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RESEARCH

Obesity as a risk factor for severe influenza infection in children and adolescents: a systematic review and meta-analysis

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Abstract

Obesity has been recently identified as a predisposing factor for a worse prognosis in viral illnesses such as SARS-CoV-2; however, its role in children with influenza is not yet clarified. The current systematic review and meta-analysis aims to assess whether obesity is a risk factor for either hospitalization or a worse prognosis when hospitalized among children infected by influenza. We systematically searched the following databases using a structured algorithm: MEDLINE, Clinicaltrials.gov, and Cochrane Central Register of Controlled Trials (CENTRAL). Statistical meta-analysis was performed using the "meta" package in R software, and included studies were evaluated using the Newcastle–Ottawa scale. Among children with influenza, obesity increased the odds of hospitalization with a pooled OR of 1.89 (95% CI [1.23, 2.9], $I^2=0$, $p=0.003$). When hospitalized, children with obesity were also more likely to have a worse outcome than their healthy-weight counterparts, with a pooled OR of 1.24 (95% Cl [1.02; 1.51], $I^2=11$, $p=0.03$). In an effort to lower heterogeneity, a leave-one-out meta-analysis was conducted. Publication bias was assessed with the visual inspection of funnel plots and the trim-and-fill method. Certainty assessment was evaluated using the GRADE score.

Conclusions: The findings of our meta-analysis suggest that obesity in children with influenza is associated with a worse prognosis, both hospitalization and ICU admission/death.

What is Known:
- *Obesity has been identified as a risk factor for non-communicable as well as communicable diseases.*
- *A previous meta-analysis failed to demonstrate a statistically significant association between obesity and influenza infection severity.*

What is New:
- *Children with high BMI and influenza infection are more likely to get hospitalized.*
- *Pediatric inpatients with increased BMI and influenza infection may have a worse prognosis.*

Keywords Obesity · Influenza · Risk factor · Hospitalization

Abbreviations

MMWR	Morbidity and mortality weekly report
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
CYA	Children and adolescents
ICU	Intensive care unit
NOS	Newcastle-Ottawa scale
CI	Confidence intervals
OR	Odds ratio
GRADE	Grading of Recommendations Assessment, Development and Evaluation
RR	Risk ratio
BMI	Body mass index

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Introduction

Rationale

An important finding during the SARS-CoV-2 pandemic is that obesity may be an independent risk factor for severe COVID-19 in children and young people [1, 2]. At the same time, we have learned about the exponential rise in childhood obesity (MMWR 21) due to prolonged quarantine measures that may consequently lead to a vicious circle of severe viral respiratory infections in children [3].

Recent translational research shows the inflammatory nature of excess adipose tissue that secretes cytokines and alters immune regulation in favor of the invading viruses. Maria Smith et al., in an attempt to explain the impact of obesity on influenza and coronavirus pathogenetic mechanisms, highlight, among others, the role of leptin resistance and lipotoxicity as well as the suppression of interferon induction and cytokine production in infected rodents and human hosts which may dampen their innate and adaptive immune responses [4]. In addition to childhood obesity's pro-inflammatory effects, mechanical as well as functional alterations on lung physiology have been highlighted, most commonly reduced lung compliance and abnormalities in lung volumes such as lower functional residual capacity (FRC) and FEV1/FVC ratios [5, 6].

As influenza infection still remains a major cause of morbidity among pediatric patients in Europe [7] and childhood obesity is reaching epidemic proportions [8], we aimed to revisit the literature concerning children with obesity infected with the influenza virus. In this regard, the most recent meta-analysis performed by Gill et al. [9] did not demonstrate a statistically significant relationship between childhood obesity and influenza-related complications, as opposed to other comorbidities. However, the numbers of patients included in the meta-analysis were considerably low to extract firm conclusions regarding the outcome of interest.

Objectives

In the current systematic review and meta-analysis, we aim to evaluate the association of obesity with influenza infection among pediatric patients.

Methods

Protocols and registration

The protocol of the present study has been registered in PROSPERO on the 6th of April 2022 (CRD42022315121).

Study design (eligibility criteria)

The current systematic review and meta-analysis is written according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [10]. The PRISMA checklist is presented in Supplementary Fig. 1. Every single study reporting data on children with obesity infected by influenza and disease severity was deemed eligible for inclusion. The study selection process was done in three consecutive steps. At first, the titles and abstracts of all search results were investigated and evaluated for relevance. The second step included full-text access to studies potentially suitable for inclusion. Finally, studies meeting our inclusion criteria were included in the systematic review, and studies reporting their results in an appropriate manner (i.e., quantitative) were included in the meta-analysis. Review articles, animal studies, and non-comparative studies (case reports, case series) were excluded. Any disagreement between the authors on the methodological approach, the retrieval of articles, and the statistical analysis was resolved through the consensus of all authors.

Inclusion criteria

Children and adolescents (CYA) less than 18 years old diagnosed with influenza infection or influenza-like illness during a period of known influenza circulation admitted in hospital settings or high dependency unit/intensive care unit (ICU).

Since childhood obesity prevalence is estimated to be 19,3% in the USA and 4 to 20% and 6 to 28% for girls and boys, respectively, in Europe, studies with a low obesity prevalence of less than 1% were excluded from the study [11, 12].

Literature search and data collection (information sources, search strategy, selection process, data collection process, data items)

Every single study reporting data on the prognosis of children/adolescents with obesity and influenza infection was eligible for inclusion. Data on obesity was collected for the following two outcomes: (1) hospitalized influenza patients vs. non-hospitalized influenza patients and (2) ward influenza inpatients vs. ICU influenza patients or deceased patients. Two reviewers (G.P.M., D.I.V.) applied the following structured algorithm: (obesity OR BMI OR "metabolic syndrome") AND (influenza OR "influenza-like illness" OR flu) AND (child* OR adolescent*) in the databases MEDLINE (1966–2022), Clinicaltrials.gov (2008–2022), and Cochrane Central Register of Controlled Trials (CENTRAL) (1999–2022). If necessary, the algorithm was altered and critical search terms were used instead, depending on the database interface. In order to achieve a wider assessment of the literature, in-text citations found within the included articles were manually screened (snowball method). No language or date restrictions were applied. The date of the last search was set at February 17, 2022. The flowchart of the literature is presented in Fig. 1. The extracted data from each study included the following: name of the first author, year of publication, study design, NOS scale evaluation, study population, country of origin, age range of the include population, month/year of enrollment, type of influenza, obesity definition, excluded populations, prevalence of obesity in the studied population, and outcome measured.

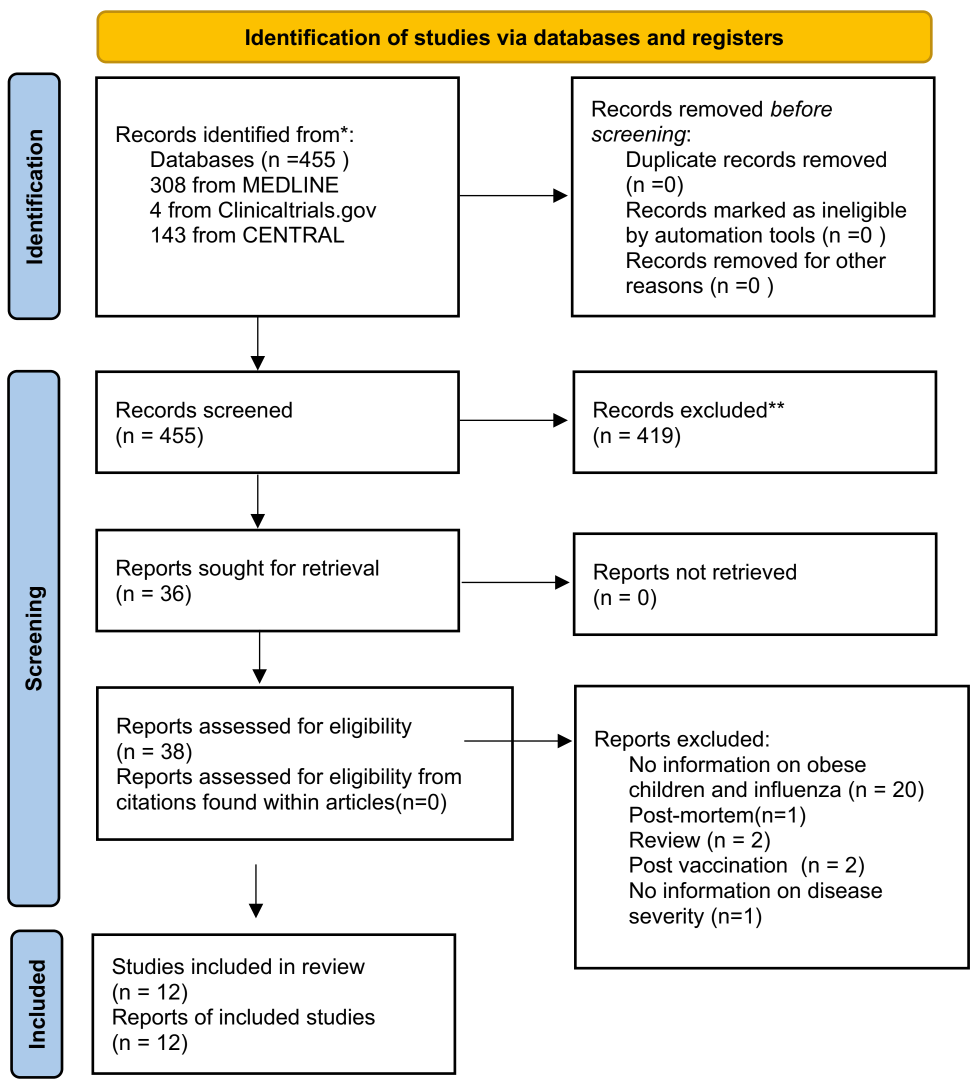
Study risk of bias assessment

Studies suitable for inclusion in our meta-analysis were independently evaluated by three researchers (G.P.M., D.I.V., P.K.) with the use of the Newcastle–Ottawa scale (NOS) [13]. This scale applies to nonrandomized studies and assigns stars (maximum score: 9) according to the selection of the study groups, comparability of the groups and the ascertainment of exposure (case–control) or outcome of interest (cohort studies).

Statistical analysis (effect measures, synthesis methods, reporting bias assessment)

The statistical meta-analysis was performed using the "meta" package in R software [14], and the confidence intervals (CI) were set at 95%. Heterogeneity among the included studies was substantial, according to the Cochrane Handbook [15], and therefore, the Der Simonian-Laird random effect model [16] was utilized to calculate odds ratios (OR) and 95% CI. Most included studies reported odds ratios; however, some did not but presented 2 × 2 tables from which we manually extracted odds ratios regarding our outcome of interest. As odds ratios are not normally distributed [17], we transformed

Fig. 1 PRISMA flow diagram 2020



them into logarithm odds ratios (logOR) in order to be able to meta-analyze them and then back-transform the final outcome into odds ratio (OR) for a better interpretation of the results. The influence of each individual study on the overall outcome was explored though leave-one-out meta-analysis; each study was consecutively omitted in order to evaluate its effect on the final estimate. Meta-regression analysis was not performed due to the fact that at least 10 studies are required in order for this analysis to be robust, according to the Cochrane Handbook [18]. Last but not least, publication bias was examined visually through funnel plots that were created together with the aid of the trim-and-fill method [19].

Certainty assessment

The credibility of outcomes was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework (ranging from very low to high). Examination of the quality of evidence was done through the following domains: study limitations, directness, consistency, precision, and publication bias [20].

Results

Study selection and study characteristics

A total of 455 studies were screened and assessed for inclusion in the current meta-analysis (see Fig. 1). Title and abstract screening led to the exclusion of 419 studies as data for children were not specified in these studies. A total of 26 studies were excluded after the full-text assessment. Two articles were reviews and therefore provided no odds ratio measure for our outcome of interest [21, 22]. One study was performed post-mortem and therefore did not provide any valuable information [23]. Two studies provided information post-vaccination [24, 25]. Another study provided no information regarding disease severity [26]. Last but not least, 20 studies failed to provide information on children with obesity and influenza infection [27–46].

Finally, a total of 7 studies were included in the quantitative analysis [47–53]. Five more studies [54–58] were included in the qualitative analysis. Study characteristics are presented in Table 1.

Risk of bias in studies

NOS scale assessment outcomes are shown in Table 1. Two studies (28,5%) scored 8 stars, two studies (28,5%) scored 7 stars, two studies (28,5%) scored 6 stars, and one study (14,2%) scored 5 stars.

Results of individual studies

Qualitative synthesis

In the USA, a study [57] on seasonal influenza using data from 274 US counties showed that a 5% increase in obesity in the pediatric population was associated with a 25% (RR 1·25, 95% CI 1·18, 1·32) increase in influenza-related hospitalization rates. A chart-review study [55] of 188 children hospitalized with seasonal influenza failed to show a significant association ($p = 0.61$) between severe obesity status (BMI ≥ 99% for age and gender) and influenza hospitalization or death due to influenza complications.

A multicenter study [54] conducted in Germany reported on 94 children hospitalized with H1N1 (2009) pandemic influenza, 6 of which needed ICU admission. In this cohort, 12 children had a BMI greater than the 90th percentile for age and sex, of which only 1 needed ICU admission. In contrast, in Taiwan, data from 61 children hospitalized with H1N1 (2009) pandemic influenza support that obesity is a significant risk factor for a worse prognosis [56]. This was not supported by the study of Ma et al. in Taiwan, where obesity was not associated with a worse prognosis for seasonal influenza pediatric cases [58].

Quantitative synthesis

A total of 7 studies were included in the meta-analysis. The analysis regarding obesity as a risk factor for hospitalization of children with influenza infection (see Fig. 2), including 4 studies [48, 49, 51, 52], led to a statistically significant association of children with obesity and hospitalization with a pooled OR 1.89 (95% CI [1.23, 2.9], $I^2 = 0$, $p = 0.003$). In addition, the analysis regarding obesity as a risk factor for a worse outcome after hospitalization (see Fig. 3), which included 4 studies [47, 48, 50, 53], showed a statistically significant association with a pooled OR equal to 1.24 (95% CI [1.02; 1.51], $I^2 = 11$, $p = 0.03$).

Results of syntheses

Leave-one-out meta-analysis

The leave-one-out meta-analysis is presented in Table 2. Regarding the outcome of poor prognosis among children with obesity already hospitalized, the sequential omission of each study provided estimates that ranged from 1.2254 (95% CI [0.9376; 1.6015] $I^2 = 40.1\%$) to 1.0756 (95% CI [0.8029; 1.4407] $I^2 = 0$).

Table 1 Study characteristics of the included studies on the impact of obesity on severe influenza infection in children and adolescents

Author, publication year	Country	Study type	Newcastle–Ottawa score (NOS)	Type of influenza (pandemic, seasonal)	Study population	Age range (in years)	Month/year of enrolment	Obesity definition	Obesity prevalence in the studied population	Excluded populations	Outcome
Okubo et al. 2017 [47]	Japan	Retrospective	8	Seasonal	27,771 patients hospitalized with bronchitis/pneumonia and influenza	0–18	07/2010–03/2015	Weight-for-length, weight-for-height and BMI according to WHO criteria	9.9%	Children with congenital diseases, malignancy, or autoimmune disease)	No association between obesity and likelihood of ICU admission [aOR: 1.00 95% CI (0.73–1.37); p:0.99]
Garcia et al. 2015 [48]	Texas	Retrospective medical record review	6	pH1N1 (2009)	696 patients with laboratory-confirmed influenza infection (316 non-hospitalized: 263 ICU admitted and 116 hospitalized with ICU admission)	0–18	04/2009–06/2010	Not mentioned	1.9%	Patients transferred from other healthcare organizations due to incomplete records	Obesity was associated with hospital admission (± ICU admission) only in the adjusted multivariate analysis [OR: 2.58, 95% CI (0.87–7.65), $p = 0.087$; aOR: 3.28, 95%CI (1.05–10.21) $p = 0.04$]
Plessa et al. 2010 [49]	Greece	Retrospective cohort	7	pH1N1 (2009)	51 hospitalized children with laboratory-confirmed influenza	0–13	10/2009–1/2010	BMI ≥ 95th percentile for age and sex according to 2000 CDC charts	16%	Not laboratory-confirmed influenza	No association between obesity and hospital admission
Morris et al. 2012 [50]	Canada	Retrospective	5	pH1N1 (2009) and seasonal	176 inpatients with pH1N1 and 200 patients with seasonal influenza. All laboratory-confirmed cases	0–18	2004–2009	BMI ≥ 95th percentile for age and sex according to 2000 CDC charts for > 2 years old	5,8%	Any children with influenza-like symptoms on or after the third day of admission	No association between obesity and ICU admission for pandemic [OR: 3.25, 95% CI (0.81–19.69)] [aOR: 4.18, 95% CI (0.76–22.95)] or seasonal influenza [OR: 1.14, 95% CI (0.22–5.99)] [aOR: 1.06, 95% CI (0.20–5.64)]
Moser et al. 2018 [51]	Mexico	Observational Cohort	8	Seasonal influenza and influenza-like-illness	1530 patients with laboratory-confirmed influenza or influenza-like illness (ILI)	0–18	04/2010–03/2014	2.0 < BMI z-score ≤ 3.0 according to WHO Child Growth standards	6.4%	Patients in the ER > 24 h and patients with missing information	Obesity was associated with hospital admission [OR: 2.20, 95% CI (1.32–3.74), $p = 0.002$]

Table 1 (continued)

Author, publication year	Country	Study type	Newcastle–Ottawa score (NOS)	Type of influenza (pandemic, seasonal)	Study population	Age range (in years)	Month/year of enrolment	Obesity definition	Obesity prevalence in the studied population	Excluded populations	Outcome
Campbell et al. 2017 [52]	USA	Retrospective case–control	6	seasonal	185 patients with laboratory-confirmed influenza infection and 185 healthy controls	2–18	01/2010–12/2013	BMI ≥ 95th percentile for age and sex according to 2000 CDC charts	11.08%	Missing data and no consent	No association between obesity and hospital admission ($p = 0.69$)
Yu et al. 2011 [53]	China	Retrospective	7	pH1N1 (2009)	3,577 patients hospitalized due to laboratory-confirmed influenza infection	2–17	09/2009–02/2010	BMI 95th–100th percentile in children aged 2–17 years (US criteria) or Chinese criteria	2%	NA	Obesity was associated with ICU admission [OR: 1.34, 95% CI (1.10–1.63); $p = .004$]
Wieching et al. 2012 [54]	Germany	Retrospective	-	pH1N1 (2009)	94 hospitalized patients with laboratory-confirmed influenza	0–18	07/2009–03/2010	≥ 99th percentile for age and gender	12.7%	Hospital infections (starting > 72 h after admission)	No association between obesity and severe influenza
Neyer et al. 2018 [55]	USA	Retrospective chart review	-	Influenza or Influenza-like-illness	188 hospitalized children with severe influenza complications	2–20	08/2010–06/2013	Severe obesity (BMI)	8%	Patients with missing anthropometric data	No association between severe obesity and hospitalization or death ($p = 0.61$)
Chen et al. 2012 [56]	Taiwan	Prospective medical record review	-	pH1N1 (2009)	61 hospitalized patients with laboratory-confirmed influenza	0–18	7/2009–12/2009	BMI ≥ 25 kg/m^2 in children ≥ 2 years of age, or a body weight ≥ 95th	6%	NA	Obesity was associated with the need for ICU care and/or death ($p = 0.008$)
Charland et al. 2013 [57]	USA	Retrospective	-	Influenza or influenza-like-illness	3.076.699 (adults and children)	0–18	2002–2008	Not mentioned	NA	Those meeting ICD code 487 criteria and not meeting ICD 486	A 5% increase in community childhood obesity was associated with a 25% ↑in hospitalization rate [RR:1.25, 95% CI (1.18–1.32)]
Ma et al. 2015 [58]	Taiwan	Retrospective	-	Seasonal	110 hospitalized patients with laboratory-confirmed influenza infection	Median age: 2.6 (IQR, 1.0–6.3)	8/2013–5/2014	Age-corrected normal range of BMI released by Taiwan Health Promotion Administration	14%	NA	No association between obesity and ICU admission ($p = 0.07$)

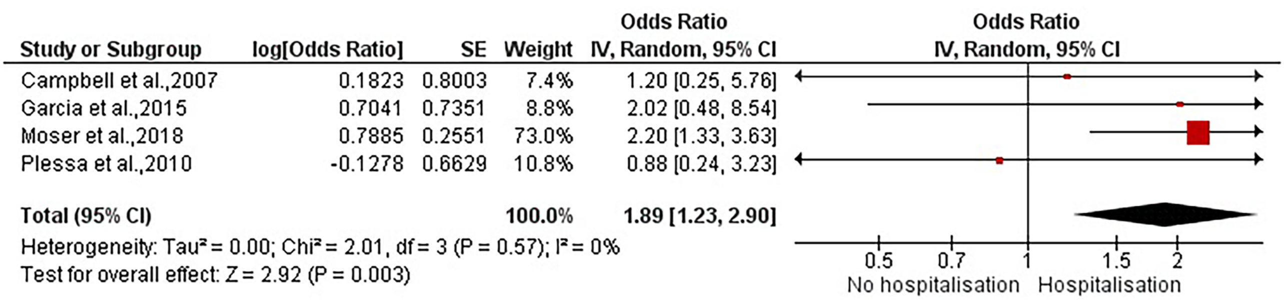


Fig. 2 Forest plot of the analysis regarding obesity as a risk factor for hospitalization of children with influenza infection

Reporting biases (publication bias)

Publication bias was evaluated with the use of funnel plots together with the aid of the trim-and-fill method. In the group regarding hospitalized and non-hospitalized children affected by Influenza, the visual inspection of the funnel plot raises high suspicion of publication bias due to its asymmetry. High suspicion of publication bias in this group is also confirmed by the trim-and-fill method as 2 missing studies were calculated (see Fig. 4). Furthermore, in the group regarding hospitalized children with influenza and children with influenza admitted to the ICU or with poor prognosis (death), the funnel plot extracted showcases a small asymmetry. Finally, this asymmetry (suspicion of publication bias) is also confirmed by the trim-and-fill method, as one missing study was calculated (see Fig. 5).

Certainty of evidence

The certainty of the evidence was moderate. Publication bias was suspected in both outcomes due to the calculation of missing studies from the trim-and-fill method. Finally, there were no major concerns with the directness, precision, and consistency domains in all outcomes. The GRADE approach is presented in Table 3.

Discussion

Childhood obesity has been associated with chronic low-grade systemic inflammation as well as a dysregulated immune response due to alterations caused by adaptive and innate immunity [59, 60]. This dysregulation of the immune system consists of an imbalance of cytokines, adipokines, immune cell subsets, and humoral factors that circulate in the excess adipose tissue [59] and has been linked with vulnerability to a variety of infectious diseases in addition to chronic non-communicable diseases [61]. Moreover, it was during the 2009 (H1N1) influenza A pandemic when obesity was first recognized as an independent risk factor for worse clinical outcomes in adults but evidence in children and young people remained scarce.

In this regard, a previous meta-analysis published in 2015 exploring possible risk factors for influenza-related complications and hospital admission, including 1782 children, reported that obesity was not a risk factor. However, the percentage of children with obesity was strikingly low (93 children) [7].

Another systematic review conducted by Mertz et al. including more than 60,000 adult and pediatric participants reveals that the evidence supporting risk factors for severe outcomes of influenza infection "*ranged from being limited to absent*." In particular, data on influenza infection outcome specific for children with obesity have not been provided. In contrast, the risk for children and adults with obesity has been estimated as a cumulative odds ratio as high as 2.77 for mortality (95%CI 1.90, 4.05) for pandemic influenza and 2.04 (95%CI 1.74, 2.39) for seasonal influenza, respectively. Finally, the authors suggest that the level of evidence was low for the specific outcome due to lack of power and lack of adjustment but not *very low* compared to other risk factors investigated.

Table 2 Leave-one-out meta-analysis

	Odds ratio (OR)	95% CI	*p*-value	τ^2	τ	I^2
Obesity as a risk factor for worse prognosis among hospitalized children infected by influenza						
Garcia et al., 2015	1.2183	[0.9934; 1.4942]	0.0579	0.0071	0.0841	17.8%
Morris et al., 2012	1.2254	[0.9376; 1.6015]	0.1366	0.0225	0.1501	40.1%
Okubo et al., 2017	1.3589	[1.1221; 1.6456]	0.0017	0.0000	0.0000	0%
Yu et al., 2011	1.0756	[0.8029; 1.4407]	0.6253	0.0000	0.0000	0%

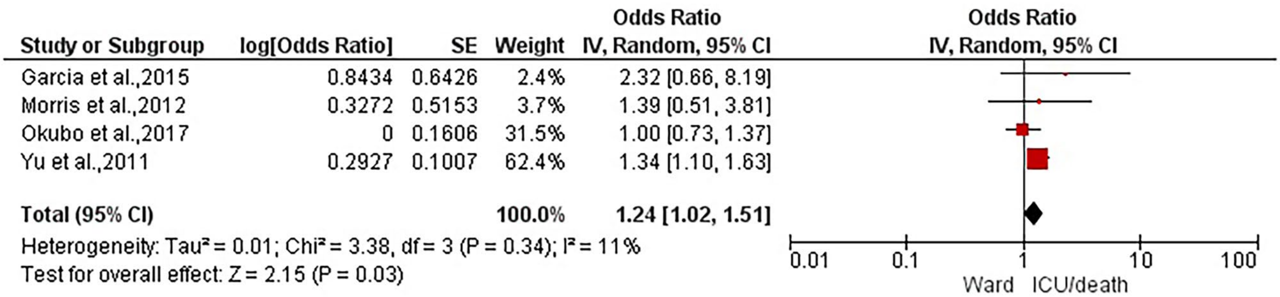
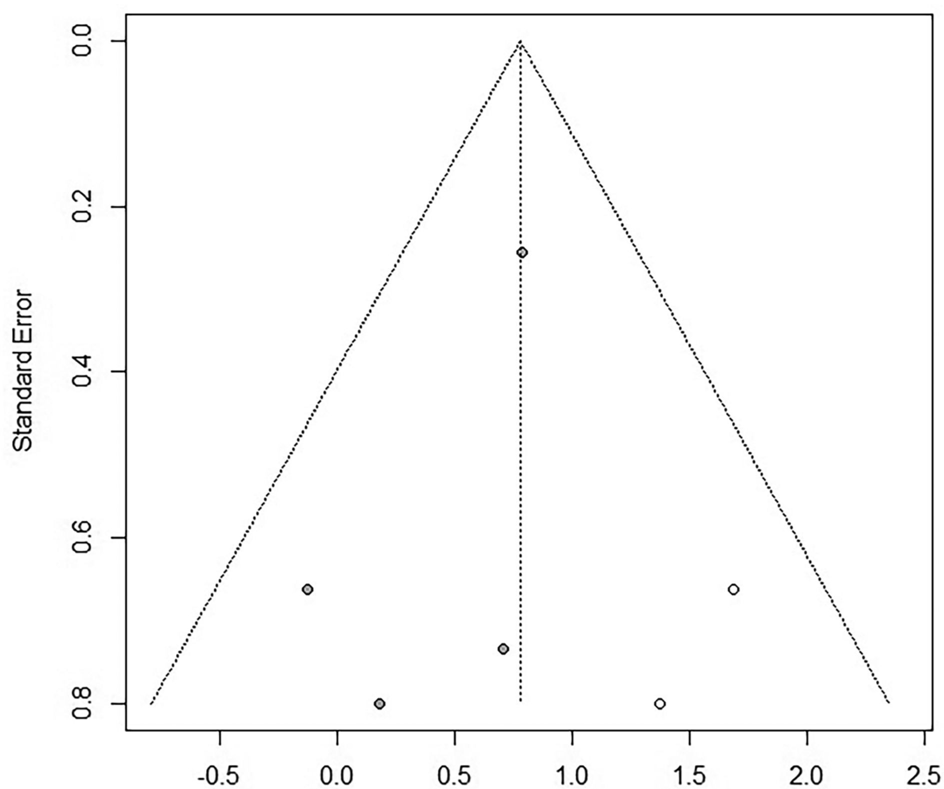


Fig. 3 Forest plot of the analysis regarding obesity as a risk factor for poor prognosis after hospitalization

Finally, Fezeu and colleagues conducted a systematic review and meta-analysis in order to explore whether obesity is linked to a higher likelihood of ICU admission or death in adult and pediatric patients with the 2009 pandemic influenza A (H1N1). The results of the sole study comprising of (59) pediatric patients [62] showed a 3.5-fold non-significant increase in the likelihood risk of ICU admission (OR: 3.50, 95%CI: 0.66–18.43) when patients had a BMI of more than 30 kg/m^2.

In our meta-analysis, obesity was found to be a risk factor for hospitalization as CYA infected with influenza were 89% more likely to be hospitalized (OR:1.89 (95% CI [1.23, 2.9], $I^2=0$, $p=0.003$), and already hospitalized patients with obesity were 24% (OR:1.24) more likely to have a worse prognosis in a statistically significant manner (95% CI [1.02;1.51], $I^2=11$, $p=0.03$). Leave-one-out meta-analysis was performed only in the group studying obesity as a risk factor for hospitalization and led to the lowering of I^2 to 0%. In addition, concerning both outcomes, there seems to be high suspicion of publication bias using both the visual inspection of funnel plots and the aid of the trim-and-fill method. Finally, the certainty assessment was moderate, mainly due to publication bias suspicion.

Fig. 4 Funnel plot of the analysis regarding obesity as a risk factor for hospitalization



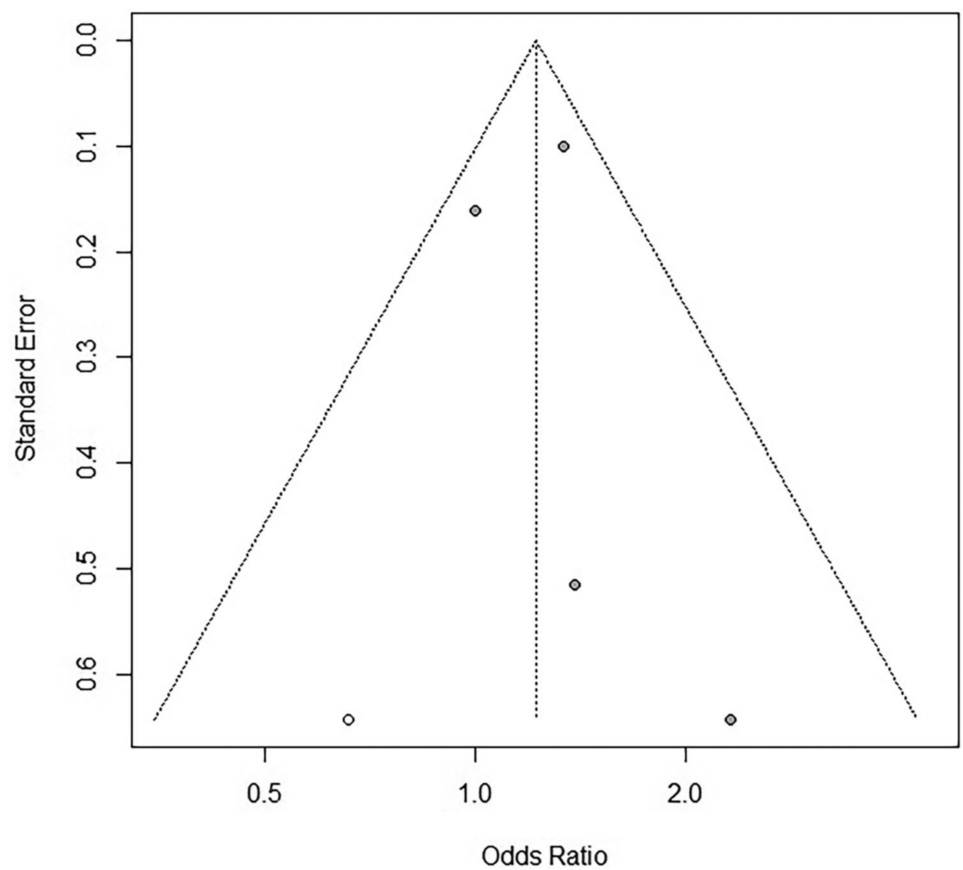


Fig. 5 Funnel plot of the analysis regarding obesity as a risk factor for poor prognosis after hospitalization

Strengths and limitations

This meta-analysis assessed whether obesity is a risk factor for hospitalization and whether it leads to an unfavorable outcome for hospitalized children. All databases were accessed using a structured algorithm, and therefore, strict inclusion criteria were met. Since most of the included studies were cohort studies, selection bias was eliminated. In the outcome regarding hospitalization, heterogeneity was non-existent, and in the outcome regarding worse prognosis, we managed to lower

Table 3 GRADE

Comparison	Study limitations	Directness	Consistency	Precision	Publication bias
Obesity as a risk factor for hospitalization among children infected by influenza	Moderate	Direct	Consistent	Precise	Suspected
Obesity as a risk factor for worse prognosis among hospitalized children (ICU admission/death)	Moderate	Direct	Consistent	Precise	Suspected
Subgroup	τ^2	**OR**	**95% CI**	**95% PI**	**Quality of evidence**
Obesity as a risk factor for hospitalization among children infected by influenza	0	1.891	[1.2336; 2.8986]	[0.7404; 4.8298]	⊕⊕⊕◯ ***Moderate***
Obesity as a risk factor for worse prognosis among hospitalized children (ICU admission/death)	0.0058	1.24	[1.0193; 1.5075]	[0.7219; 2.1287]	⊕⊕⊕◯ ***Moderate***

the inter-study heterogeneity with the aid of the leave-one-out meta-analysis. Ultimately, our publication bias evaluation was thorough, and it managed to present a high suspicion of publication bias through the trim-and-fill method.

The main limitation of this meta-analysis is that the results are based mostly upon crude odds ratios, which can lead to an overestimation of the true risk [63]. Moreover, the studies included are observational, implying that data were extracted in a non-standardized manner and underreporting may have occurred, introducing bias in the meta-analysis. Additionally, the quality of studies was not within the strengths of this meta-analysis, and our results describe a high suspicion of publication bias.

Finally, BMI *z*-scores and percentiles seem to be weakly associated with true adiposity in children [64]; thus, in most studies, BMI categories may not reflect the relevant immune dysfunction caused by obesity. The definition of obesity also varied between studies in the qualitative synthesis, limiting the ability to analyze the data.

Implications for practice and future research

Our meta-analysis shows a higher likelihood of severe influenza infection among children and adolescents with obesity. Policymakers and clinical practitioners may consider obesity among the risk factors for severe influenza when drawing preventive or therapeutic strategies including vaccination and prompt antiviral treatment. Furthermore, given the logarithmic rise of childhood obesity and morbid obesity in the SARS-CoV-2 pandemic era, public health policies should attempt to fight the obesity epidemic in order to counteract the unfavorable outcomes of viral infections in children. We believe our meta-analysis adds important clinical data on the management of obese children with influenza infection.

Conclusion

Our findings suggest that among children with influenza infection, children with obesity are at an increased risk of hospitalization or worse prognosis when hospitalized than their healthy-weight counterparts. For future research, to better evaluate the risk of children with obesity and influenza infection in the community, larger prospective cohort studies with well-defined obese populations are needed.

Registration and protocol CRD42022315121.

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Author contribution **Dimitra-Irinna Vitoratou:** study design, data curation, formal analysis, investigation, visualization, writing – original draft, writing – review and editing. **Gerasimos-Panagiotis Milas:** data curation, formal analysis, investigation, methodology, software, validation, visualization, writing – original draft, writing – review and editing. **Paraskevi Korovessi:** writing – review and editing, supervision. **Stavroula Kostaridou:** writing – review and editing, supervision. **Patra Koletsi:** conceptualization, study design, supervision, validation, writing – original draft, writing – review and editing.

Availability of data and material Not applicable.

Code availability Not applicable.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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