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REVIEW

Chronic low-level inflammation in childhood obesity: systematic review and meta-analysis of key biomarkers

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ABSTRACT

Childhood obesity is associated with chronic low-level inflammation, which is considered a key mechanism in the development of insulin resistance, dyslipidemia and increased cardiovascular risk. Increased levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP) and high-sensitivity CRP (hs-CRP) have been reported in children with obesity, but research results are contradictory, and pooled quantitative estimates of the levels of these biomarkers for the pediatric population have not yet been conducted.

The aim of the study was to systematize data on inflammatory biomarkers in children with obesity and to compare their levels quantitatively with control groups.

A systematic search of publications was conducted in the databases PubMed, Scopus, Web of Science, Semantic Scholar, e-Library and Google Scholar (until August 2025). Observational studies were included in children and adolescents aged 6–18 years with obesity diagnosed according to WHO criteria or national standards, which reported levels of CRP, hs-CRP, IL-6 or TNF-α.

The meta-analysis included 21 studies with a total of 11,193 participants. Children with obesity showed a significant increase elevated levels of all the inflammatory cytokines studied. The most pronounced difference was noted for CRP, g = –1.30 (95% CI: –2.32; –0.29), whereas hs-CRP, g = –0.70 (95% CI: –1.01; –0.39), IL-6, g = –0.51 (95% CI: –0.80; –0.21) and TNF-α, g = –0.60 (95% CI: –0.97; –0.24) demonstrated moderate, but stable and significant effects.

To our knowledge, this is the first meta-analysis to summarize data on inflammatory cytokines in children with obesity. hs-CRP showed a more moderate effect size but more stable and reproducible results which make it suitable for clinical use. Importantly, these findings gain additional significance when viewed in the context of studies in adolescents, adults, and the elderly, where dynamic of inflammatory cytokines are associated with subclinical vascular changes, cardiovascular events, and mortality. Elevated levels of these markers in childhood may serve as an early biological signal of long-term cardiometabolic risk.

Key Words: child; adolescent; pediatric; chronic disease; early diagnostic

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Introduction

Childhood obesity is accompanied by the formation of chronic low-level inflammation, which is considered as a key pathogenetic link in the development of insulin resistance, lipid metabolism disorders and cardiovascular complications. A number of studies have shown that the levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP) and high-sensitivity CRP (hs-CRP) in children with obesity are significantly higher than in their peers with normal body weight [1–4].

IL-6 and TNF-α are actively produced by adipose tissue, contribute to its infiltration by macrophages and maintenance of the inflammatory response, which is associated with the development of insulin resistance and other complications [5, 6]. CRP and hs-CRP reflect the release of inflammation to the systemic level and have high value as available markers of the risk of

developing insulin resistance, lipid metabolism disorders, non-alcoholic fatty liver disease and cardiovascular complications in children [3, 7, 8].

The research results remain contradictory: increased TNF-α is not detected in all samples [9], and the levels of CRP and hs-CRP can vary significantly even in the same child [10]. In addition, the influence of gender, age, stage of puberty, and regional characteristics on the levels of inflammatory markers has not been sufficiently studied [4, 11]. Furthermore, there are no pooled quantitative estimates of their levels specifically in children and adolescents with obesity, which determines the need for a systematic review and meta-analysis.

The aim of this meta-analysis is to systematize data on key inflammatory biomarkers (CRP, hs-CRP, IL-6, TNF-α) in children with obesity, to quantify the differences in each of them compared with the control groups, and to assess robustness of these effects depending on age and regional characteristics.

Methods

Eligibility criteria

The review included observational studies (cohort, cross–sectional, case-control) performed in children and adolescents aged 6 to 18 years with obesity, diagnosed according to the criteria of the World Health Organization (WHO) [12] or according to national standards (for example, International Obesity Task Force (IOTF) [13], Centers for Disease Control and Prevention (CDC) [14], Indian Academy of Pediatrics (IAP) [15]).

The control groups consisted of children with normal body weight. The main condition for inclusion was the availability of quantitative data on the levels of at least one of the inflammatory biomarkers – IL-6, TNF-α, CRP or hs-CRP, presented as mean with standard deviation (SD) or median and interquartile range (IQR), allowing the conversion of median and interquartile range to mean and SD according to the method of Wan et al. [16]. Publications in English, Russian and Chinese were taken into account.

Studies involving people over the age of 18, as well as studies involving patients with syndromic or monogenic forms of obesity, were excluded from the analysis. Publications in which participants had chronic inflammatory diseases (autoimmune, infectious, oncological, and others) were not included, there was no control group, or quantitative data suitable for calculating standardized mean differences (SMD) were not provided. Studies using inappropriate biological matrices (for example, saliva or urine), as well as interventional studies, were also excluded if they reported only post-therapeutic parameters without baseline values.

Data Synthesis and Analysis

For synthesis, studies were grouped by biomarkers: IL-6, TNF-α, CRP and hs-CRP. The main comparison was conducted between children with obesity and control groups with normal body weight. A subgroup analysis was provided by age (<12 years and ≥12 years), the region of the study and methods of biomarker analysis (serum or plasma, enzyme-linked immunosorbent assay (ELISA) and other methods). The ‘gender’ variable was not analyzed separately, since in most of the included studies, comparisons between groups were

carried out without calculating average values and SD by gender, and biomarker data were provided only for a combined (mixed) sample.

Information sources

The literature was searched in the following bibliographic databases: PubMed, Scopus, Semantic Scholar, Web of Science, eLibrary and Google Scholar. Additionally, a manual search was performed through the literature lists of the included publications and previously published reviews. The literature search covered the period from January 2010 to July 2025. Search completion date: August 27, 2025.

Search strategy

The search was conducted using combinations of keywords and MeSH terms covering the topics of obesity, childhood, and inflammatory biomarkers (IL-6, TNF-alpha, CRP, and hs-CRP). Example of a search query used in the PubMed database: ("Obesity"[Mesh] OR obesity [tiab] OR obese[tiab]) AND ("Child"[Mesh] OR child*[tiab] OR adolescent*[tiab] OR pediatric[tiab]) AND ("C-Reactive Protein"[Mesh] OR CRP[tiab] OR hs-CRP[tiab] OR "Interleukin-6"[Mesh] OR IL-6[tiab] OR "Tumor Necrosis Factor-alpha"[Mesh] OR TNF-alpha[tiab]) AND ("2010/01/01"[Date – Publication]: "2025/07/31"[Date – Publication]).

The search expressions have been adapted to the syntax of each database. Publications containing a comparison of biomarker levels in obese and normal-weight children were taken into account, preferably indicating the mean, SD, and sample size. A manual search was also conducted through the literature lists of the included publications.

Data collection and selection process

The data extraction and selection process were performed by two independent reviewers using standardized tables (M.U. and X.D.). In case of discrepancies, a discussion was held before the agreement. When necessary, supplementary materials (e.g., appendices) were consulted for clarification. Automated tools were not used for data extraction and selection process.

Data items

The main outcomes were quantitative indicators of the levels of inflammatory biomarkers: IL-6, TNF-α, CRP and hs-CRP. Values presented as the mean with SD or median and IQR were extracted from each study, followed by conversion using standard methods.

If the study reported data on the same biomarker at several time points or subgroups, the baseline values presented for the entire sample were selected for the main analysis. When several suitable measurement methods were available in a single study, priority was given to values obtained from serum or plasma and the most widely used laboratory methods (for example, ELISA).

Additionally, data on the following characteristics were extracted: age of participants, gender, region of the study, degree of obesity, biological matrix (serum, plasma, urine, saliva), biomarker analysis method (ELISA, immunoturbidimetry), as well as criteria for the diagnosis of obesity (WHO, IOTF, CDC, IAP). If the study lacked clear indications of obesity criteria or a matrix, assumptions were made based on the context: the text of the method, tables, or standards adopted in the country of the study.

Risk of bias and certainty evidence

The methodological quality (risk of bias) was assessed by two independent reviewers (M.U. and X.D.) using the Newcastle–Ottawa Scale, adapted for cross-sectional and cohort studies. Each study was evaluated in three domains: selection of participants, group comparability, and ascertainment of the outcome.

Funnel plots were used to assess the risk of publication bias, as well as the Egger's regression test for asymmetry with a number of studies included of ≥10. In addition, the resilience index (fail-safe N) was calculated evaluate the robustness of the pooled result to potential unpublished data.

Certainty of the evidence for each biomarker (IL-6, TNF-α, CRP/hs-CRP) was assessed using a GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation). The assessment took into account: the risk of bias, inconsistency of results, indirectness, imprecision of estimates, and the likelihood of publication bias.

Synthesis methods

The SMD with the Hedges' g correction was used as the primary effect measure for all outcomes: IL-6, TNF-α, CRP and hs-CRP. 95% confidence intervals (95% CI), statistical significance (p-values), and measures of heterogeneity were indicated for each result.

The inclusion of studies in the quantitative synthesis was based on pre-established criteria. A separate meta-analysis was performed for each biomarker (IL-6, TNF-α, CRP/hs-CRP). Studies that presented averages and SD or medians and IQR with the possibility of conversion according to Wan et al., [16] were included in the calculation of the SMD. Studies without a control group or quantitative data were analyzed only descriptively.

Conversion of medians, conversion of units. In order to present the data in a single format, in some cases, the conversion of indicators was performed. In the absence of averages and SD, but with a median and IQR, calculations were performed using the Wan et al., [16] method. In cases where only quartile values Q1 (first quartile), median and Q3 (third quartile) were presented, the formulas were used: Mean = (Q1 + Median + Q3) / 3; SD = (Q3 – Q1) / 1.35. Studies without the possibility of restoring missing quantitative indicators (for example, if there are only percentages or only graphs) were not included in the meta-analysis. All transformations were recorded in the data extraction table.

To visually present the results, tables with the characteristics of the included studies were used, as well as forest plots constructed separately for each biomarker. The tables included information about the country, design, age, sample size, biomarkers, analysis methods, and criteria for diagnosing obesity. The forest plots displayed a standardized difference in averages (Hedges' g) with 95% CI for each study and the overall effect. Visualization was performed using the MAJOR module in Jamovi.

For the meta-analysis, a random-effects model was used with a variance estimate using the REML (Restricted Maximum Likelihood) method, which allowed for the expected clinical and methodological heterogeneity between studies. Effect sizes were calculated as SMD. Accordingly, negative SMD values indicate higher biomarker concentrations in children with obesity, whereas positive values indicate higher concentrations in the control group.

To assess heterogeneity, the statistics I^2 (percentage of variation due

to heterogeneity), τ^2 (estimate of the variance of random effects) and the Cochran Q-test (Q) with the corresponding p-value were used. All calculations were performed in Jamovi version 2.6.44 using the MAJOR (Meta-Analysis & Joint Regression) module. Heterogeneity was assessed using a subgroup analysis by age (<12 and ≥12 years), region, and biomarker analysis methods. The variable "gender" was not taken into account, as most studies provided data only for mixed samples. To assess the robustness of the results, a sensitivity analysis was carried out with the alternate exclusion of individual studies. Additionally, models with fixed and random effects were compared. There were no significant changes in the final estimates.

Direction of effect

For all inflammatory biomarkers included in the meta-analysis (CRP, hs-CRP, IL-6, TNF-α), SMD were calculated as mean_control – mean_obesity. Because children with obesity consistently demonstrated higher concentrations of these biomarkers across studies, this calculation results in negative SMD values.

According to Cochrane recommendations for continuous outcomes [17], effect directions may be inverted for graphical clarity; however, the original direction was retained to preserve consistency with the extracted data and to avoid additional data transformations.

Therefore, across all forest plots, negative SMD values indicate higher biomarker levels in the obesity group, whereas positive values would indicate higher levels in the control group.

Results

Study selection

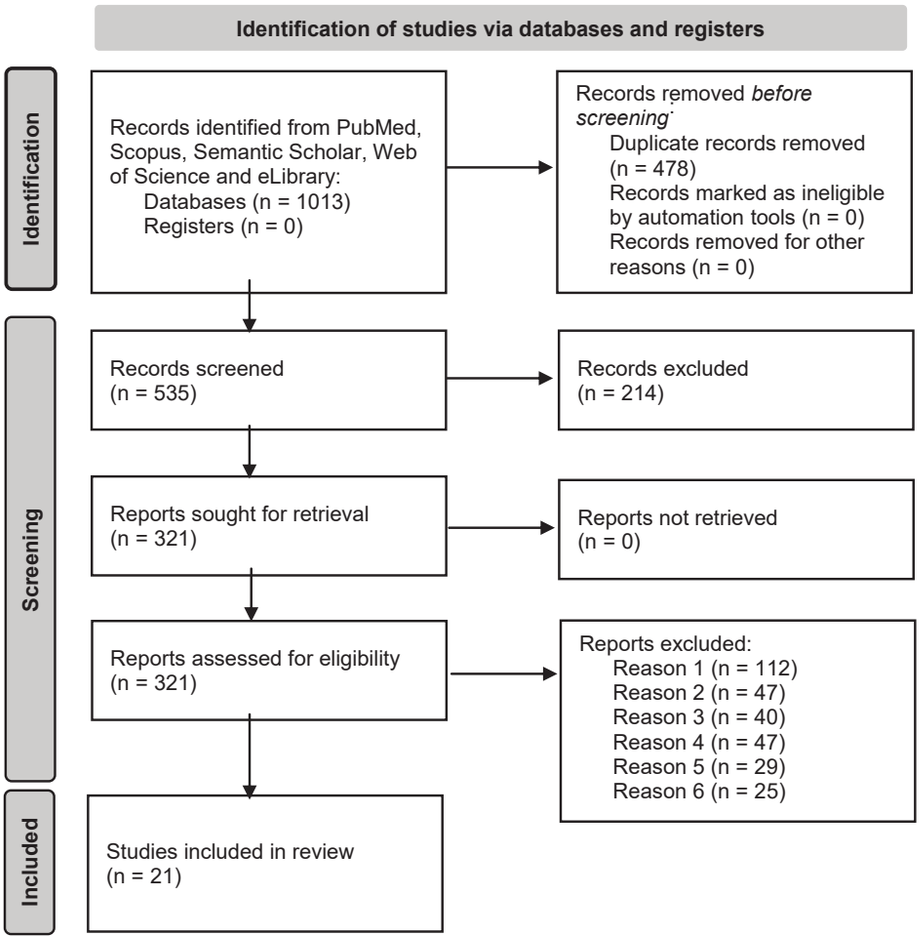
The systematic search across six bibliographic databases yielded 1013 records. After duplicates were removed and automatic filtering based on their relevance, 535 publications were allowed to be screened. At the initial review stage (titles and abstracts), 214 entries were excluded. The full texts of the remaining 321 studies were assessed for eligibility, of which 300 publications were excluded for the reasons shown in the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) diagram (Fig. 1). The meta-analysis included 21 studies, with a total cumulative sample size of 11,193 children and adolescents (6038 children with obesity and 5155 normal-weight peers). The age of the participants ranged from 6 to 18 years old, and in most of the studies, the samples were mixed by gender. The geography of the research covered Europe, Asia, America and the Middle East.

The reasons for excluding publications at the stage of analyzing the full text are presented in the PRISMA Flow Diagram (Fig. 1). The main reasons included: lack of quantitative data, use of an inappropriate biological matrix (for example, saliva or urine), absence of a control group, and methodological limitations. A full list of excluded publications with reasons is available on request.

Study characteristics

The review included 21 studies published between 2010 and 2025. Geographically, the studies covered countries in Europe, Asia, North and South America, as well as the Middle East. Most of the studies had a cross-sectional

FIG. 1. PRISMA 2020 Flow Diagram for Study Selection



Note: Of the 321 full-text articles assessed for eligibility, 271 were excluded for the following reasons: (1) no relevant biomarkers assessed (n = 112); (2) inappropriate biological matrix, such as saliva or urine (n = 47); (3) no control group (n = 40); (4) insufficient quantitative data for meta-analysis (n = 47); (5) conference abstract, thesis, book chapters or book (n = 29); (6) other reasons, including adult samples, syndromic obesity, or post-treatment data only (n = 25).

design; cohort and case–control studies were less common. The age of the participants ranged from 5 to 18 years, while in most cases the analysis was carried out on samples of mixed gender. The sample size ranged from 20 to more than 500 participants. Obesity was diagnosed according to WHO, IOTF, CDC criteria or national standards (for example, IAP).

The studies differed in the type of biomarkers studied (IL-6, TNF-α, CRP, hs-CRP), the method of laboratory analysis (ELISA, immunoturbidimetry, etc.) and the biological matrix (serum, plasma, urine, saliva). Detailed characteristics of each study are presented in Table 1.

Exercise effects on C-reactive protein

Pooled data from 12 studies assessing the level of CRP in children with obesity are shown in the forest plot (Fig. 2). The combined score was g = –1.30 (95% CI: –2.32; –0.29), p = 0.012, indicating a statistically significantly higher CRP level in children with obesity. Heterogeneity turned out to be extremely high (I^2 = 99.09%, Q(11) = 195.62, p < 0.001, τ^2 = 3.15), indicating significant

Table 1. Characteristics of the included studies

Report label, Country; design	Sample size (OB / C)	Age (mean or range), years	Sex (M/F)	Biomarkers Measured	Matrix	Method	Obesity definition	Comparison groups	Risk of Bias
Aleman_2024, Argentina, CS [18]	58 / 20	9–12	M/F	IL-6, TNF-α, hs-CRP	Plasma	ELISA, chemilumi-nescence	WHO BMI percentile > 97%	OB vs NW (sex-split)	Medium
Gokulakrishnan_2024, India, CS [19]	40 / 40	5–18	M/F	IL-6, hs-CRP	Serum	ELISA (Abbkine, DBC)	BMI ≥27 (IAP criteria)	OB vs NW	Medium
Kassem_2022, Israel, CS [20]	63 / 64	10–12	Mixed	CRP	Serum	Roche, Cobas-8000	WHO BMIZ >2 SD (2007)	OB vs NW	Medium
Cura-Esquivel_2023, Mexico, CS [21]	86 / 21	6–18 (mean ≈ 10.5)	Mixed	IL-6, TNF-α, MCP-1, CRP	Serum	ELISA (Bio-Techne, etc.)	BMI ≥85th percentile (CDC)	OB vs NW	Medium
Skvortsova_2025, Russia, CS [22]	188 / 23	10–15	Mixed	IL-6, TNF-α, CRP	Plasma	ELISA (Vector-Best)	SDS BMI > +2 (WHO)	OB vs NW	Medium
Lang_2024, USA, CS [23]	48 / 59	6.6 ± 2.7	Mixed	IL-6, CRP, TNF-α	Plasma	Bio-Plex ELISA + Lab	CDC BMI percentiles	OB vs NW	Low
Podeanu_2025, Romania, CS [24]	50 / 18	6–14 (median 10.5)	Mixed	Ferritin, Iron, CRP, IL-6	Serum	ELISA + Clinical Chemistry	BMI ≥ 95th percentile (WHO)	OB vs NW	Medium
Marginean_2019, Romania, CS [25]	77 / 87	5–18	Mixed	CRP	Serum	Cobas Integra 400 (Roche)	BMI percentile ≥85 (CDC/WHO)	OB vs NW	Medium
Fernandez_2025, Spain, CS [26]	39 / 0	10–14	Mixed	IL-6, TNF-α	Serum	ELISA (R&D Systems, Abyntek)	BMI >85th percentile (WHO)	OB vs NW	High
Giordano_2011, Italy, CS [27]	59 / 40	Median 11.8 (2.3–15.1)	Mixed	hs-CRP, TNF-α	Serum	ELISA, immuno turbidimetry	BMI > 95th percentile (Italy)	OB vs NW	Medium
Chavira_2020, Mexico, CS [28]	46 / 77	8.8 ± 1.3	Mixed	IL-6, TNF-α, CRP	Serum	Luminex (Milliplex)	BMI > +2 SD (WHO)	OB vs NW	Low
Yasin_2023, UAE, CS [29]	57 / 57	6–13 (mean ≈10.6)	M:40/F:17 per group	hs-CRP, IL-6, TNF-α	Serum	ELISA	CDC BMI ≥ 95th percentile	OB vs NW	Medium
Christaki_2022, Greece, CS [30]	81 / 40	8.93 ± 2.23	F:78 / M:43	hs-CRP, cortisol, insulin	Serum	ELISA, ECLIA, Nephelometry	BMIZ (IOTF)> 1	OB vs NW	High
Simoes_2021, Brazil, CS [31]	43 / 49	12–17	F:22/24, M:21/25	IL-6, IL-13, IL-10, TNF-α	Serum	Luminex xMAP	BMIZ ≥ 2	OB vs Eutrophic	Medium
Wolters_2024, Europe (8 countries), long [32]	340 / 1108	6.6 – 12.4	Mixed	IL-6, CRP, TNF-α	Serum	ELISA + model-based est.	BMI z-score ≥ 2	OB vs NW	Low
Tam_2010, Australia, long [33]	23 / 36	15	Female	IL-6	Serum	Multiplex bead assay	IOTF (BMI ≥ 85th %)	OB vs NW	Medium
Lund_2020, Denmark, CS [34]	1353 / 839	6–18	Mixed	hs-CRP, WBC, resistin	Serum	ELISA, immuno-fluorescence	Danish BMI percentiles	OB vs NW	Low
Chang_2015, Taiwan, CS [35]	19 / 16	6–13	Male	hs-CRP, IL-6, TNF-α	Plasma	ELISA	BMI ≥ 95th percentile	OB vs NW	Medium
Juliaty_2021, Indonesia, CS [36]	40 / 40	13–15	Mixed	hs-CRP, TNF-α, IL-6	Serum	ELISA	BMI ≥ 95th percentile	OB vs NW	Medium
Marginean_2020, Romania, CS [5]	91 / 102	5–18	Mixed	CRP, IL-6, TNF-α	Serum	ELISA	BMI ≥ 85th percentile	OB + OW vs NW	Medium
Maffeis_2022, Italy, cc [37]	56 / 28	6–17	Mixed	TNF-α, IL-6, IL-10, IL-33	Serum	ELISA	WHO > +1 SD	OB + Asthma vs NW + Asthma	Medium

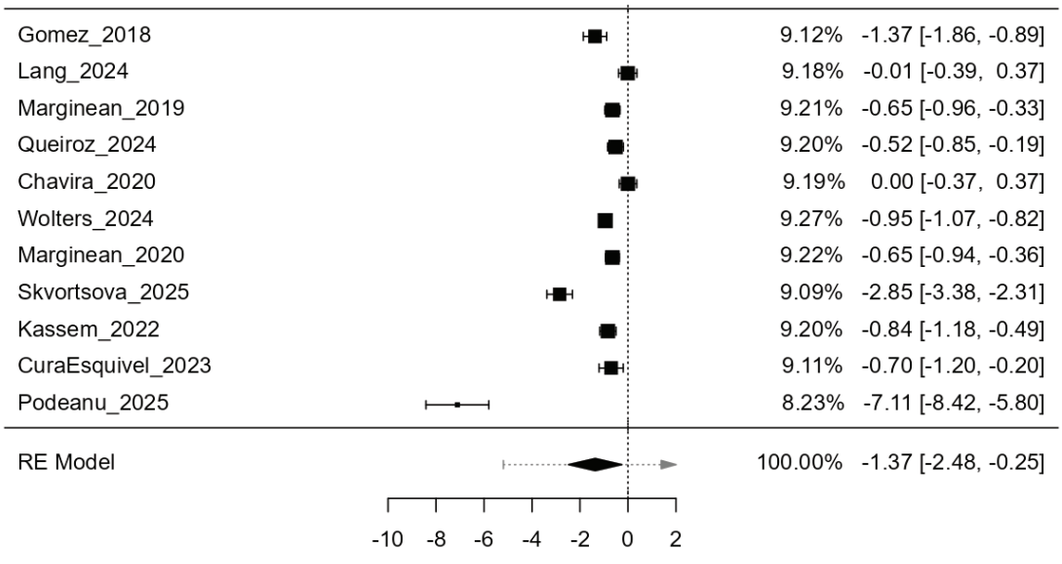
Note: In studies where the initial data were presented as median and IQR, the mean values and standard deviations were calculated using the method of Wan et al. [16], if possible. The main characteristics of the studies (n = 21) included in meta-analysis: country of origin, design, sample size, age, biomarkers, methods of analysis and criteria of obesity.
BMI – body mass index; BMIZ – body mass index z-score; C – control; CC – case-control (case-control study); CDC – Centers for Disease Control and Prevention; CRP – C-reactive Protein; CS – cross-sectional (cross–sectional study); ECLIA – electrochemiluminescence immunoassay; ELISA – enzyme-linked immunosorbent assay; hs-CRP – high-sensitivity C-reactive protein; IAP – Indian Academy of Pediatrics; IL-6 – interleukin-6; IL-10 – interleukin-10; IL-13 – interleukin-13; IL-33 – interleukin-33; IOTF – International Obesity Task Force; IQR – the interquartile range; long – longitudinal (longitudinal study); M/F – male/female; mean ± SD – mean with standard deviation; MCP-1 – monocyte chemoattractant protein-1; mixed – combined (non-segregated by gender) sample; NW – normal weight; OB – obesity; OW – overweight; SDS – standard deviation score; TNF-α – tumor necrosis factor-α; WBC – white blood cells; WHO – World Health Organization.

variability between studies. The analysis of the publication bias revealed the asymmetry of the funnel plot and a statistically significant result of the Egger test ($p < 0.001$), which suggests the presence of a publication bias.

Exercise effects on highly sensitive C-reactive protein

Pooled data from 7 studies assessing the level hs-CRP in children with obesity are shown in the forest plot (Fig. 3). The combined score was $g = -0.70$ (95% CI: –1.01; –0.39), $p < 0.001$, which indicates a statistically significantly higher level of hs-CRP in children with obesity compared with normal-weight peers. Heterogeneity was moderately high ($I^2 = 77.96\%$, $Q(6) = 22.58$, $p < 0.001$, $\tau^2 = 0.12$), indicating the presence of variability between studies. Checking for publication bias did not reveal significant asymmetry: the Begg's test ($p = 0.773$) and the Egger regression test ($p = 0.776$) did not reach the level of statistical significance. Thus, the presence of a pronounced bias in publications is not confirmed.

FIG. 2. Forest plot showing standardized mean differences (Hedges' g) and 95% confidence intervals for C-reactive protein levels in children with obesity compared with normal-weight peers

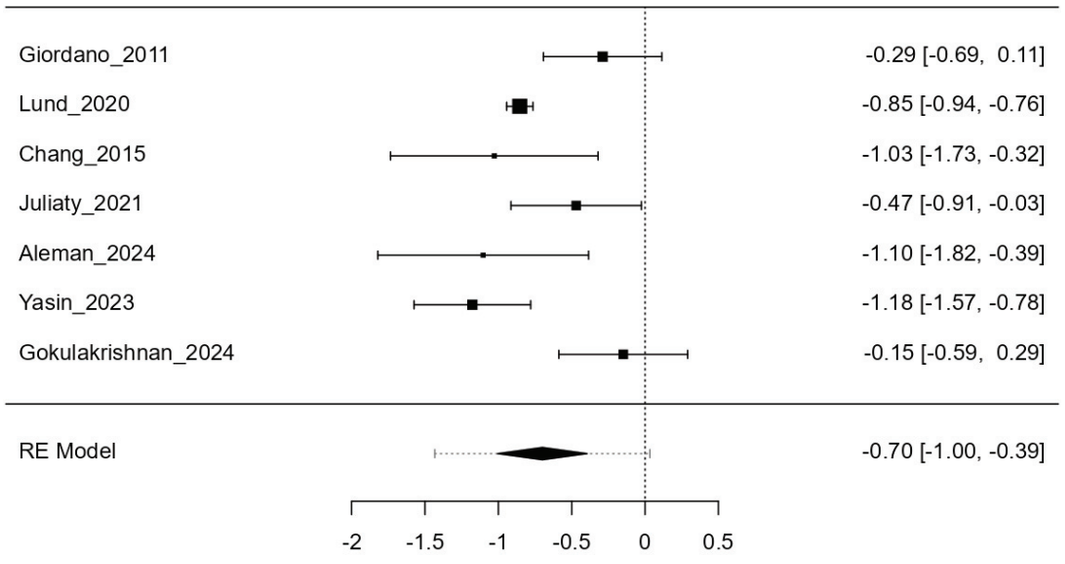


Note: The standardized mean difference (SMD) was calculated as the difference between the control group (group one) and the obesity group (group two). Accordingly, negative SMD values indicate higher biomarker concentrations in children with obesity, whereas positive values indicate higher concentrations in the control group. For example, for C-reactive protein, negative values on the left side of the forest plot reflect higher levels in the obesity group.
RE Model – random-effects model.

Exercise effects on interleukin-6

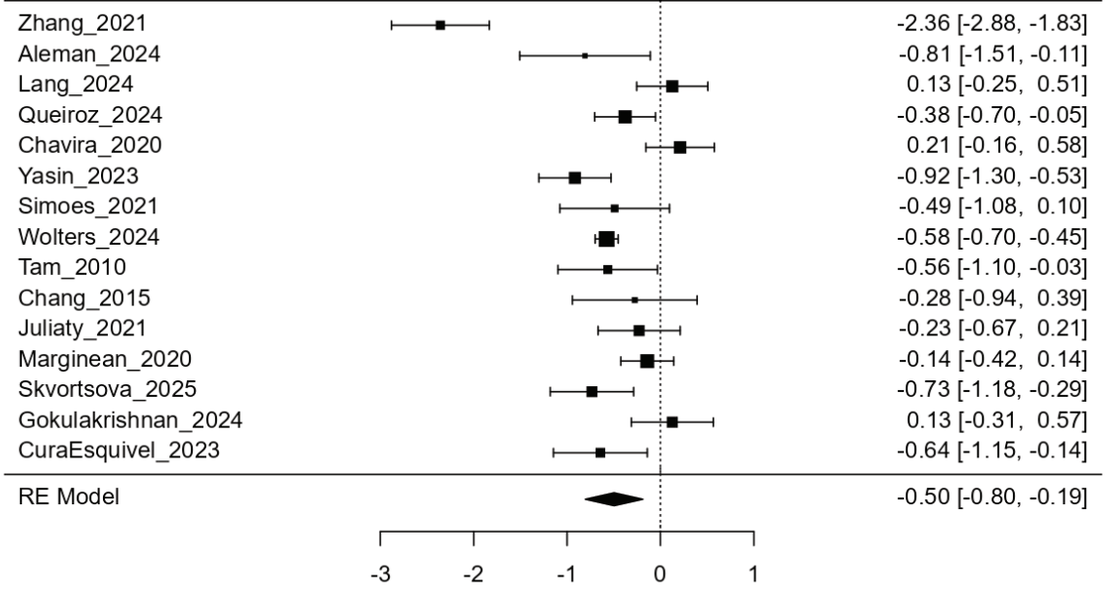
Pooled data from 15 studies assessing the level of IL-6 in children with obesity are shown in the forest plot (Fig. 4). The combined score was $g = -0.51$ (95% CI: –0.80; –0.21), $p < 0.001$, indicating statistically significantly higher levels of IL-6 in children with obesity compared with normal-weight peers. Heterogeneity analysis revealed a high level of variability between studies ($I^2 = 89.37\%$, $Q(15) = 97.71$, $p < 0.001$, $\tau^2 = 0.30$). The indicators for assessing publication bias showed no signs of asymmetry: the Begg test ($p = 0.306$) and the Egger test ($p = 0.332$) were statistically insignificant. the trim-and-fill method did not impute any missing studies, which indicates that there is no pronounced publication bias.

FIG. 3. Forest plot showing standardized mean differences (Hedges' g) and 95% confidence intervals for the level of highly sensitive C-reactive protein in children with obesity compared with normal-weight peers



Note: Negative values indicate higher highly sensitive C-reactive protein in children with obesity. The standardized mean difference was calculated as control minus obesity; thus, negative values indicate higher biomarker levels in children with obesity and positive values indicate higher levels in controls. RE Model – random-effects model.

FIG. 4. Forest plot showing standardized mean differences (Hedges' g) and 95% confidence intervals for interleukin-6 levels in children with obesity compared normal-weight peers

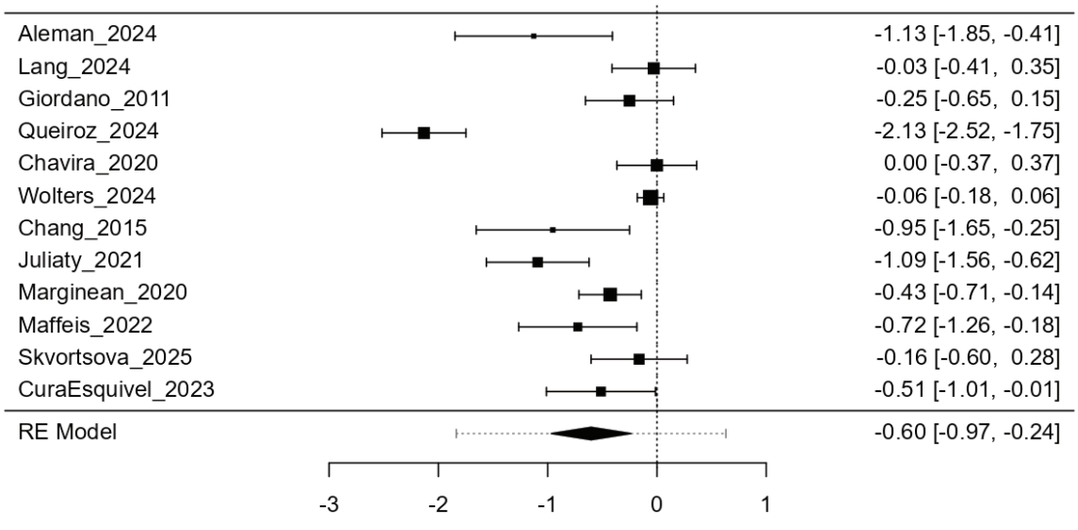


Note: Negative standardized mean difference (SMD) values correspond to higher interleukin-6 levels in the obesity group. SMD was calculated as control minus obesity; thus, negative values indicate higher biomarker levels in children with obesity and positive values indicate higher levels in controls.
RE Model – random-effects model.

Exercise effects on tumor necrosis factor-α

The level of TNF-α was significantly higher in children with obesity compared with normal-weight peers. According to the data of 12 included studies, the SMD was g = –0.60 (95% CI: –0.97; –0.24), p = 0.001, which indicates the presence of a stable effect. Heterogeneity analysis revealed a high degree of inter-study variability (I^2 = 91.86%, Q(11) = 130.77, p < 0.001, τ^2 = 0.36), reflecting differences in sample characteristics, measurement methods and study designs. Visualization of individual and combined effects is shown in the forest plot (Fig. 5).

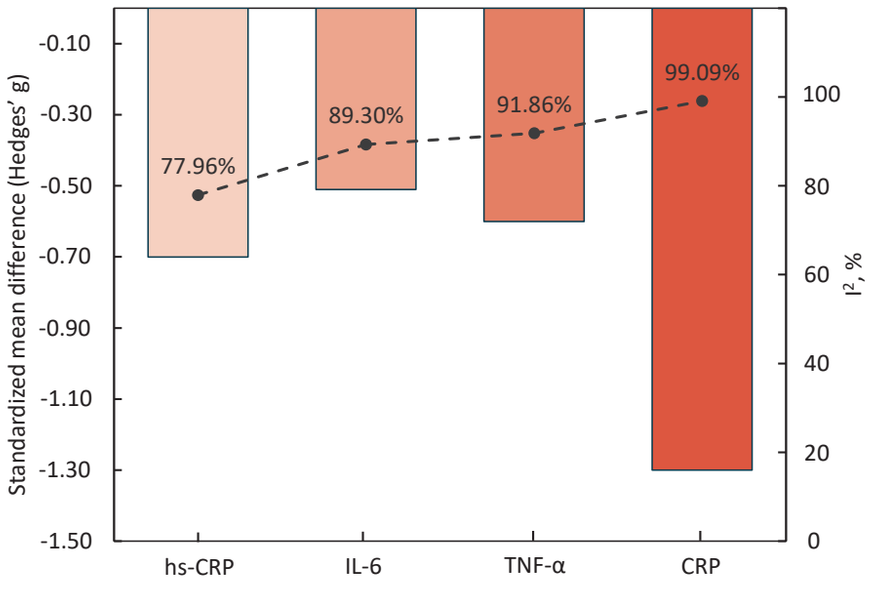
FIG. 5. Forest plot showing standardized mean differences (Hedges' g) and 95% confidence intervals in the levels of tumor necrosis factor-α in children with obesity compared with normal-weight peers



Note: Negative standardized mean difference (SMD) values indicate higher tumor necrosis factor-α in children with obesity. SMD was calculated as control minus obesity; thus, negative values indicate higher biomarker levels in children with obesity and positive values indicate higher levels in controls.
RE Model – random-effects model.

The meta-analysis confirmed that the levels of all the studied biomarkers of inflammation (CRP, hs-CRP, IL-6 and TNF-α) in children with obesity are statistically significantly higher than in their peers with normal-weight peers. The largest effect size was observed for CRP (g = –1.30), which indicates its high sensitivity to inflammatory changes, whereas for hs-CRP (g = –0.70), IL-6 (g = –0.51) and TNF-α (g = –0.60), the effects were moderate. At the same time, the differences between the studies were characterized by substantial heterogeneity, the highest for CRP ($I^2 \approx 99\%$), slightly lower for IL-6 and TNF-α ($I^2 > 89\%$), and relatively lower for hs-CRP ($I^2 \approx 77\%$) (Fig. 6). This leads to the conclusion that, despite the greater effect of CRP, hs-CRP is a more reproducible marker in clinical and epidemiological studies. Additional analysis by age and geographical region revealed no significant moderating effects, which indicates the universality of the observed association. Taken together, these results confirm that CRP and hs-CRP are the most informative markers of inflammation in children with obesity, while hs-CRP is characterized by better stability of assessment, while IL-6 and TNF-α provide valuable insights into the chronic inflammatory status, but are less reliable due to the high heterogeneity of data.

FIG. 6. Inflammatory Biomarkers in Pediatric Obesity



Note: Bars represent the standardized mean difference (Hedges' g) between normal-weight controls and children with obesity. Negative values indicate higher biomarker levels in the obesity group. The dashed line with dots shows heterogeneity (I^2, %, percentage of variation due to heterogeneity). CRP demonstrated the largest effect size but with the highest heterogeneity, while hs-CRP showed a moderate effect with lower variability across studies. CRP – C-reactive protein; hs-CRP – high-sensitivity CRP; IL-6 – interleukin-6; TNF-α – tumor necrosis factor-α.

Results of syntheses

The included studies had a predominantly observational design (cross-sectional, cohort). The sample sizes ranged from 24 to 300 participants. Most of the studies contained sufficient statistical reporting; however, not all cases were adjusted for confounding factors (for example, gender and age). The overall risk of bias was assessed as moderate, taking into account methodological heterogeneity and differences in determining the status of obesity.

Statistically significant differences were obtained between obese and normal-weight children by all biomarkers:

- CRP: g = –1.30 (95% CI: –2.32; –0.29); $p = 0.012$; $I^2 = 99.09\%$
- hs-CRP: g = –0.70 (95% CI: –1.01; –0.39); $p < 0.001$; $I^2 = 77.96\%$
- IL-6: g = –0.51 (95% CI: –0.80; –0.21); $p < 0.001$; $I^2 = 89.37\%$
- TNF-α: g = –0.60 (95% CI: –0.97; –0.24); $p = 0.001$; $I^2 = 91.86\%$

In all cases, biomarker levels were higher in children with obesity. Heterogeneity ranged from moderate to high.

To assess possible factors potentially explaining the heterogeneity, analyses were performed with the inclusion of variables 'geographical region' (Europe, Asia, America) and 'age category' (under 12 years old, 12 years and older, mixed samples) in the model. The calculations were performed using the Mixed-Effects Model in the Jamovi environment (module MAJOR).

No statistically significant moderating effects were found for regions and age groups: for CRP (p = 0.136 and p = 0.309), hs-CRP (p = 0.479 and p = 0.320), IL-6 (p = 0.565 and p = 0.982), TNF-α (p = 0.278 and p = 0.679). Heterogeneity remained high (I^2 from 75% to 99%).

In all subgroups, a uniform direction of effect was observed – an increase in the levels of inflammatory biomarkers in children with obesity compared with the control group. However, regional and age differences did not explain the high heterogeneity of the results.

Sensitivity analyses confirmed the robustness of the results obtained: the exclusion of individual studies did not affect the significance and direction of the effects.

Reporting biases and certainty of evidence

The risk of reporting bias was assessed using funnel plot, the Begg's test, and Egger's test were performed for all four syntheses. The asymmetry and statistically significant Egger test values (CRP: $p < 0.001$; TNF-α: $p = 0.031$) indicate a possible publication bias. At the same time, the trim-and-fill method did not impute any missing studies, and high values of Fail-safe N (CRP = 1338; TNF-α = 353) confirm the stability of the results.

For hs-CRP and IL-6, the bias tests were statistically insignificant ($p > 0.3$), and there was no visual asymmetry, which does not confirm the presence of a pronounced reporting bias.

The overall certainty of the evidence was assessed by considering research design, consistency of results, and the risk of bias. The certainty was rated as moderate for CRP, hs-CRP, and IL-6, and low for TNF-α, the latter primarily due to signs of publication bias and high heterogeneity. A detailed summary of the GRADE certainty assessments for all four biomarkers is presented in Table 2. This table integrates the effect sizes, heterogeneity, publication bias assessments, and final certainty ratings to support the strength and reliability of our conclusions.

Table 2. Summary of findings: Inflammatory biomarkers in children with obesity

Biomarker	No. of studies	Total participants	Effect (Hedges' g, 95% CI)	Direction of effect	Certainty of evidence (GRADE)	Explanation
CRP	12 observational studies	N = 2788 (obesity 1649 / control 1139)	–1.30 (–2.32; –0.29)	Higher CRP in children with obesity	Moderate	Large effect size but extremely high heterogeneity (I^2 = 99.09%) and evidence of publication bias (Egger $p < 0.001$). Upgraded for magnitude and robustness (large fail-safe N).
hs-CRP	7 observational studies	N = 2640 (obesity 1044 / control 1596)	–0.70 (–1.01; –0.39)	Higher hs-CRP in children with obesity	Moderate	Downgraded for high heterogeneity (I^2 = 77.96%). No serious concerns regarding risk of bias, indirectness or publication bias (Begg and Egger tests non-significant; trim-and-fill added no studies).
IL-6	15 observational studies	N = 2640 (obesity 1044 / control 1596)	–0.51 (–0.80; –0.21)	Higher IL-6 in children with obesity	Moderate	Downgraded for very high heterogeneity (I^2 = 89.37%). No serious concerns about imprecision, indirectness or publication bias; effect direction consistent across studies.
TNF-α	12 observational studies	N = 2678 (obesity 1582 / control 1096)	–0.60 (–0.97; –0.24)	Higher TNF-α in children with obesity	Low	Downgraded for very high heterogeneity (I^2 = 91.86%) and for publication bias (Egger $p = 0.031$). Effect consistent but precision and heterogeneity reduce confidence.

Note: CRP – C-reactive protein; Egger p – p-value of Egger's regression test; GRADE – Grading of Recommendations, Assessment, Development and Evaluation; Hedges' g – standardized mean difference with Hedges' correction; hs-CRP – high-sensitivity CRP; IL-6 – interleukin-6; I^2– percentage of variation due to heterogeneity; TNF-α – tumor necrosis factor-α; 95% CI – 95% confidence interval.

Discussion

This study is the first meta-analysis to combine data on four key inflammatory biomarkers (CRP, hs-CRP, IL-6, and TNF-α) in children with obesity. The results obtained demonstrate that the increase in their levels is universal and is detected in different age groups and countries. From a practical point of view, CRP and hs-CRP are of the greatest importance: these markers are available in routine clinical practice and can be used for early detection of subclinical inflammation and metabolic risks in children. IL-6 and TNF-α complement the picture as key mediators of the inflammatory response, confirming the pathophysiological basis of the association between obesity and chronic inflammation.

These findings are consistent with previously published systematic reviews and meta-analyses that have shown a positive association of obesity with increased CRP levels in different populations, including children[38, 39]. For children, pooled estimates for CRP and hs-CRP have primarily been reported in the context of metabolic syndromes [7]. As for IL-6 and TNF-α, the data are less systematic and often presented as secondary outcomes in reviews [40– inflammatory, and dysmetabolism biomarkers in children and adolescents. Here, we performed a meta-analysis of existing studies to shed light on the elusive correlations of childhood and adolescent obesity with physiological indicators of stress, inflammation, and metabolism before and after lifestyle interventions. Observational studies, meta-analyses, narrative and systematic reviews were excluded. From a total of 53 articles, 11 were selected according to specific criteria. The biomarkers examined were circulating glucose, insulin, HDL, LDL, triglycerides, adiponectin, leptin, CRP, TNF-alpha, interleukin (IL 42]. Nationally representative studies have also confirmed an increase in CRP in children with obesity starting from preschool age [43, 44].

The physiological basis of the identified changes is well described in the literature. In obesity, hypertrophied adipocytes and adipose tissue-infiltrating macrophages become a source of pro-inflammatory cytokines, primarily IL-6 and TNF-α, which stimulate the synthesis of CRP in the liver. An additional contribution to the maintenance of the inflammatory background is made by leptin, the level of which is increased in overweight [45–48].

Thus, individual cross-sectional studies consistently indicated an increase in CRP, IL-6, and TNF-alpha in children with obesity, however, these data were fragmented, methodologically heterogeneous, and did not allow for a holistic view of the scale of the phenomenon [43, 49]. For the first time, our meta-analysis synthesized results for the four most studied markers, providing a consolidated quantitative assessment based on a large pooled dataset. This not only complements the literature data, but also significantly increases the level of evidence: it becomes obvious that the characteristic shifts in inflammatory markers in obesity, previously described mainly in adults, are reproduced in the pediatric population, which gives the results direct clinical significance.

The data obtained in our meta-analysis on increased levels of CRP, hs-CRP, IL-6, and TNF-α in children with obesity acquire additional significance in the light of studies conducted in other age groups. A comparison of the results indicates that these markers reflect not only the current state of inflammation, but also participate in the formation of long-term cardiometabolic risk, starting in adolescence and up to the elderly populations.

In adolescence, the association of hs-CRP with early subclinical vascular changes was shown: in a prospective ALSPAC study, higher levels of hs-CRP

at age 17 predicted an increase in intima–media thickness (IMT) and arterial stiffness by age 24 [50]. In cohorts of adolescents with obesity and metabolic syndrome, increased hs-CRP was also associated with increased IMT and markers of endothelial dysfunction [51, 52]. Evidence for IL-6 is more limited, but genetic variability in the IL-6 gene region has shown an association with increased IMT, which confirms the pathophysiological role of this cytokine in vascular remodeling [53]. For TNF-α, data have been obtained that in children with obesity and adolescents, concentrations of the soluble TNF-α type 1 receptor are higher and correlate with body mass index, waist circumference, triglycerides, and glucose levels, reflecting early activation this inflammatory pathway [54].

In adulthood, the associations of inflammatory markers with clinical outcomes become even more evident. For hs-CRP, it has been shown that its increase predicts the risk of myocardial infarction, stroke, cardiovascular and general mortality in various populations, including patients with coronary heart disease, heart failure and hypertension [55–58]. IL-6 in this age group is also a strong predictor of both subclinical changes (IMT progression, plaque lesion) and major cardiovascular events and mortality, and its prognostic value remains after correction for hs-CRP [59–61]. Higher TNF-α levels in adults are associated with the risk of recurrent myocardial infarction, stroke, and cardiovascular mortality [62–64].

In older populations, the associations of these markers with adverse outcomes persist and intensify. Elevated levels of CRP and hs-CRP are associated with the risk of myocardial infarction, stroke, heart failure, as well as cardiovascular and total mortality [65–67]. For IL-6, meta-analyses and large cohort studies (ARIC, STABILITY) have confirmed that this cytokine predicts coronary heart disease, stroke, heart failure, atrial fibrillation, and mortality [59, 61, 68]. For TNF-α, it has been shown that its increase is associated with an increase in overall mortality in centenarians [69].

The totality of these data confirms that the increase in CRP, hs-CRP, IL-6, and TNF-α detected in children with obesity reflects early mechanisms of inflammation, which manifest themselves as subclinical vascular changes in adolescence and are subsequently persistently associated with severe cardiovascular outcomes and mortality in adults and the elderly. This allows us to consider inflammatory markers as early biological indicators of an unfavorable prognosis, which retain clinical significance throughout life.

The studies included in the meta-analysis were characterized by significant heterogeneity in design, sample size, and methods for measuring inflammatory markers. Various criteria for determining obesity (WHO, IOTF, national standards) were used, which could introduce additional variability in the results. Not all studies provided data separated by gender and age, which limits the possibility of analyzing effect modifiers. In addition, some of the studies had a relatively small sample size, which reduces the statistical power and precision of the individual estimates obtained.

This review also has a number of methodological limitations. The literature search was limited to certain databases and time frames, which does not exclude the possibility of missing relevant publications. Some of the studies were excluded due to the lack of necessary statistical data for conducting a meta-analysis. A number of studies required the conversion of median values and interquartile ranges into averages and SD (the method of Wan et al. [16]), which could introduce an additional methodological error. Finally, it is impossible to exclude the presence of publication bias, in which studies with negative or insignificant results could not be published.

The results obtained highlight the clinical significance of chronic low-level inflammation as an integral component of childhood obesity. The established steady increase in the levels of inflammatory markers underlines their importance as indicators of an increased risk of an adverse trajectory of obesity in the pediatric population. hs-CRP holds the greatest clinical utility, which is characterized by reproducibility, accessibility, and moderate variability, making it a promising tool for early screening and monitoring. CRP exhibits the highest sensitivity, but its high heterogeneity limits its use as a universal marker. IL-6 and TNF-α are key mediators of the inflammatory process in obesity. Their use in routine clinical practice is still limited by assay complexity and a lack of standardized cut-off values. At the same time, data from cohort studies confirm a stable association of these markers with subclinical vascular changes in adolescents, as well as with severe cardiovascular outcomes and mortality in adults and the elderly.

From a practical point of view, these results indicate that the increase in inflammatory markers in children with obesity is not an isolated laboratory finding, but reflects the beginning of a pathological process that retains prognostic significance throughout life. This justifies the need to include the assessment of inflammatory markers in a comprehensive examination of children with obesity and adolescents, and also highlights the importance of comparing data from different age groups.

In the future, it is advisable to conduct research to trace the dynamics of associations of inflammatory biomarkers from childhood to old age. The most promising direction is an expanded systematic review and meta-analysis involving various age cohorts and age meta-regression, which will allow quantifying how the strength of the relationship between inflammation, subclinical vascular changes and clinical outcomes changes throughout life. This approach will provide an evidence base for the use of CRP, hs-CRP, IL-6, and TNF-α as early biomarkers of long-term prognosis.

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