Sigit *et al.*, 2020)—moreover, the studies above involved adult participants. Several systematic reviews also suggested that MetS studies in children should take into account ethnicity along with age and sex-specific thresholds, particularly in generating MetS definition(Friend, Craig and Turner, 2013; Reisinger *et al.*, 2021).

Nevertheless, the underlying mechanism linking those modifiable factors and MetS remains to be determined. A few studies indicated that biological factors such as omentin(Sun *et al.*, 2022), adiponectin(Sigit *et al.*, 2021), leptin(Sigit *et al.*, 2021), and or insulin-like growth factor (IGF-1)(Aguirre *et al.*, 2016) possibly mediate the relationship between those factors and MetS in children. This assumption is based on facts that factors such as imbalanced food intake (Izadi and Azadbakht, 2015; Hayuningtyas *et al.*, 2021) and lack of physical activity (Floegel *et al.*, 2014) are associated significantly with changes in those biological factors. However, those findings are mainly observed in adult samples, while studies among children and adolescents are scarcely available.

Therefore, the primary objective of the current systematic review is to elucidate biological factors (insulin-like growth factor-1 and adiponectin) that possibly mediate the relationship between those risk factors and MetS in Malay-Austronesia children, especially Indonesian and Malaysian samples. Upon available literature, this current review will also differentiate that relationship before and after the COVID-19 pandemic.

METHODS

Study Design

This is a systematic review of prospective cohort studies. The review work is performed by following the guidelines of PRISMA (Page *et al.*, 2021) and is registered at PROSPERO (https://www.crd.york.ac.uk/prospero/) with CRD42023471481 as the registry number.

Literature Searches

The literature search is performed on PubMed, Scopus, Web of Science, Google Scholar and two local databases from Indonesia (GARUDA, Garba Rujukan Digital, https://garuda.kemdikbud.go.id/) and Malaysia (MYCITE, Malaysian Citation Index, https://mycite.mohe.gov.my/). All prospective cohort studies in English and Malay-Austronesia languages that examine the relationship between dietary intake, physical activity, insulin-like growth factors system, adiponectin, leptin, omentin and at least one component of metabolic syndromes such as obesity (body mass index, body composition),, in healthy children (1 to 12 years old) and adolescent (13 to 18 years old) will be eligible for this review (**Table 1**). Studies that involved children and adolescents with certain conditions, such as children with disability, genetic disorders (e.g. Down syndrome, Laron syndrome), and chronic diseases such as diabetes, TBC (tuberculosis) and HIV-AIDS are ineligible.

Table 1. Eligibility Criteria for Population, Intervention/Exposure, Control/Comparator, Outcome, Time Frame, Study Design and Settings

Population	Intervention/ exposure	Comparators	Outcomes	Timing	Setting	Study Design
Children Exposure from age of 1 and 12 years of age Outcomes start from 1 year and two months until age of 18 years old.	(Dietary intakes OR physical activity) AND (Insulin-like growth factor OR adiponectin) 1). Dietary intakes Total nutrient intakes (carbohydrate, protein, fat, vitamin, mineral) in grams, gram/kg body weight, % of energy (apply only to macro-nutrients) 2) Physical activity Time spent to perform physical activity in minutes per day, metabolic equivalents task (Mets)/minute 3) Biological factors: Insulin-like growth factor 1 and its six binding protein as well as adiponectin in µg/ml.	High versus low dietary intake, physical activity or the biological factors (e.g. tertile)	Metabolic Syndromes 1. Obesity according to anthropometric measures or indices (body mass index [z score], waist circumference, body composition [e.g. skin fold, percent body fat]) 2. Hyperlipidemia is generated from lipid panel (blood) analysis to determine the cholesterol level (LDL, HDL, VLDL, including triglycerides (TGs)) in mg/dl 3). Insulin resistance (IR) is either measured by glucose tolerance, euglycemic hyperinsulinemia test expressed in mg/dl or other proxies such as HOMA –IR (homeostasis model assessment) or ratio TGs/HDL. 4). Blood pressure is measured by either manual or digital sphygmomanometer and expressed as mmHg	Exposures in children 1-12 years old that can be divided in age groups (<2, 3-5, 6-12 years of age)	Studies conducted in Malayaustronesia regions	Prospective cohorts (including case-control studies

Search Strategy

Literature from inception to December 31st 2023, is systematically searched with various relevant keywords. Keywords that will be applied to the search consist of a combination of dietary intakes (food OR diet OR nutrition OR intake OR energy OR protein OR carbohydrate OR fat OR vitamin OR mineral), physical activity (exercise OR physical activity), biological factors (adiponectin OR insulin-like growth factor [IGF OR growth hormone OR somatomedin]) OR metabolic syndromes (obesity OR overweight OR body mass index OR body composition OR fat mass OR metabolic syndrome OR insulin resistant [blood glucose OR glucose tolerance OR insulin] OR lipid profile [triglycerides OR triacylglycerol OR low-density lipoprotein OR high-density lipoprotein OR hyperlipidemia] OR blood tension [systole OR diastole OR hypertension]) OR COVID-19.

Similarly, using local language keywords such as *makanan OR asupan OR gizi OR diet OR energi OR protein OR karbohidrat OR lemak OR vitamin OR mineral* (dietary intakes), *olahraga OR aktivitas fisik* (physical activity), *adiponektin OR insulin-like growth factor-1* (biological factors), *sindrom metabolik OR resistensi insulin [gula darah OR toleransi gula darah OR insulin], obesitas OR kegemukan OR index massa tubuh OR lemak tubuh, gangguan lipid [hiperlipidemia, trigliserida, lemak jahat], tekanan darah [darah tinggi, sistol, diastol]* (Metabolic syndromes) OR COVID19. In Malaysian languange, the search strategy is: (*makanan* OR *pengambilan* OR *pemakanan* OR diet OR *tenaga* OR protein OR *karbohidrat* OR *lemak* OR vitamin OR mineral) OR (*sukan* OR *aktiviti fizikal*) OR (*adiponektin* OR insulin-like growth factor-1) AND (*obesiti* OR *kegemukan* OR *indeks jisim tubuh* OR *lemak tubuh* OR *hiperlipidemia*, *trigliserid*, *lemak jahat], tekanan darah (tekanan darah tinggi)* OR *darah tinggi (hipertensi*)OR *sistol* OR *diastol* OR *sindrom metabolik* OR *kerintangan insulin* OR *gula darah* OR *toleransi gula darah* OR insulin OR COVID19. Detail on search strategies for each database is available on **Table 2**.

Table 2. Search Strategies Across Databases

No.	*Databases (Total 6)*	*Search Terms*
1	**PubMed**	(food OR diet OR nutrition OR intake OR energy OR protein OR carbohydrate OR fat OR vitamin OR mineral) OR (exercise OR physical activity) OR (adiponectin OR leptin OR omentin OR insulin-like growth factor OR IGF OR growth hormone OR somatomedin) AND (obesity OR overweight OR body mass index OR body composition OR fat mass OR metabolic syndrome OR insulin resistant OR blood glucose OR glucose tolerance OR insulin OR lipid profile OR triglycerides OR triacylglycerol OR low density lipoprotein OR high density lipoprotein OR hyperlipidaemia OR blood tension OR systole OR diastole OR hypertension) OR (COVID19)
2	**Scopus**	*TITLE-ABS-KEY* *(food OR diet OR nutrition OR intake OR energy OR protein OR carbohydrate OR fat OR vitamin OR mineral) OR (exercise OR physical activity) OR (adiponectin OR leptin OR omentin OR insulin-like growth factor OR IGF OR growth hormone OR somatomedin) AND (obesity OR overweight OR body mass index OR body composition OR fat mass OR metabolic syndrome OR insulin resistant OR blood glucose OR glucose tolerance OR insulin OR lipid profile OR triglycerides OR triacylglycerol OR low density lipoprotein OR high density lipoprotein OR hyperlipidaemia OR blood tension OR systole OR diastole OR hypertension) OR (COVID19)*
3	**Web of Science**	(food OR diet OR nutrition OR intake OR energy OR protein OR carbohydrate OR fat OR vitamin OR mineral) OR (exercise OR physical activity) OR (adiponectin OR leptin OR omentin OR insulin-like growth factor OR IGF OR growth hormone OR somatomedin) AND (obesity OR overweight OR body mass index OR body composition OR fat mass OR metabolic syndrome OR insulin resistant OR blood glucose OR glucose tolerance OR insulin OR lipid profile OR triglycerides OR triacylglycerol OR low density lipoprotein OR high density lipoprotein OR hyperlipidaemia OR blood tension OR systole OR diastole OR hypertension) OR (COVID19)
4	**Google Scholar**	Where my words occur: in the title of the article: 1. With all of the words: metabolic syndrome With at least one of the words: obesity OR overweight OR body mass index OR body composition OR fat mass OR metabolic syndrome OR insulin resistant OR blood glucose OR glucose tolerance OR insulin OR lipid profile OR triglycerides OR triacylglycerol OR low density lipoprotein OR high density lipoprotein OR hyperlipidaemia OR blood tension OR systole OR diastole OR hypertension

No.	*Databases (Total 6)*	*Search Terms*
		2. With all of the words: dietary intakes With at least one of the words: food OR diet OR nutrition OR intake OR energy OR protein OR carbohydrate OR fat OR vitamin OR mineral OR exercise OR physical activity 3. With all of the words: physical activity With at least one of the words: exercise OR physical activity 4. With all of the words: hormones With at least one of the words: adiponectin OR leptin OR omentin OR insulin-like growth factor OR IGF OR growth hormone OR somatomedin
5	**GARUDA**	*(makanan OR asupan OR gizi OR diet OR energi OR protein OR karbohidrat OR lemak OR vitamin OR mineral*) OR (*olahraga OR aktivitas fisik) OR (adiponektin OR insulin-like growth factor-1*) AND *(obesitas OR kegemukan OR index massa tubuh OR lemak tubuh OR hiperlipidemia, trigliserida, lemak jahat], tekanan darah OR darah tinggi OR sistol OR diastol OR sindrom metabolik OR resistensi insulin OR gula darah OR toleransi gula darah OR insulin OR* (COVID19)
6	**MYCITE**	(*makanan* OR *pengambilan* OR *pemakanan* OR diet OR *tenaga* OR protein OR *karbohidrat* OR *lemak* OR *vitamin* OR mineral) OR (*sukan* OR *aktiviti fizikal*) OR (*adiponektin* OR insulin-like growth factor-1) AND (*obesiti* OR *kegemukan* OR *indeks jisim tubuh* OR *lemak tubuh* OR *hiperlipidemia*, *trigliserid*, *lemak jahat*], *tekanan darah (tekanan darah tinggi)* OR *darah tinggi* (*hipertensi*)OR systole OR diastole OR *sindrom metabolik* OR kerintangan insulin OR *gula darah* OR *toleransi gula darah* OR insulin OR (COVID-19)

Study Selection and Extraction

Articles identified from 6 databases will be imported into the citation manager (Endnote), and duplicates will be deleted. Two investigators work independently to search and screen literature and assess the eligibility of those articles using the web tool Rayyan (https://rayyan.qcri.org). Discussion with the fifth (AD) and sixth (MH) researchers will be performed when a conflict of inclusion criteria emerges. The reasons for the exclusion of any articles are recorded. Each eligible article will be further extracted on sample characteristics (e.g. age, sex, puberty status), dietary intakes, physical activity, metabolic syndromes, and other confounding factors. Information on the article source, publication date and author are also recorded (Table 3). Accuracy and completeness of data extraction will be checked by the fifth and sixth researchers independently (See Table 4)

Table 3. Data Extraction Template for Eligible Prospective Cohort Studies

Author (year)	Setting	Study design	Population	Exposures	Method of assesment	Follow up time	Type of outcome	Confounding factors

Table 4. Task Distribution

Task	Reseacher teams						
	Author 1	Author 2	Author 3	Author 4	Author 5	Author 6	
Develop search strategy	√		√	√		√	Pilot test the search strategy, using Rayyan (https://rayyan.qcri.org) blind mode.
Search and screen eligible articles		√	√	√	√		title, abstract, full text. See eligiblity criteria
Data extraction		√	√	√	√		Study design, participant characteristic and recruitment, dietary intake/physical activity, biological factors

Task	Reseacher teams						
	Author 1	**Author 2**	**Author 3**	**Author 4**	**Author 5**	**Author 6**	
							(IGF-1, adiponectin), outcomes, follow up, drop out, confounders
Risk of bias assessment	√					√	
Data synthesis and meta-analysis	√	√	√	√	√	√	
Data intepretation	√					√	
Manuscript writing	√	√	√	√	√	√	
Manuscript Submission	√						

Result Synthesis and Meta-Analysis

Findings from all eligible studies will be summarized and synthesized following the predefined research questions that link each exposure (behavioral and biological factors) with each outcome (e.g., obesity and metabolic syndromes). Significant, non-significant, linear and non-linear statistical analyses from the included studies will also be extracted. Studies with graphical findings will be extracted with Web plot digitizer(Rohatgi, 2022). Meta-analysis will be performed with R package meta (38) assuming that the included studies are heterogeneous. Forest plot and I^2 will be produced to visualize the result of meta-analysis and to assess the heterogeneity of the studies, respectively (Tawfik *et al.*, 2019). Publication bias will also be determined using the R package with meta bias function and is visualized by funnel plot.

Risk of Bias Assessment

National Institute of Health tool for observational studies will be used to assess the quality of assessment (National Heart, Lung, and Blood Institute, 2021). The tool covers 14 criteria ranging from clear and precisely stated research questions to whether confounding variables are considered in the analysis (See **Table 5**). The quality will be rated as good, fair and poor.

Table 5. National Institute of Health Tool for Quality Assessment of Observational Studies

Questions	Yes	No	Other*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure or exposure measured as a continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			

Questions	Yes	No	Other*
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

* CD, cannot determine; NA, not applicable; NR, not reported

RESULTS AND DISCUSSION

This study is expected to shed light on how behavioural and biological factors are interconnected and subsequently influence metabolic syndromes in children and adolescents of Malayaustronesia origin. However, the outcome definition in paediatric samples is still equivocal in which many other studies reporting that definition mostly rely on adult criteria (e.g. adult panel treatment) (Friend, Craig and Turner, 2013; Reisinger *et al.*, 2021). This may affect the review finding in particularly for study reporting categorical outcomes. Measurement method variability in the exposures will also add a challenge in performing statistical methods to elicit how the interplay between behavioural and biological factors is associated with metabolic syndrome.

CONCLUSION

This review utilizes relevant databases to optimize the searching of eligible studies**.** Eligible studies will be extracted by more (four) researchers who work independently with a predefined data extraction template. There is a possibility some studies report significant findings on IGF-1 binding protein instead of total IGF-1, or its molar ratio will challenge the statistical analysis.

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Conflict of Interest and Funding Disclosure

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Author Contributions

DA conceived the study; BM and RS developed a search strategy; DA and MA would perform the literature search and match the studies with eligibility criteria. TU, BM, RS, and HH would extract the study's findings. DA and MA would assess and tabulate the quality of extracted studies. BM, RS and MA would perform the data synthesis and meta-analysis. DA, TU, and HH would interpret the findings. DA wrote the draft protocol manuscript; All authors critically reviewed, read and approved the final manuscript.

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