ESCOLA BAHIANA DE MEDICINA E SAÚDE PÚBLICA

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LARA CARVALHO SEIXAS

IMPACTO DO ESTADO NUTRICIONAL NOS DESFECHOS CLÍNICOS DA INFECÇÃO PELO VÍRUS DA DENGUE: UMA REVISÃO SISTEMÁTICA E META-ANÁLISE

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Trabalho de Conclusão de Curso apresentado à Escola Bahiana de Medicina e Saúde Pública, como parte dos requisitos para obtenção do título de Bacharel em Biomedicina.

Orientadora: Prof. Dra. Luana Leandro Gois.

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Este Trabalho de Conclusão de Curso foi julgado adequado à obtenção do grau de Bacharel em Biomedicina e aprovada em sua forma final pelo Curso de Biomedicina da Escola Bahiana de Medicina e Saúde Pública.

Salvador, 1 de novembro de 2024.

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RESUMO

Nas últimas décadas a incidência de casos de dengue aumentou de forma exponencial, crescendo como uma preocupação de saúde pública global. Dessa forma, investigar fatores como o estado nutricional pode ajudar a identificar indivíduos mais vulneráveis à dengue grave e a desenvolver uma estratégia de prevenção adequada para esses indivíduos. Portanto, essa revisão sistemática e meta-análise tem como objetivo investigar a associação entre o estado nutricional e os desfechos clínicos da infecção pelo vírus da dengue. Ao total, foram consultadas cinco bases de dados: *PubMed*, *SciELO*, LILACS, *ScienceDirect* e Google Acadêmico, a fim de selecionar artigos elegíveis para a revisão e meta-análise. Os desfechos clínicos analisados foram dengue com sinais de alerta, dengue grave, hospitalização (ou permanência em unidade de terapia intensiva) e óbito. Os parâmetros para fatores de risco foram desnutrição, supernutrição e obesidade. O protocolo *Joanna Briggs Institute Critical Appraisal Checklist* foi utilizado para avaliar a qualidade dos estudos. A análise dos dados foi realizada utilizando o software STATA v 13.0. A heterogeneidade foi calculada usando a medida estatística I^2, e resultados com valores de $p < 0{,}05$ foram considerados estatisticamente significativos. Um total de 158 artigos foram identificados nas bases de dados eletrônicas, sendo 29 artigos incluídos na revisão sistemática e 27 artigos na meta-análise. A desnutrição foi associada a um menor risco de dengue grave. Por outro lado, a supernutrição foi considerada um fator de risco para dengue grave, bem como para hospitalização (ou permanência em unidade de terapia intensiva). Como variável de exposição independente, a obesidade também foi um fator de risco para dengue grave e hospitalização. Essa revisão trouxe associações relevantes entre o estado nutricional e diferentes graus de severidade da dengue com o intuito futuro de aperfeiçoar o enfrentamento da dengue com base nas particularidades do estado nutricional.

Palavras-chave: Dengue, Estado nutricional, Desnutrição, Severidade, Revisão sistemática ou meta-análise.

ABSTRACT

In the last decades, the incidence of dengue cases has increased exponentially, becoming a global public health concern. Thus, investigating factors such as nutritional status can help identify individuals more susceptible to severe dengue and develop an appropriate prevention strategy for these individuals. Therefore, this systematic review and meta-analysis aims to investigate the association between nutritional status and clinical outcomes of dengue virus infection. PubMed, SciELO, LILACS, ScienceDirect and Google Scholar databases were used to search for eligible articles for the review and meta-analysis. The clinical outcomes analysed were dengue with warning signs, severe dengue, hospitalisation (or stay in an intensive care unit) and death. The parameters for risk factors were undernutrition, overnutrition and obesity. The Joanna Briggs Institute Critical Appraisal Checklist was used to assess the quality of the studies. Data analysis was performed using STATA v 13.0 software. Heterogeneity was assessed using the I^2 measure, and results with p-values < 0.05 were considered statistically significant. A total of 158 articles were identified from the electronic databases, 29 articles were included in the systematic review and 27 articles in the meta-analysis. Undernutrition was associated with a lower risk of severe dengue. On the other hand, overnutrition was found to be a risk factor for severe dengue, as well as for hospitalisation (or stay in an intensive care unit). When obesity was analysed as an independent exposure variable, the meta-analysis showed that obesity was a risk factor for severe dengue. This study has limitations that include nutritional status and dengue definitions, possible publication bias, heterogeneity of results and study design biases. These findings brought relevant associations concerning the nutritional status and different degrees of dengue severity in order to enable appropriate prognosis and access to medical care to better manage dengue fever according to the specificities of patients' clinical conditions.

Keywords: Dengue, Nutritional status, Malnutrition, Dengue severity, Systematic review or meta-analysis.

SUMÁRIO

1. ARTIGO CIENTÍFICO

Impact of nutritional status on dengue virus infection outcomes: A systematic review and meta-analysis

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ABSTRACT

Objective: In the last decades, the incidence of dengue cases has increased exponentially, becoming a global public health concern. Thus, investigating factors such as nutritional status can help identify individuals more susceptible to severe dengue and develop an appropriate prevention strategy for these individuals. Therefore, this systematic review and meta-analysis aims to investigate the association between nutritional status and clinical outcomes of dengue virus infection.

Methods: PubMed, SciELO, LILACS, ScienceDirect and Google Scholar databases were used to search for eligible articles for the review and meta-analysis. The clinical outcomes analysed were dengue with warning signs, severe dengue, hospitalisation (or stay in an intensive care unit) and death. The parameters for risk factors were undernutrition, overnutrition and obesity. The Joanna Briggs Institute Critical Appraisal Checklist was used to assess the quality of the studies. Data analysis was performed using STATA v 13.0 software. Heterogeneity was assessed using the I^2 measure, and results with p-values < 0.05 were considered statistically significant.

Results: A total of 158 articles were identified from the electronic databases, 29 articles were included in the systematic review and 27 articles in the meta-analysis. Undernutrition was associated with a lower risk of severe dengue. On the other hand, overnutrition was found to be a risk factor for severe dengue, as well as for hospitalisation (or stay in an intensive care unit). When obesity was analysed as an independent exposure variable, the meta-analysis showed that obesity was a risk factor for severe dengue. This study has limitations that include nutritional status and dengue definitions, possible publication bias, heterogeneity of results and study design biases.

Conclusion: These findings brought relevant associations concerning the nutritional status and different degrees of dengue severity in order to enable appropriate prognosis and access to medical care to better manage dengue fever according to the specificities of patients' clinical conditions.

Keywords: Dengue, Nutritional status, Malnutrition, Dengue severity, Systematic review or meta-analysis.

INTRODUCTION

Dengue fever is an acute febrile viral infection caused by an RNA virus of the Flaviviridae family (1). As a vector-borne disease, it is transmitted by the bite of infected mosquitoes of the genus *Aedes*, especially the primary vector *Aedes aegypti*, mainly found in tropical and subtropical regions (2,3). In the last decades, the incidence of dengue fever has increased exponentially and has become a global public health concern (2). Nowadays, more than a hundred countries are considered endemic for dengue fever, and it is estimated that more than 100 million people are infected and 40,000 die from severe dengue each year (4,5).

Since dengue can present itself with various clinical manifestations and an unpredictable course, several epidemiological studies have sought to identify prognostic risk factors for dengue fever severity (6). Currently, it is known that secondary infections by different dengue serotypes, host factors and also the presence of comorbidities (e.g. diabetes, chronic kidney disease, hypertension) are the major causes of progression to severe dengue (6–10).

An essential factor in the progression of infectious diseases such as the dengue virus is nutritional status, defined as the relationship between nutrient intake and energy expenditure of the individual (11). Nutritional status can affect the immune system and reduce the efficiency of the immune response to various pathogens, favouring the development of disease (12). Previous studies have investigated the association between nutritional status and dengue severity. Some studies have associated both undernutrition and overnutrition with greater chances of severe dengue and Dengue shock syndrome (DSS) (13–15). Although few studies found no associations between nutritional status and dengue, they suggest a potential risk despite limitations, in particular a limited number of participants and incomplete data collection (16–18).

Considering that the influence of nutritional status on the pathogenesis of dengue is still not well understood, it is of notable interest to understand how variations in nutritional status could trigger different mechanisms of the immune response in the context of dengue fever (10). Current dietary habits, often characterised by a nutrient-poor diet and ultra-processed foods, combined with a modern sedentary lifestyle, with lower levels of physical activity, can result in noncommunicable diseases like obesity, which in turn can lead to complications of dengue fever (19). On the other hand, low-income populations are undernourished and more exposed to the risk of virus transmission in regions with inadequate infrastructure, which favours a stronger vector-host interaction (20,21). Furthermore, investigating factors such as nutritional status can help identify individuals more susceptible to severe dengue and develop an appropriate prevention strategy for these individuals. The aim of this systematic review and meta-analysis was to investigate the association between nutritional status and clinical outcomes of dengue virus infection. It also describes the possible clinical outcomes of dengue infections in the presence of nutritional deficiencies due to undernutrition or overnutrition.

METHODS

This systematic review and meta-analysis was conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)(22). The study followed the Population Intervention Comparison Outcome Study Design (PICOS) strategy to establish the research question: "What is the influence of nutritional status on the clinical outcome of patients with dengue?". This review protocol was registered in PROSPERO under the ID CRD42024549257.

Literature searching and selection criteria

Five databases were consulted: National Library of Medicine (PubMed), Scientific Electronic Library Online (SciELO), Latin American and Caribbean Literature in Health Sciences (LILACS), ScienceDirect and Google Scholar. For this search, the descriptors from the Health Sciences Descriptors/Medical Subject Headings (DeCS/MeSH) platform (23), were combined with Boolean operators (OR and AND) to create search algorithms for each database as described in Table 1. Manual searches of the citations from included articles and general searches were also performed according to selection criteria.

Table 1 – Search algorithm used on each database.

Database	Search terms
PubMed	((("dengue"[MeSH Terms] OR "dengue"[All Fields] OR ("dengue"[All Fields] AND "fever"[All Fields]) OR "dengue fever"[All Fields] OR ("severe dengue"[MeSH Terms] OR ("severe"[All Fields] AND "dengue"[All Fields]) OR "severe dengue"[All Fields]) OR ("dengue haemorrhagic fever"[All Fields] OR "severe dengue"[MeSH Terms] OR ("severe"[All Fields] AND "dengue"[All Fields]) OR "severe dengue"[All Fields] OR ("dengue"[All Fields] AND "hemorrhagic"[All Fields] AND "fever"[All Fields]) OR "dengue hemorrhagic fever"[All Fields]) OR ("severe dengue"[MeSH Terms] OR ("severe"[All Fields] AND "dengue"[All Fields]) OR "severe dengue"[All Fields] OR ("dengue"[All Fields] AND "shock"[All Fields] AND "syndrome"[All Fields]) OR "dengue shock syndrome"[All Fields])) AND (("nutritional status"[MeSH Terms] OR

	("nutritional"[All Fields] AND "status"[All Fields]) OR "nutritional status"[All Fields] OR ("malnutrition"[MeSH Terms] OR "malnutrition"[All Fields] OR "malnutrition s"[All Fields] OR "malnutritional"[All Fields] OR "malnutritions"[All Fields]) OR ("thinness"[MeSH Terms] OR "thinness"[All Fields] OR "underweight"[All Fields] OR "underweights"[All Fields]) OR ("obeses"[All Fields] OR "obesity"[MeSH Terms] OR "obesity"[All Fields] OR "obese"[All Fields] OR "obesities"[All Fields] OR "obesity s"[All Fields]) OR ("overweight"[MeSH Terms] OR "overweight"[All Fields] OR "overweighted"[All Fields] OR "overweightness"[All Fields] OR "overweights"[All Fields])) AND "humans"[MeSH Terms])) NOT "Review"[Publication Type])
SciELO	((dengue) OR (dengue fever) OR (severe dengue) OR (dengue hemorrhagic fever) OR (dengue shock syndrome)) AND ((nutritional status) OR (malnutrition) OR (obesity) OR (overweight) OR (underweight))
LILACS	((dengue) OR (dengue fever) OR (severe dengue) OR (dengue hemorrhagic fever) OR (dengue shock syndrome)) AND ((nutritional status) OR (malnutrition) OR (obesity) OR (overweight) OR (underweight))
ScienceDirect	TITLE-ABS-KEY ((dengue fever) OR (severe dengue) OR (dengue hemorrhagic fever) OR (dengue shock syndrome)) AND ((nutritional status) OR (malnutrition) OR (obesity) OR (overweight) OR (underweight))
Google Scholar	allintitle: ((“dengue fever”) OR (“severe dengue”) OR (“dengue hemorrhagic fever”) OR (“dengue shock syndrome”)) AND ((“nutritional status”) OR (“malnutrition”) OR (“obesity”) OR (“overweight”) OR (“underweight”))

The inclusion criteria for the selection of studies were: (I) complete original articles in Portuguese, English or Spanish, (II) patients infected with the dengue virus, (III) studies evaluating nutritional status associated with different severity of dengue, (IV) studies reporting odds ratio (OR), risk ratio (RR), hazard ratio (HR) or prevalence ratio (PR) as a measure of association. In addition, articles with the following characteristics were excluded: (I) articles in the format of thesis, case report, case series, review or meta-analysis, (II) studies in animal models or *in vitro* without patients, (III) participants with co-infection.

This study was guided by the 2009 WHO Dengue Guidelines (24) for the classification of cases to facilitate clinical management of the disease. The WHO (2009) defines dengue without warning signs (may present leukopenia, positive tourniquet test); dengue with warning signs (DwWS), including symptoms such as fluid accumulation and mucosal bleeding, and requiring medical attention for possible progression to severe dengue (SD), characterized by plasma leakage, severe bleeding and involvement of other organs (24,25).

However, some studies have used WHO Guidelines from 1997, which include definitions such as dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS), that can be further subdivided into grade I, with nonspecific symptoms and only a positive tourniquet test; grade II, with additional spontaneous bleeding; grade III and IV, which are classified as DSS (26).

Given the different classifications of dengue, the following nomenclatures for dengue cases were used in this systematic review: (I) classic or asymptomatic dengue fever as dengue without warning signs; (II) dengue haemorrhagic fever (DHF) grade I and grade II as dengue with warning signs; (III) dengue shock syndrome (DSS), DHF grade III and IV as severe dengue (27). Thus, the clinical outcomes analysed were dengue with warning signs, severe dengue, hospitalisation (or stay in an intensive care unit) and death due to dengue.

Likewise, the classifications of nutritional status were assessed according to the anthropometric indices addressed in the included studies, using different measures (weight-for-height, height-for-age and weight-for-age) expressed in percentiles, Z-score, body mass index (BMI) or mean standard deviation percentage, to investigate the possibility of distinct established associations. The results of these associations were adequate for the parameters: undernutrition, overnutrition and obesity, according to the criteria of each included study.

Data extraction

The search for articles took place between the 26th and 28th of June 2024. A database was created in Microsoft Excel version 17.0 with information on the selection and indexing of articles. Initially, two independent reviewers (SEIXAS, LC and PARANÁ, VC) screened reports based on the article's title and abstract, considering the authorship, year of publication and type of study. The consensus for inclusion of the articles was reached jointly by all authors.

The following data were collected for the selected articles: study design, country of study, number of patients included in the studies, distribution and characterisation of the sample, criteria used in dengue (methods used to confirm the diagnosis, prevalence of clinical manifestations and clinical outcomes), criteria used to assess nutritional status, and measures of association (OR, RR or HR). Individual patient factors such as age and gender were also recorded.

Methodological Quality Assessment

To assess the methodological quality of the selected articles, the Joanna Briggs Institute (JBI) protocol (28) was used to examine the possible risks of bias in the included articles. The articles were assessed by two independent reviewers, considering the following criteria: study design; population selection; criteria for assessing the collection and measurement of results (based on existing definitions or systems); and the validation of statistical analysis (systematic error or internal validation). Studies were classified as low, medium, and high risk of bias if 70% or more, 50% to 69%, and 50% or less of the responses on the checklist were ‘yes’, respectively (29).

Meta-analysis

In order to perform the meta-analysis, the type of study, outcome analysed, risk factors associated with the outcome and corresponding measures of association (such as OR, RR, or HR), were collected from each article together with the confidence intervals (CI). The data used for the meta-analysis were grouped and analysed using STATA/MP software version 13.0. Articles with homogeneous measures of association and outcomes were selected for analysis so that they could be combined and included in the synthesis of results. Subgroup analyses based on the study design and dengue case classification (whether defined DHF/DSS or DwWS/SD) were performed to further assess the statistical heterogeneity of the studies. Furthermore, the incorporated data of the effect measures (OR, RR) were presented using forest plots and I^2 statistics – which have values ≤25% indicating low heterogeneity, 26%–74% indicating moderate heterogeneity and values ≥75% indicating high heterogeneity – including the individual confidence interval of each study (29).

Thus, articles classified as high heterogeneity, at high risk of bias or as outliers were justified and adjusted based on the size of the study and the calculated risk of bias, in order not to compromise the results and to produce analyses with more precise confidence intervals. This allowed us to improve the precision of the hypotheses and identify possible reasons for discordant results. Results with p-values < 0.05 were considered statistically significant.

The results of the meta-analysis were only included in this study if they met the following criteria: (I) the risk factor was analysed by at least three studies and (II) with a heterogeneity of less than 75%. Studies evaluated as having a high risk of bias were not included in the analyses.

RESULTS

A total of 158 articles were identified from five electronic databases. After excluding duplicates, 138 reports were screened based on title and abstract, resulting in 72 studies that proceeded to full-text reading. Moreover, 22 articles from secondary systematic research were added, totalling 94 reports assessed for eligibility. Therefore, 65 articles were excluded as they did not meet the criteria. Finally, a total of 29 articles were included in the review. However, only 27 studies could be included in the meta-analysis (Fig. 1).

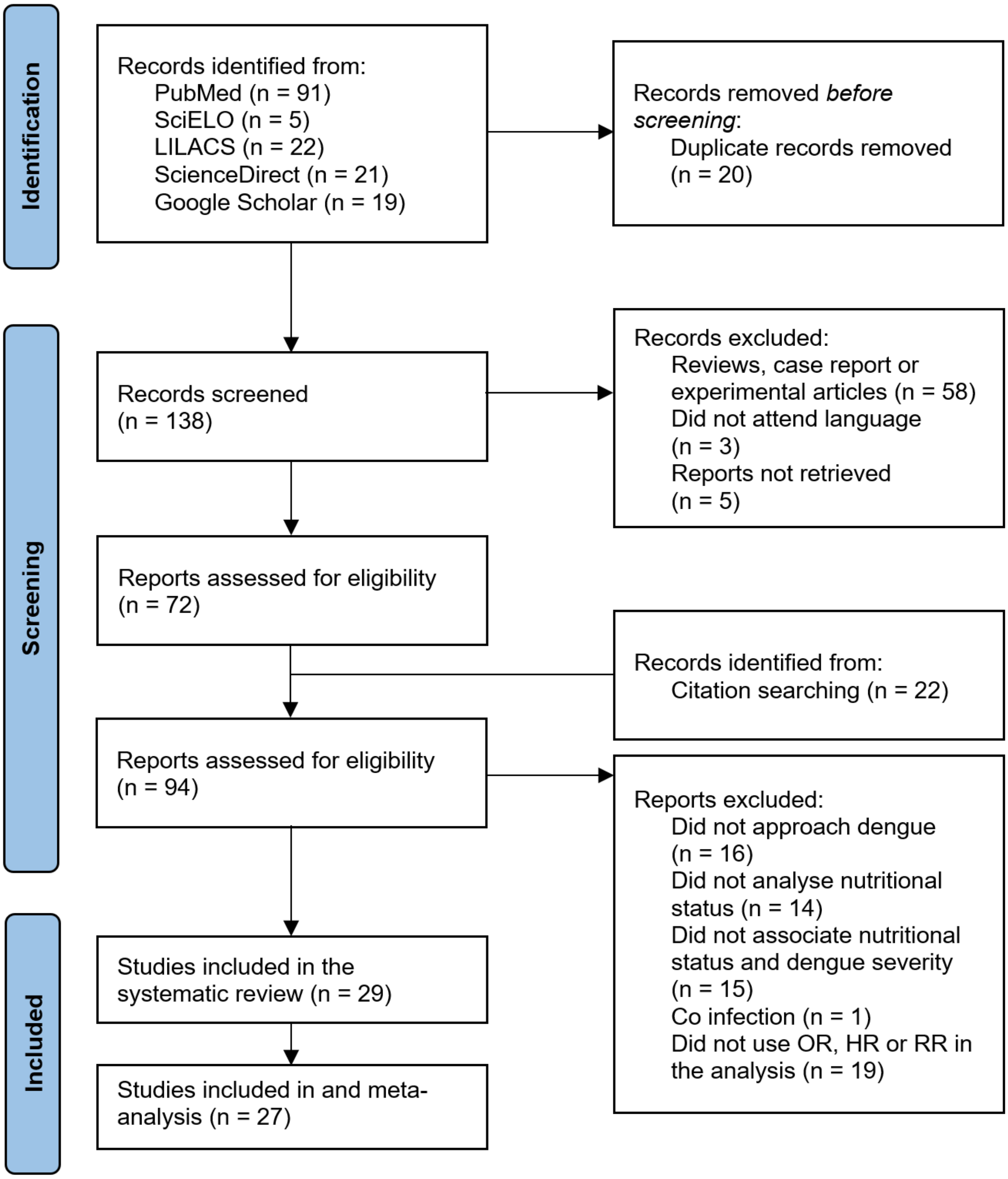

Figure 1 – Flow diagram for selecting and screening articles for inclusion in the systematic review and meta-analyses.

Descriptive analysis of the included articles

Regarding the study design of the included articles, ten (34.5%) were cohort studies, ten (34.5%) were case-controls and nine (31.0%) were cross-sectional studies. The total number of participants in this review was 16,564 subjects, of which 24 studies included only children and five articles included adolescents and adults. By country of publication, ten articles were published in Indonesia, eight in Thailand, three in Malaysia, two in Vietnam, two in Sri Lanka, one in Paraguay, one in Bangladesh and one in Taiwan (Table 2).

Given different classifications of dengue, 12 studies used the WHO 1997 Dengue Guidelines (26), 11 studies used the WHO 2009 Dengue Guidelines (24) and two studies used both classifications in their analysis. As Thisyakorn and Nimmannitya (30) published their article before 1997, they used the WHO 1986 dengue classification (31) which may be equivalent to the WHO 1997 classification as it defines DHF and DSS. The same condition applies to Malavige *et al.* (32) and Pichainarong *et al.* (33) as they used the WHO 1999 guidelines (34), and Linardi *et al.* (35) who used the WHO 2011 Dengue and Dengue Haemorrhagic Fever Guidelines (36).

In describing clinical outcomes, 24 articles (82.8%) reported dengue fever with warning signs (DwWS), 26 articles (89.7%) reported severe dengue fever (SD), 11 articles (37.9%) reported death as an outcome of dengue fever and seven articles (24.1%) reported hospitalisation or stay in an intensive care unit. Zulkipli et al. (15) and Chiu et al. (37) did not describe dengue as DwWS or SD although they described and analysed the severity of dengue fever.

Of twenty-nine studies, twelve (41.3%) studies analysed undernutrition and twenty-six (89.7%) studies analysed overnutrition, while nine (31.0%) studies analysed both undernutrition and overnutrition as the exposure. The measurement of undernutrition and overnutrition varied between studies: three (10.35%) articles used weight for age (w/a), four (13.8%) articles used weight for height (w/h), thirteen (44.8%) articles used BMI, three articles (10.35%) used height for age (h/a) in conjunction with one or more standards and six (20.7%) articles did not report any measurement tools.

Twelve (41.4%) articles did not find relevant results on whether undernutrition or overnutrition is a risk factor for dengue outcomes. Nevertheless, seventeen (58.6%) reports found an association between the severity of dengue fever and nutritional status. In sixteen articles, overnutrition was observed as a risk factor for dengue fever severity. However, Nguyen *et al.* (38) also showed opposing results for severe manifestations as obesity was associated with respiratory failure but not with mortality or acute liver failure. Regarding the correlation with undernutrition, the results of the five articles were discordant. While three studies found undernutrition to be a protective factor for severe dengue fever, the other two articles indicated that malnourished patients have a higher risk of developing severe dengue fever.

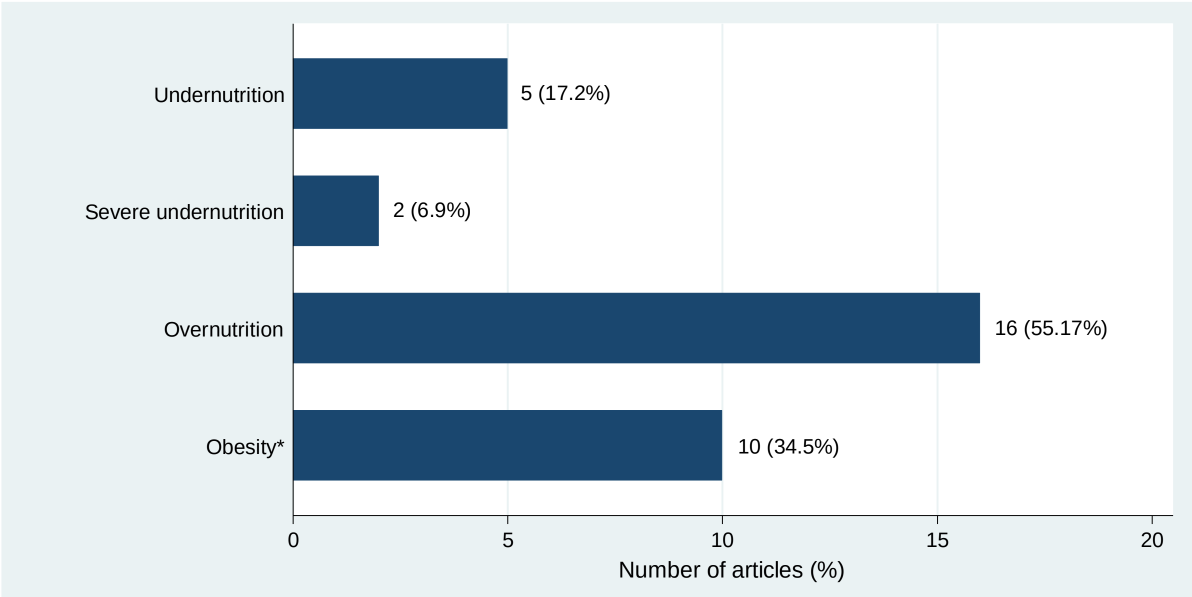

Figure 2 – Graphic of articles that found an association between dengue severity and nutritional status.
*Obesity was considered an independent variable.

Quality Assessment

According to the assessment of study quality using the JBI protocol, seventeen (58.6%) reports were assessed as high quality, nine (31.0%) reports as moderate quality and three (10.4%) as low quality (Table 2).

TABLE 2 - Main characteristic of each study.

Author, year	Country (study period)	Study Design	Type of population – N	Nutritional Status criteria	Clinical outcomes	Male, n (%)	Age group	Association found	Risk of bias
Thisyakorn; Nimmannitya (1993) (30)	Thailand (NR)	Cross-sectional	Children with DHF/DSS – 409	Gomez Classification (39)	Malnutrition prevalence in DHF children	44 (44%)*	<5 years: 40 (40%) 5-10 years: 40 (40%) 10-15years: 20 (20%)[a]	No	High (37.5%)
Kalayanarooj; Nimmannitya (2005) (13)	Thailand (1995-1999)	Cross-sectional	Children with dengue fever – 5,266	Percentage of ideal body weight (%IBW) – Standard growth curve for Thai children from the Department of Health (2000) (40,41)	Susceptibility to DHF, DSS, encephalopathy, fluid overload and hepatic dysfunction	Malnutrition = 219 (52.3%)* Normal = 1,284 (63.6%)* Obesity = 574 (52.4%)*	Mean (SD): Dengue = 7.9±3.8 Control = 5.8±3.5	Yes	Moderate (62.5%)
Nguyen et al. (2005) (42)	Vietnam (1997-2002)	Case-control	< 12 months old infants with DHF – 778	Z-score – NCHS (43)	Susceptibility to DSS, prolonged shock, gastrointestinal bleeding, respiratory failure, and encephalopathy	Case = 138 (56,3%) Control = 276 (51,8%)	Mean: Case = 6.8 months; Control = 7 months	No	Low (80.0%)
Dewi; Tumbelaka; Sjarif (2006) (44)	Indonesia (2003-2004)	Cohort	Children with DHF/DSS – 101	NR[b]	Susceptibility to DHF	54 (54%)	Mean (SD): 6,5±3,6 years	No	Moderate (60.0%)
Malavige et al. (2006) (32)	Sri Lanka (Apr-Jul 2004)	Cohort	Children with dengue fever – 104	BMI percentile – NCHS 2000 (45)	Susceptibility to DHF	43 (41,2%)	Mean (SD): 7,9±2,9 years	No	Moderate (54.6%)
Pichainarong et al. (2006) (33)	Thailand (2002-2003)	Case-control	Children aged 0-14 years with dengue fever – 210	Standard growth curve for Thai children from the Department of Health (2000) (41)	Susceptibility to DSS	105 (50%)	NR[b]	Yes	Low (100.0%)
Junia; Garna; Setiabudi (2007) (14)	Indonesia (2004-2005)	Case-control	Children aged <14 years with dengue fever – 600	Percentage of ideal body weight (%IBW) – NCHS/WHO (40,43)	Susceptibility to DSS	Case = 93 (46,5%) Control = 203 (50,8%)	Mean (SD): Case = 7,1±3,2 years Control = 7,3±3,5 years	Yes	Low (70.0%)
Laoprasopwattana et al. (2010) (46)	Thailand (1989-2007)	Cohort	<15 years old DHF patients with and without AKI[c] – 75	Z-score – (NR[b])	Risk of AKI and fatality in DHF-caused AKI	AKI = 14 (56,0%) No AKI = 23 (46,0%)	Mean (SD): AKI = 9.1± 3.6 No AKI = 8.8 ±3.2	Yes	Low (72.7%)
Widiyati; Laksanawati; Prawirohartono	Indonesia (2008-2011)	Case-control	<18 years old DHF patients – 342	BMI with standard deviation – WHO Growth Chart (2006) (47)	Susceptibility to DSS	Case = 55 (47.4%)	1-4 years: 117 (51.8) 5-0 years: 137 (40.1) 10-14 years: 121 (35.4)	No	Low (80.0%)

Author, year	Country (study period)	Study Design	Type of population – N	Nutritional Status criteria	Clinical outcomes	Male, n (%)	Age group	Association found	Risk of bias
(2013) (18)						Control = 122 (54.0%)	15-18 years: 27 (7.9)		
Lovera et al. (2016) (48)	Paraguay (2011-2013)	Cohort	<15 years old children with dengue fever – 471	NR[b]	Susceptibility to DSS	241 (51%)	Mean (SD): 10±4 years	No	Moderate (63.6%)
Saniathi et al. (2018) (49)	Indonesia (2015-2016)	Case-control	Children aged 6 months – 12 years with DHF – 80	Waterlow percentage of ideal body weight (IBW) – NCHS/WHO (43,50)	Susceptibility to DSS	Case = 19 (47,5%) Control = 25 (62,5%)	Mean (SD): Case = 7.40 ± 3.6 years Control = 7.21 ± 3.5 years	Yes	Moderate (60.0%)
Tan et al. (2018) (51)	Malaysia (Apr-Jul 2015)	Cross-sectional	> 12 years who were positive for non-structural protein 1 (NS1) dengue antigen – 335	BMI – NCHS/WHO (43)	Warning signs, severe dengue manifestation, hospitalization >3 days, mortality and ICU admission	190 (56.4)	Mean (range): 30.2 years (12.3–73.2)	Yes	Low (100.0%)
Diptyanusa et al. (2019) (52)	Thailand (2012-2017)	Cohort	> 18 years old dengue fever patients with and without AKI[c] – 1,484	BMI – adjusted for Asian population parameters (53)	Risk of AKI	748 (50,4%)	Mean (range): 28 years (22–40)	Yes	Low (80.0%)
Kurnia; Suryawan (2019) (54)	Indonesia (mar-may 2019)	Case-control	Children with DHF/DSS – 44	BMI – CDC Growth Chart (43)	Susceptibility to DSS	28 (63.6%)	Mean (SD): 11.11 ± 4.271 years	Yes	Moderate (60.0%)
Baiduri et al. (2020) (55)	Indonesia (NR)	Cohort	Children aged 2 months – 18 years with dengue fever – 67	BMI – WHO (2007) and CDC (2000) (45,47)	Susceptibility to severe dengue	32 (47,8%)	≤ 5 years = 11 > 5 years = 56	Yes	Low (72.7%)
Cundawan; Wihanto; Wijono (2020) (56)	Indonesia (2018-2019)	Case-control	Children aged 5-14 years with dengue fever – 84	NR[b]	Susceptibility to DSS	51 (60,7%)	5-9 years = 49 (58.3) 10-14 years = 35 (41.7)	Yes	High (30.0%)
Maneerattanasak; Suwanbamrung (2020) (57)	Thailand (2017-2018)	Cross-sectional	Children aged 1-14 years with dengue fever – 572	Z-score – WHO (2006/2007) and Thai Growth Chart (47,58)	Warning signs and severe dengue manifestation	303 (52.97)	12-60.9 months = 87 (15.21) 61-120.9 months = 208 (36.36) 121-179.9 months = 277 (48.43)	Yes	Low (100.0%)
Putri; Wahyono (2020) (59)	Indonesia (2018-2020)	Case-control	Toddlers in Sumbawa Regency – 242	NR[b]	Susceptibility to DHF	NR[b]	NR[b]	Yes	Low (70.0%)

Author, year	Country (study period)	Study Design	Type of population – N	Nutritional Status criteria	Clinical outcomes	Male, n (%)	Age group	Association found	Risk of bias
Armenda et al. (2021) (60)	Indonesia (2016-2020)	Cohort	Children with DSS admitted to paediatric intensive care unit (PICU) – 146	Z-score – WHO (47)	Susceptibility to DSS, mortality and prolongated stay in PICU	78 (53,4%)	Infant = 16 (11.0) 1–5 years = 48 (32.9) > 5 years = 82 (56.1)	No	Low (80.0%)
Linardi; Suryawan; Widiasa (2021) (35)	Indonesia (2019-2020)	Case-control	> 18 years old DHF/DSS patients – 1126	Percentage of ideal body weight (%IBW) (40)	Susceptibility to DSS	Case = 28 (66.7%) Control = 47 (56%)	Median (min-max): Case = 10 (3–17) Control = 11 (1–17)	Yes	High (40.0%)
Zulkipli et al. (2021) (15)	Malaysia (2016-2017)	Cohort	>18 years old dengue fever patients – 173	BMI – WHO (2017) (61)	Warning signs and severe dengue manifestation	90 (52,1%)	Mean (SD): Obese (37.6±16.72 y), Overweight (38.8±11.69 y) Normal (36.2±13.63 y) Underweight (38.3±17.24 y)	Yes	Low (90.9%)
Kurahashi et al. (2022) (62)	Thailand (2014-2015)	Cross-sectional	Children aged <14 years old – 225	Weight Standard Deviation Score (WSDS) – Thai Growth Chart (41)	Susceptibility to severe dengue	29 (38,7%)	Median (IQR): 7 (4, 11)	No	Moderate (75.0%)
Ng et al. (2022) (63)	Malaysia (2017-2019)	Case-control	>18 years old dengue fever patients – 468	BMI – WHO (2004) (64)	Severe dengue manifestations	Case = 57 (48,7%) Control = 171 (48,7%)	Median (IQR): Case = 40 (29–49) Control = 38 (28–48)	No	Low (100.0%)
Te et al. (2022) (17)	Thailand (2017-2019)	Cross-sectional	< 18 years old children with acute dengue infection – 355	BMI with standard deviation – WHO Growth Chart (2006/2007) (47)	Severe dengue manifestations	221	Median (IQR): 15 (12–16)	No	Moderate (62.5%)
Ahmed; Islam (2023) (65)	Bangladesh (Jun-Nov 2022)	Cohort	Patients with dengue – 72	NR[b]	Severe dengue manifestations	33 (42,4%) 19 (57,6%)	≤ 5 years = 13 > 5 years = 59	Yes	Moderate (54.5%)
Chiu et al. (2023) (37)	Tawain (2014-2015)	Cross-sectional	>18 years old dengue fever patients – 1,417	BMI – WHO recommendations for Asian populations (53)	Warning signs, severe dengue manifestations, ICU stay, mortality	689 (48.6%)	Mean (range): 57.9 (18–92)	No	Low (87.5%)
Nguyen et al. (2023) (38)	Vietnam (2013-2021)	Cross-sectional	<18 years old DSS patients – 858	BMI with standard deviation – WHO Growth Chart (2006/2007) (47)	Warning signs, severe dengue manifestations, dengue related-mortality, mechanical ventilation requirements	454 (53%)	Median (IQR): 7.3 (5–10)	Yes	Low (100.0%)

Author, year	Country (study period)	Study Design	Type of population – N	Nutritional Status criteria	Clinical outcomes	Male, n (%)	Age group	Association found	Risk of bias
Sami et al. (2023) (66)	Bangladesh (Jun-Nov 2022)	Cohort	Dengue patients – 308	NR[b]	Susceptibility to severe dengue	205 (66,6%)	12-20 years = 32 (10.4) 21-30 years = 147 (47.7) 31-40 years = 69 (22.4) 41-50 years = 17 (5.5) >60 years = 9 (2.9)	No	Moderate (54.6%)
Jeewandara et al. (2024) (67)	Sri Lanka (2022-2023)	Cross-sectional	Children aged 10 to 18 years from attending schools – 1,152	BMI percentile – NCHS/WHO (43)	Dengue hospitalisations	NR[b]	NR[b]	Yes	Moderate (75.0%)

* Only dengue patients' data was available.
[a] Ratio male to female (m/f)
[b] Not reported (NR)
[c] Acute Kidney Injury (AKI)

Meta-analysis

Twenty-four articles used odds ratio (OR) as a measure of association and five articles used relative risk (RR). Of the included reports, 15 (51.7%) performed multivariate analyses, eight (27.6%) performed univariate analyses and six (20.7%) articles did not describe the type of analysis performed. In the studies that performed multivariate analyses, age, gender, ethnicity, secondary dengue infection and laboratory findings were identified as confounding factors.

The meta-analysis was stratified by measures of association, dengue severity (outcome) and nutritional status (exposure). Considering all criteria, 20 studies were included in the meta-analysis. Three studies were excluded as the data could not be reliably extracted (56,59,62).

The results of the meta-analysis showed that undernutrition was associated with a lower risk of severe dengue (OR: 0.78, 95% CI: 0.66–0.89) (Fig. 3). Due to insufficient data, the outcomes of dengue with warning signs (DwWS), death and hospitalisation in undernutrition were not analysed. Taking notice of the impact that the measure of height-for-age (H/A) had on the meta-analysis results, we performed an additional analysis without the anthropometric measure. In this analysis, the association between undernutrition and severe dengue was no longer found (Fig. S1). On the other hand, overnutrition was found to be a risk factor for severe dengue (OR: 1.11, 95% CI: 1.03–1.20), as well as for hospitalisation (or stay in an intensive care unit) (OR: 1.82, 95% CI: 1.28–2.36) (Fig. 4b, 4d). Overnutrition was not associated with dengue with warning signs or death (Fig. 4a, 4c). When obesity was analysed as an independent exposure variable, the meta-analysis showed that obesity was a risk factor for severe dengue (OR: 1.11, 95% CI: 1.02–1.21) and hospitalisation (OR: 1.82, 95% CI: 1.28–2.36) (Fig. 5d, 5d).

Subgroup analyses on the outcome of severe dengue for overnutrition were performed based on the study design and dengue case classification. In study design analysis, cohort and cross-sectional studies were pooled and showed an association between overnutrition and severe dengue (OR: 1.10, 95% CI: 1.01–1.19). The case-control meta-analysis revealed that overnutrition was associated with severe dengue, having a higher odds ratio (OR: 1.64, 95% CI: 1.12–2.16) (Fig. 6). Based on dengue cases classification, articles were pooled on whether described DHF/DSS and revealed no association between overnutrition and severe dengue.

Articles that followed WHO 2009 guidelines showed that overnutrition was not associated with severe dengue as well (Fig. 7).

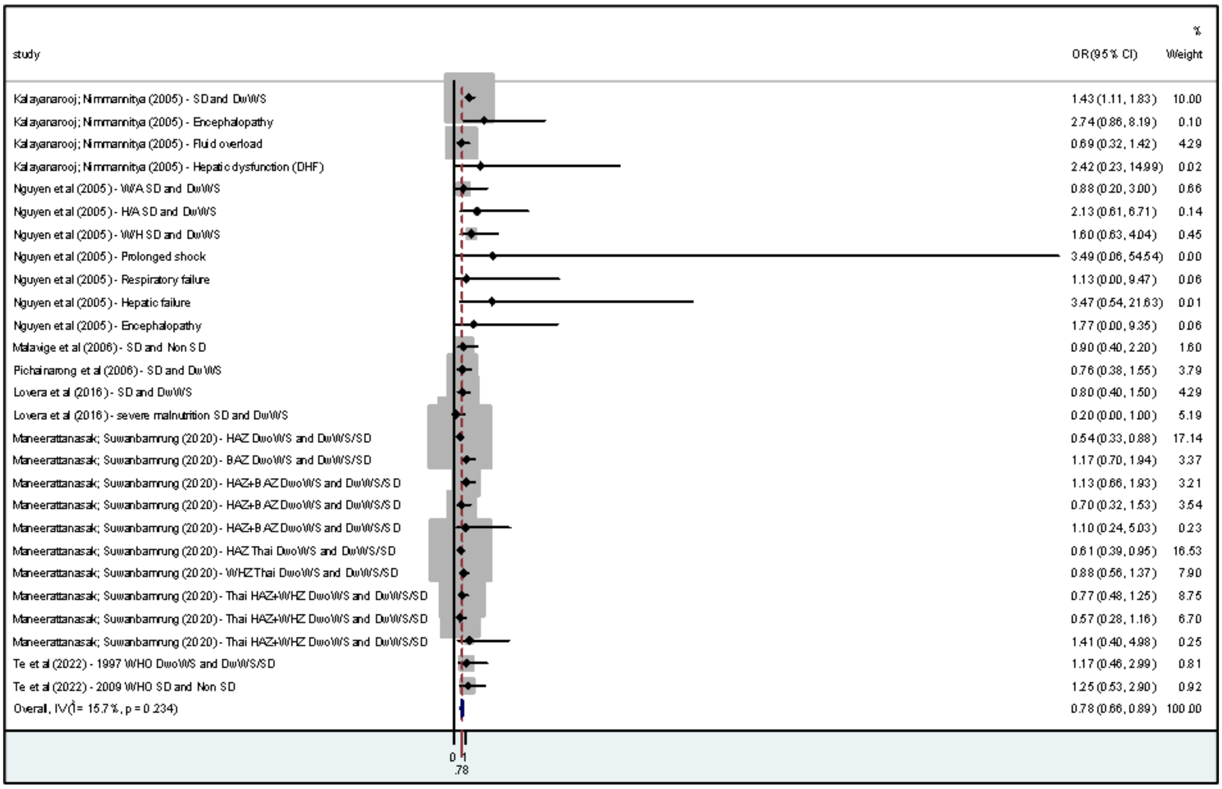

Figure 3 – Meta-analysis: Forest plot of the association between undernutrition and severe dengue.
Abbreviations: OR, Odds ratio. CI, Confidence interval. Severe dengue. DwWS, Dengue with warning signs. DwoWS, Dengue without warning signs. W/A, weight-for-age. H/A, height-for-age. W/H weight-for-height. HAZ, Height-for-age Z-score. BAZ, BMI-for-age Z-score. WHZ, Weight-for-height Z-score.

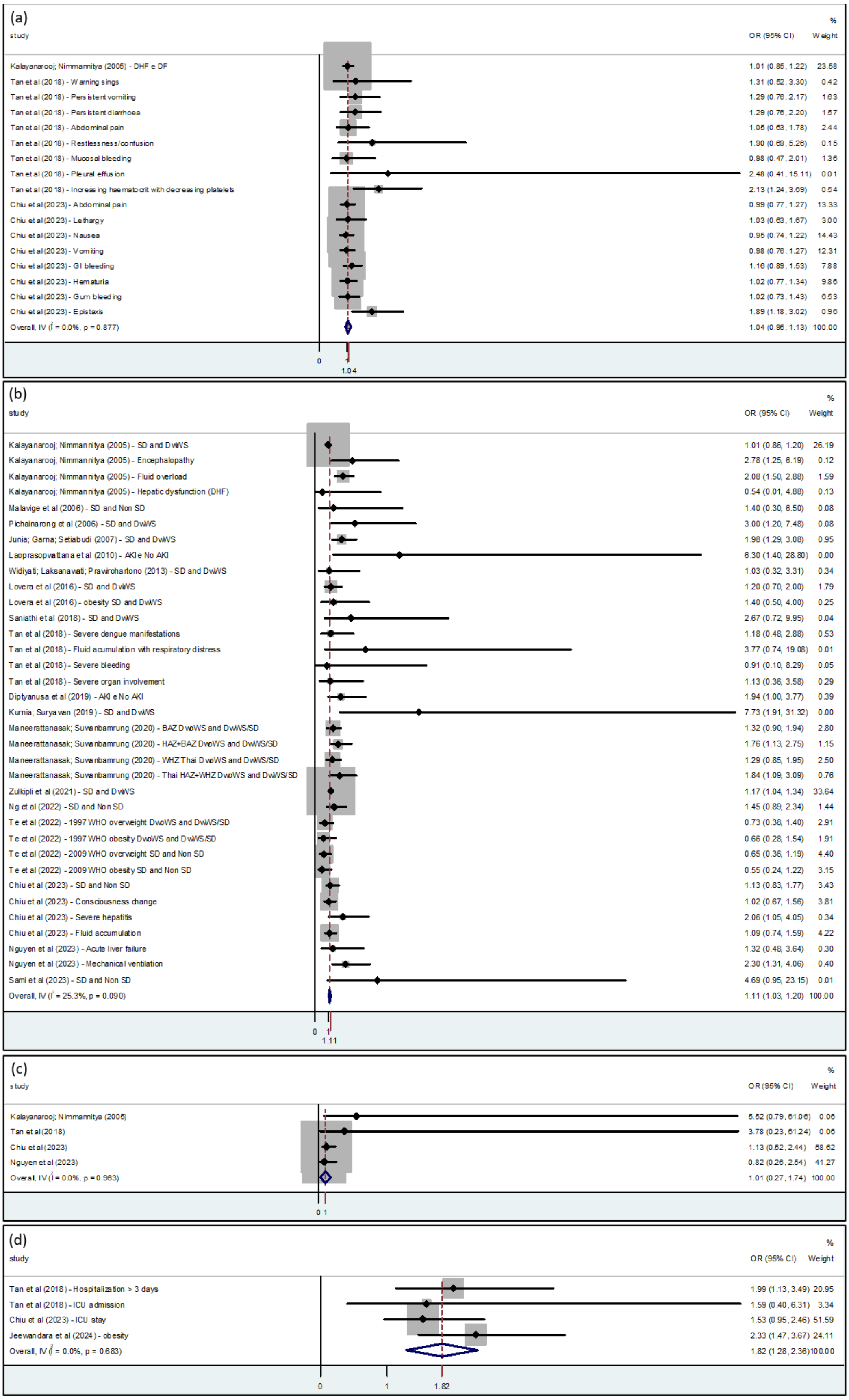

Figure 4 – Meta-analysis results for the exposure of overnutrition. (a) Forest plot of dengue with warning signs. (b) Forest plot of severe dengue. (c) Forest plot of death. (d) Forest plot of hospitalisation/ICU.
Abbreviations: OR, Odds ratio. CI. Confidence interval. SD, Severe dengue. DwWS, Dengue with warning signs. DwoWS, Dengue without warning signs. AKI, Acute kidney injury. ICU, Intensive care unit. HAZ, Height-for-age Z-score. BAZ, BMI-for-age Z-score. WHZ, Weight-for-height Z-score.

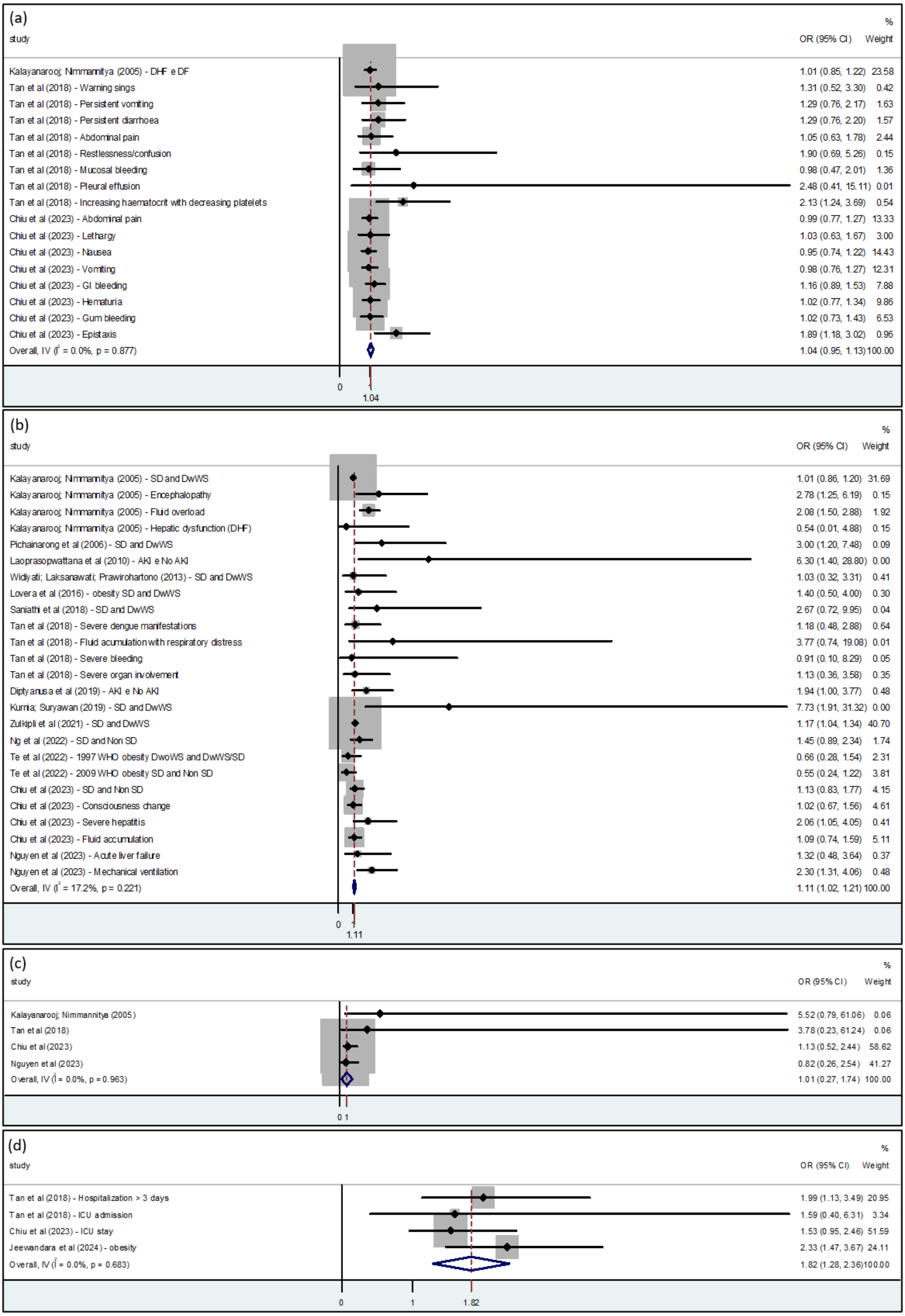

Figure 5 – Meta-analysis results for the exposure of obesity. (a) Forest plot of dengue with warning signs. (b) Forest plot of severe dengue. (c) Forest plot of death. (d) Forest plot of hospitalisation/ICU.
Abbreviations: OR, Odds ratio. CI. Confidence interval. SD, Severe dengue. DwWS, Dengue with warning signs. DwoWS, Dengue without warning signs. AKI, Acute kidney injury. ICU, Intensive care unit.

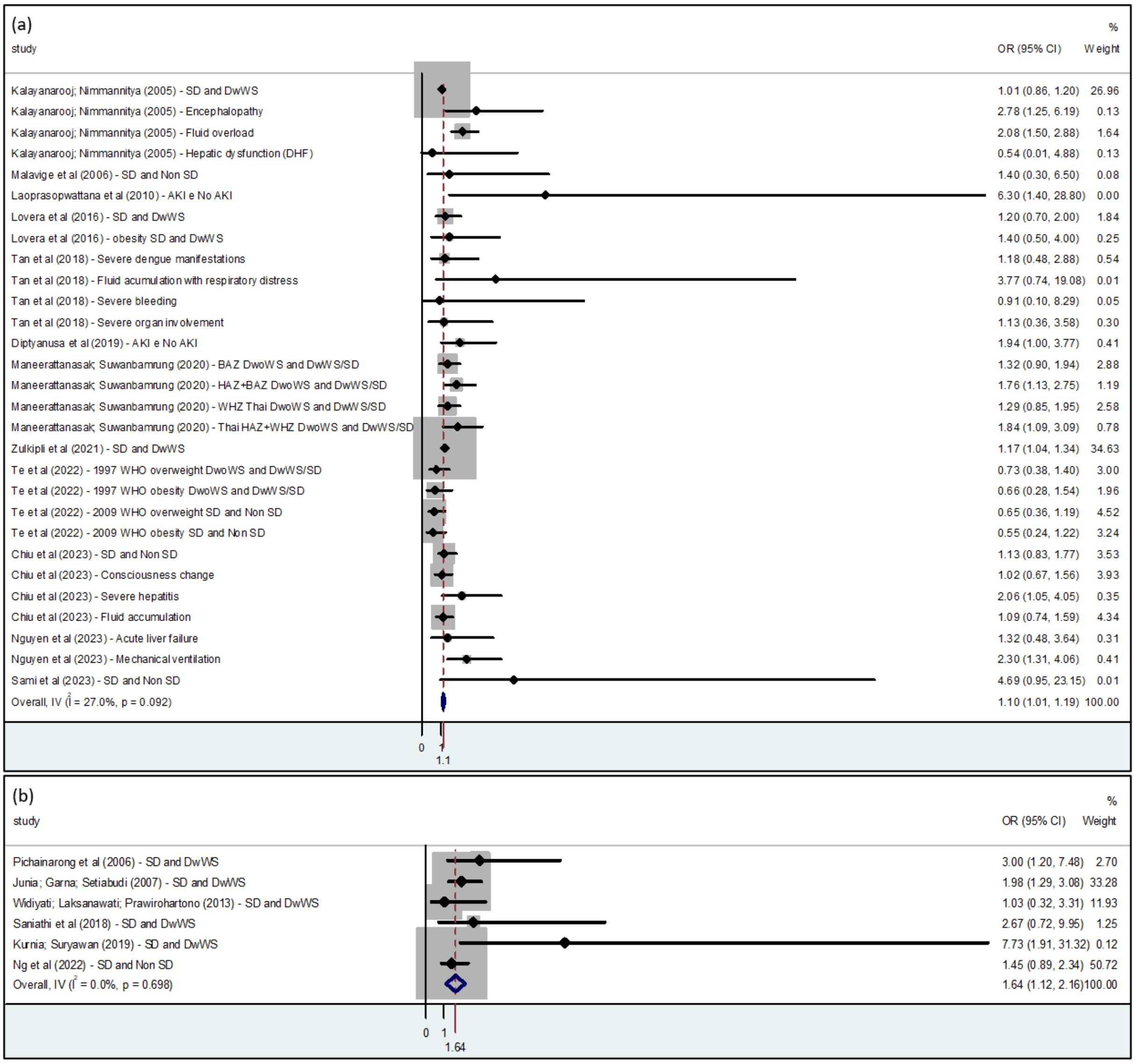

Figure 6 – Meta-analysis results for the exposure of overnutrition of the outcome of severe dengue. (a) Forest plot of Cohort and Cross-sectional studies. (b) Forest plot of Case-control studies.
Abbreviations: OR, Odds ratio. CI. Confidence interval. SD, Severe dengue. DwWS, Dengue with warning signs. DwoWS, Dengue without warning signs. HAZ, Height-for-age Z-score. BAZ, BMI-for-age Z-score. WHZ, Weight-for-height Z-score.

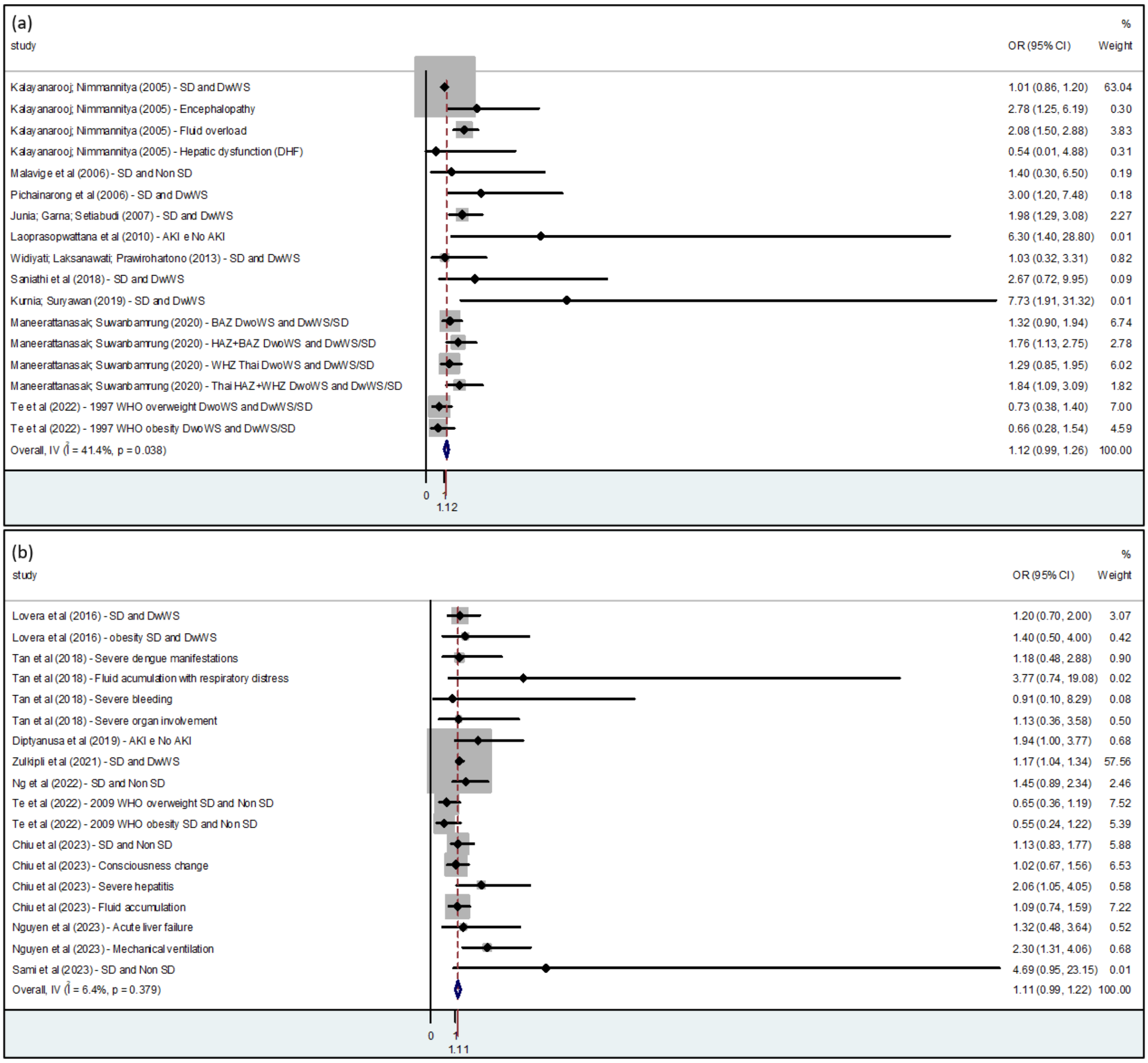

Figure 7 – Meta-analysis results for the exposure of overnutrition of the outcome of severe dengue. (a) Forest plot of DHF/DSS classification. (b) Forest plot of SD classification.
Abbreviations: OR, Odds ratio. CI. Confidence interval. DHF/DSS, Dengue haemorrhagic fever/Dengue shock syndrome. Severe dengue. DwWS, Dengue with warning signs. DwoWS, Dengue without warning signs. HAZ, Height-for-age Z-score. BAZ, BMI-for-age Z-score. WHZ, Weight-for-height Z-score.

DISCUSSION

The meta-analysis results showed that individuals with undernutrition have a lower risk of developing severe dengue fever. Although it is not certain how undernourishment affects the immune system, it is known that undernutrition impairs both innate and adaptive immunity (68). Indeed, undernutrition impairs the immune response by reducing the dendritic cells (DC) population, circulating B and T-lymphocytes, also decreasing the lymphocyte response to antigens and favouring Th2 cytokines profile over Th1 cytokines, with low levels of IL-2, IL-12, IFN-γ and so forth (68–70). The impairment of DC may have particular importance as the DENV has a tropism for DCs, macrophages, and monocytes. In addition, dengue virus infection triggers an inflammatory response with high plasmatic levels of chemokines and cytokines activated by non-infected DC since DENV impairs the DCs' function and suppresses the IFN signalling pathway response (71–73). Overall, these results suggest that undernourished dengue patients may have a lower inflammatory response due to having lower circulating DC and, consequently, are less susceptible to more severe manifestations of dengue. In previous studies, this association has also been related to a lower immune response (33,42,57).

In the additional analysis without the measure of height-for-age (H/A), the association between malnutrition and severe dengue was no longer found. Similar results were observed in a previous meta-analysis (74) and studies published (48,57). The few studies that specifically addressed the role of malnutrition as a risk factor for severe dengue provide suggestive evidence but no statistical relevance.

The variation in results may be explained by different definitions of malnutrition used in the analysis, as studies used distinct anthropometric measures to evaluate nutritional status. In particular, the study of Maneerattanasak and Suwanbamrung (57) brought up the concept of stunting – classified as low H/A – and it was an essential factor in understanding undernutrition as a protective factor for the severity of dengue in children, as it results from chronic undernutrition and chronic inflammation (68,75). Undernutrition is a cause and consequence of maintaining the course of this immune dysfunction in different forms (besides low H/A, but also wasting (low weight-for-age)). Therefore, multiple pathways are involved to impair the immune response in the face of an infection such as dengue fever (68).

Overnutrition and obesity have been associated with severe dengue fever. This association could be due to the chronic low-grade inflammation triggered by adipokines in adipose tissue, impairing endothelial and platelet function (76,77). Endothelial and platelet dysfunction may promote severe dengue manifestations, such as severe plasma leakage leading to shock or fluid accumulation with respiratory distress (76). Therefore, overnutrition could lead to more intense immune responses following a viral infection such as dengue virus infection.

Subgroup meta-analysis of study design revealed that overnutrition was a risk factor for developing severe dengue in both analyses, although case-control studies presented a higher odds ratio. This difference may have happened since case-control studies are commonly used to assess a correlation between one exposure and the severity course of a disease such as dengue fever (78,79). On the other hand, subgroup analysis based on dengue case classification showed overnutrition was not a risk factor for severe dengue in both analyses, dengue haemorrhagic fever (DHF)/dengue shock syndrome (DSS) or Severe dengue (SD). The concepts of DHF/DSS differ from WHO 2009 in terms of severity and clinical management (80). Since the reported dengue outcomes were adjusted in this review, comparisons or equivalences between different classifications of dengue cases may not be as accurate. DHF definitions are considered inadequate in describing all the nuances of the disease course of dengue fever. Regarding WHO 2009 Guidelines, although they might not fulfil all criteria for DHF, they do expand on how to recognise and predict the prognosis of a dengue patient to have better clinical management (80–82). Although both forest plots found no association, DHF/DSS analysis indicated a moderate heterogeneity (41.4%), which may be due to methodological differences and, therefore, could be more prone to confounding factors (83).

We found that overnutrition is a risk factor for hospitalisation and admission to UCI, as it correlates with the severity of dengue manifestations. Severe dengue manifestations may proceed to emergency states that require mechanical ventilation and shock (DSS) control, therefore leading to admission or a longer stay in the ICU (38,51). No associations were found between overnutrition and mortality. This result may be due to the fact that few articles evaluate dengue fever in relation to nutrition, leading to a less accurate analysis (84).

No association with overnutrition was found for DwWs. Nonetheless, this result could be explained by the fact that warning signs are unspecific symptoms that may not be directly related to the severity of dengue fever (85). However, when analysing classic early symptoms of dengue fever as epistaxis and increasing haematocrit with decreasing platelets, an association with the severity of dengue fever was found, as a hallmark of dengue fever severity is endothelial dysfunction (86), as described by Tan *et al.* (51) and Chiu *et al.* (37).

Most studies did not consider comorbidities as confounding factors that could directly affect nutritional status with immune impairment. Obesity, for example, is usually associated with metabolic syndrome, hypertension, and infectious disease complications (87–89). On the other side, malnutrition could also be associated with opportunistic infections such as pneumonia, anaemia or even gastroenteritis (90).

The present review has some limitations. Besides dengue classification and comorbidities, assessing nutritional status is a complex process that requires a comprehensive evaluation of the individual, as it involves the analysis of anthropometric measures and the intake of macro- and micronutrients (68). Therefore, the results cannot be accurately reported in this review as the analysis was based on anthropometric measures. In addition, most of the studies included in this review investigated individuals aged 0-18 years. As most studies enrolled hospitalised patients rather than the general population, our result could have a bias since that analysed more severe dengue cases. Publication bias is a concern for this review as it may have been driven by the small-study effect, which is the possibility of including small studies with overstated estimates while discounting those without statistically significant effects that may have a lower probability of being published (91).

Considering Southeast Asia is the main region approached in this review, most affected countries suffer from an overlap of socioeconomic problems, such as fragile health systems amidst political and economic instability, social inequalities and deficient basic sanitation, which results in fewer control measures for the proliferation of the mosquito, despite distinct serotypes prevalence (92,93). Similarly, undernutrition and overnutrition are mutually existent due to the socioeconomic problems mentioned above (19,94). Therefore, this study may be of considerable utility to regions that are also endemic to dengue fever, since they align with global trends in dengue endemic countries.

In conclusion, this systematic review and meta-analysis showed relevant associations between nutritional status and different severities of dengue fever disease, i.e., the risk for severe dengue and hospitalisation and ICU admission rates. However, further research on this issue is important to enable appropriate prognosis and access to medical care to better manage dengue fever according to the specificities of patients' clinical conditions.

DECLARATIONS OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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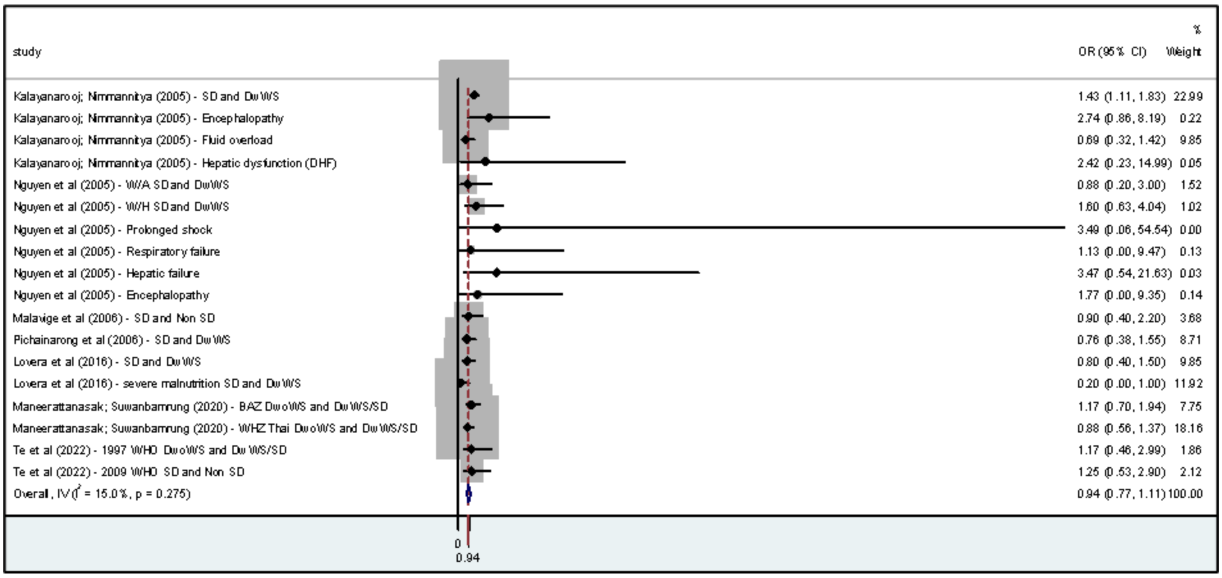
APPENDIX



Supplementary Figure 1 – Meta-analysis: Forest plot of the association between undernutrition and severe dengue without the measure height-for-age (H/A).

Abbreviations: OR, Odds ratio. CI, Confidence interval. Severe dengue. DwWS, Dengue with warning signs. DwoWS, Dengue without warning signs. W/A, weight-for-age. W/H weight-for-height. BAZ, BMI-for-age Z-score. WHZ, Weight-for-height Z-score.

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