Obesity and Arterial Stiffness in Children
Systematic Review and Meta-Analysis

Anita T. Cote, Aaron A. Phillips, Kevin C. Harris, George G.S. Sandor, Constandina Panagiotopoulous, Angela M. Devlin

Objective—Childhood obesity is associated with risk factors for cardiovascular disease. Arterial stiffness is considered one of the earliest detectable measures of vascular damage. There is controversy in the literature regarding the effects of childhood obesity on arterial stiffness. The objective of this study is to systematically review the literature and to conduct a meta-analysis comparing measures of central arterial stiffness in children and adolescents with obesity to healthy body mass index controls.

Approach and Results—Literature searches were conducted using databases (eg, MEDLINE, EMBASE) and citations cross-referenced. Studies assessing central pulse wave velocity or β-stiffness index were included. A random effects meta-analysis of the standardized mean difference and 95% confidence intervals in arterial stiffness between children with obesity and control children was performed for each arterial stiffness measure. A total of 523 studies were identified. Fifteen case–control studies were included, with 2237 children/adolescents (1281 with obesity, 956 healthy body mass index controls) between 5 and 24 years of age. All studies measuring carotid and aortic β-stiffness index and 10/12 studies measuring central pulse wave velocity reported greater arterial stiffness in children/adolescents with obesity compared with controls. A random effects meta-analysis was performed revealing a significant effect of obesity on pulse wave velocity (standardized mean difference=0.718; 95% confidence interval=0.291–1.415), carotid β-stiffness index (0.862; 0.323–1.402), and aortic β stiffness index (1.017; 0.419–1.615).

Conclusion—These findings indicate that child/adolescent obesity is associated with greater arterial stiffness. However, further research is needed to address confounders, such as pubertal status, that may affect this relationship in children. In the future, these techniques may be useful in risk stratification and guiding clinical management of obese children to optimize cardiovascular outcomes. (Arterioscler Thromb Vasc Biol. 2015;35:1038-1044. DOI: 10.1161/ATVBAHA.114.305062.)

Key Words: aortic stiffness ■ carotid stiffness ■ pulse wave velocity ■ youth

Childhood obesity, defined as body mass index (BMI) at or above the 95th percentile for age and sex,1 is a growing concern as almost one third of North American children and adolescents are reported to be overweight/obese.2–4 Associated with adverse vascular changes in adulthood,5,6 it is now apparent that childhood obesity promotes immediate cardiovascular damage, well in advance of adulthood.7 Central arterial stiffness (ie, encompassing primarily the aorta and carotid segments of the arterial vasculature), considered one of the earliest detectable manifestations of vascular insult,8 may be measured noninvasively.8–10 Age-related arteriosclerotic progression is accelerated through a variety of cardiovascular risk factors, obesity being one of paramount importance.11 In a recent review, we noted numerous reports of elevated central arterial stiffness in children with obesity when compared with healthy weight children.1 However, there are some conflicting reports in the literature, and not all studies have reported greater arterial stiffness in children with obesity.12,13 Given the importance of arterial stiffness as an indicator of future cardiovascular risk,14 a systematic review and meta-analysis of the available literature is warranted.

Central measures of arterial stiffness are most strongly correlated with cardiovascular disease as compared with those taken from peripheral arterial segments15 and display greater predictive value for cardiovascular events as compared with clinical risk factors, pulse pressure, and indicators of atherosclerosis.16 In particular, aortic pulse wave velocity (PWV) is a robust predictor of cardiovascular events and all-cause mortality.14 The strength of PWV in predicting cardiovascular events and mortality is further demonstrated by its inclusion in the recent European hypertension guidelines, which recommends PWV as an optional assessment in the management of hypertension.17 In addition to regional stiffness, a local measure of central arterial stiffness, β stiffness index, provides a direct...
assessment of aortic or carotid wall stiffness, less dependent on blood pressure, and is considered advantageous over systemic arterial stiffness.\(^9\)\(^,\)\(^10\)\(^,\)\(^18\) Within these parameters, the magnitude of central arterial stiffness in children with obesity is not known, which may provide a more accurate indication of future cardiovascular morbidity and mortality risk in these children. The objective of this study was to systematically review the literature pertaining to associations between arterial stiffness, as measured by central PWV and β stiffness, and obesity in children and adolescents.

### Materials and Methods

Materials and Methods are available in the online-only Data Supplement.

#### Table 1. Results of the OVID Literature Search

<table>
<thead>
<tr>
<th>No.</th>
<th>Population of interest search term</th>
<th>No. Searches (18 November 2014)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Child</td>
<td>3534656</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Adolescent</td>
<td>3048696</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Overweight</td>
<td>106639</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Obese</td>
<td>208395</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Obesity</td>
<td>541618</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Vascular stiffness</td>
<td>3319</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Vascular compliance</td>
<td>1478</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Vascular elasticity</td>
<td>238</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Vascular resistance</td>
<td>112558</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Arterial stiffness</td>
<td>17539</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Arterial compliance</td>
<td>4430</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Arterial elasticity</td>
<td>1066</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Arterial resistance</td>
<td>1888</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Artery stiffness</td>
<td>1391</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Artery compliance</td>
<td>5788</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Artery resistance</td>
<td>3426</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Pulse wave velocity</td>
<td>17227</td>
<td></td>
</tr>
</tbody>
</table>

| Combined population of interest search terms 18 | 1 or 2 | 6583352 |
| Combined characteristic search term 19 | 3 or 4 or 5 | 856852 |
| Combined arterial stiffness search term 20 | 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 | 170348 |

| Combined population of interest, population characteristic, outcome variable search terms 21 | 18 and 19 and 20 | 523 |

#### Results

##### Characteristics of the Studies

The literature search identified 523 potential publications, and after data extraction, 15 papers remained (Table 1 and Figure 1). The 15 studies collectively included 2237 children ranging in age from 5 to 24 years. Children with obesity represented 1281 of these children (age=13.0±2.3 years), with the remaining 956 serving as healthy BMI controls (age=12.8±2.4 years). Obesity was defined as a BMI ≥95th percentile for their sex and age. Reported absolute BMI ranged from 23.9 to 37.2 (obese, youngest to eldest cohort) and 15.5 to 22.3 (controls). Only 3 studies reported BMI z-scores,\(^19\)\(^–\)\(^21\) and 1 study used it in their regression analysis but did not report the mean values.\(^15\) As such, we were unable to assess the linear relationship between arterial stiffness and BMI z-scores, and children were assessed based on their categorization as obese or as a healthy BMI control. We did not assess linear relationships between arterial stiffness and absolute BMI because of the different ages and sex of the children in the studies. Boys and girls were analyzed as 1 group in all but 1 study;\(^20\) thus, our analysis is not able to distinguish sex-specific differences. A summary of the characteristics for the 15 studies is provided in Table 2.

The 12 studies reporting central PWV\(^12\)\(^,\)\(^19\)\(^–\)\(^27\)\(^,\)\(^30\)\(^,\)\(^32\) were of good methodological quality (Downs and Black scores ranged from 14 to 16). All but 2 of these papers\(^12\)\(^,\)\(^21\) reported increased arterial stiffness in the children with obesity compared with healthy BMI controls. Five of these studies accounted for blood pressure in their analysis.\(^12\)\(^,\)\(^23\)\(^–\)\(^27\)\(^,\)\(^30\)\(^,\)\(^32\) Six of these studies determined PWV using the carotid-femoral wave forms gated to the ECG,\(^12\)\(^,\)\(^23\)\(^–\)\(^27\)\(^,\)\(^30\)\(^,\)\(^32\) 2 studies used Doppler ultrasound traces from the ascending and descending aorta,\(^23\)\(^,\)\(^25\) whereas 4 studies used a single-point method of PWV determination using carotid β stiffness, diastolic blood pressure, and blood density.\(^19\)\(^,\)\(^20\)\(^,\)\(^22\)\(^,\)\(^26\)

There were 4 studies assessing carotid β stiffness,\(^19\)\(^,\)\(^20\)\(^,\)\(^26\)\(^,\)\(^28\) all reporting a higher carotid β stiffness index in the children with obesity. Similarly, in the 4 studies assessing aortic β stiffness,\(^25\)\(^,\)\(^27\)\(^,\)\(^29\)\(^,\)\(^31\) all reported a higher aortic β stiffness index in the children with obesity. Methodological quality was also considered good as Downs and Black scores ranged from 14 to 15 and 14 to 15 for carotid and aortic β stiffness, respectively.

##### Meta-Analysis

Heterogeneity was confirmed with a statistically significant \(P<0.001\) Q statistic (201.8, 17.5, and 20.5) and \(I^2\) \(95\%\) confidence intervals=0.718, 95% confidence intervals=0.291–1.145, \(z=3.297, P<0.001;\) Figure 2), carotid β stiffness index (SMD=0.862, 95% confidence intervals=0.323–1.402, \(z=3.119, P<0.001;\) Figure 2), and aortic β stiffness index (SMD=1.017, 95% confidence intervals=0.419–1.615, \(z=3.343, P=0.001;\) Figure 4). Overall effect size for each stiffness measure remained statistically significant throughout the 1-study-removed procedure (\(P<0.001, P<0.025, \) and \(P<0.019\) for PWV, carotid β stiffness, and

### Nonstandard Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>PWV</td>
<td>pulse wave velocity</td>
</tr>
<tr>
<td>SMD</td>
<td>standardized mean difference</td>
</tr>
</tbody>
</table>
aortic β stiffness, respectively. Publication bias could not be ruled out on visual inspection of the funnel plots (Figure 5). The trim-and-fill method resulted in a lowering of the overall effect size for PWV (SMD=0.529) and carotid β stiffness index (SMD=1.205) but still favored greater stiffness in obese versus controls (P<0.05). Overall effect size for aortic β stiffness index did not change, as a result of the trim-and-fill procedure. Expressed as odds ratios (95% confidence intervals), greater odds of arterial stiffness with obesity was found for PWV (3.7, 1.7–8.0), carotid β stiffness (4.8, 1.8–12.7), and aortic β stiffness (6.3, 2.1–18.7).

**Discussion**

This study aimed to determine the association of obesity and central measures of arterial stiffness in children and adolescents. All but 2 investigations reported greater arterial stiffness in children with obesity compared with healthy BMI controls. The included studies ranged from small to large sample sizes; however, the advantage of a meta-analysis is that larger studies are given more weight in the summary statistic, and the random effects model accounts for differences in measurement and patient samples used in the various studies. Overall, the meta-analysis found children with obesity have increased arterial stiffness than children with a healthy BMI, with strong agreement between different measures of

**Table 2. Characteristics of Individual Studies Included in the Meta-Analysis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Obese</th>
<th>PWV</th>
<th>Carotid β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabrera-Rego 2014</td>
<td>Cuba</td>
<td>66 (37.9)</td>
<td>11.3</td>
<td>One-point (carotid)</td>
</tr>
<tr>
<td>Celik 2011</td>
<td>Turkey</td>
<td>30 (60.0)</td>
<td>13.2</td>
<td>Doppler ultrasound</td>
</tr>
<tr>
<td>Hacihamdioglu 2014</td>
<td>Turkey</td>
<td>61 (50.8)</td>
<td>13.2</td>
<td>cf-PWV</td>
</tr>
<tr>
<td>Harris 2012</td>
<td>Canada</td>
<td>61 (44.0)</td>
<td>13.8</td>
<td>Doppler ultrasound</td>
</tr>
<tr>
<td>Hvidt 2014</td>
<td>Denmark</td>
<td>92 (54.4)</td>
<td>12.7</td>
<td>cf-PWV</td>
</tr>
<tr>
<td>Jin 2013</td>
<td>China</td>
<td>71 (28.2)</td>
<td>10.0</td>
<td>One-point (carotid)</td>
</tr>
<tr>
<td>Koopman 2011</td>
<td>Canada</td>
<td>21 (19.0)</td>
<td>14.2</td>
<td>cf-PWV</td>
</tr>
<tr>
<td>Lurbe 2012</td>
<td>Spain</td>
<td>284 (44.0)</td>
<td>12.0</td>
<td>2D echo</td>
</tr>
<tr>
<td>Nunez 2010</td>
<td>Spain</td>
<td>45 (28.9)</td>
<td>12.4</td>
<td>One-point (carotid)</td>
</tr>
<tr>
<td>Ozcetin 2012</td>
<td>Turkey</td>
<td>42 (57.1)</td>
<td>10.1</td>
<td>2D echo</td>
</tr>
<tr>
<td>Pac 2010</td>
<td>Turkey</td>
<td>37 (40.5)</td>
<td>13.9</td>
<td>2D echo</td>
</tr>
<tr>
<td>Pandit 2011</td>
<td>India</td>
<td>95 (46.3)</td>
<td>11.0</td>
<td>One-point (carotid)</td>
</tr>
<tr>
<td>Pierce 2013</td>
<td>USA</td>
<td>86 (57.0)</td>
<td>16.9</td>
<td>cf-PWV</td>
</tr>
<tr>
<td>Polat 2008</td>
<td>Turkey</td>
<td>56 (46.0)</td>
<td>11.5</td>
<td>2D echo</td>
</tr>
<tr>
<td>Urbina 2010</td>
<td>USA</td>
<td>234 (70.1)</td>
<td>18.1</td>
<td>cf-PWV</td>
</tr>
</tbody>
</table>

PWV indicates pulse wave velocity.

*Percent female.
central arterial stiffness. As the studies in this review are all case–control design (Level 3 evidence) with methodological quality limited to a score of 17, the findings indicate a strong association between childhood obesity and arterial stiffness over inferences regarding causality.

Several terms in the literature are used synonymously with arterial stiffness, such as compliance, distensibility, and elasticity. There are many indices of arterial stiffness that may be derived from various methods of measurements. Regional (ie, aortic PWV) and local (ie, common carotid artery) measurements are direct indications of the stiffness of the artery wall, with carotid-femoral PWV considered the gold standard. Other noninvasive indices of arterial stiffness are hampered by methodological issues and assumptions or do not relate to cardiovascular outcomes. This review focused on direct measures of central arterial stiffness that have high predictive value for cardiovascular morbidity and mortality and that may be practically applied in pediatric populations.

Two of the 15 investigations reported greater arterial stiffness in children and adolescents with healthy BMI compared with those with obesity, reporting instead a positive relationship between blood pressure and PWV independent of obesity. Children with obesity have a higher risk of hypertension; however, the relationship between hypertension and arterial stiffness in children is unclear. In adults, arterial stiffening as a precursor to hypertension is becoming more apparent, and stiffness in children is unclear. In adults, arterial stiffening as a precursor to hypertension is becoming more apparent, and stiffness in children is unclear.

There are several factors that may influence arterial stiffness. In the general adult population, PWV increases with increasing age and blood pressure levels. However, in children, the influence of age on PWV is less clear and may be confounded by pubertal status. One study in a healthy population of children between the ages of 3 to 18 years, reported that PWV remained unchanged during childhood but started to increase in girls at 10.4 years and in boys at 12.1 year, suggesting an influence of pubertal status rather than age. Sex and pubertal status, through changes in vasoactive hormone concentrations, are critical factors known to influence arterial wall properties and function. Although age and sex was often matched or controlled for in the 15 studies analyzed in this review, pubertal status was not, except for one study that assessed children at a Tanner stage 2II. Furthermore, the time course of pathological adaptation (increased arterial stiffness) to obesity is not known, and it is unclear how age, sex, or pubertal status may interact with obesity and affect arterial stiffness in children.

Understanding the effects of excess adiposity and elevated blood pressure on arterial stiffness in children is complex. To discern increases in BMI and blood pressure, which occur normally during growth and development, from pathological elevations in children, evaluation of standardized scores must be included. Age and sex are accounted for in BMI z-scores, and age, sex, and height are accounted for in blood pressure z-scores. In the absence of this standardization, comparing absolute values of BMI and blood pressure in children within a wide age range make interpretation of the data challenging. For example, a 9-year-old boy at the 5th percentile for height would be published more often and faster than those with nonsignificant or negative results. However, the adult literature demonstrates a robust association between arterial stiffness and cardiovascular risk, deeming the current findings in children (based on the pooled analysis) highly probable.
with a systolic blood pressure of 113 mmHg is considered hypertensive, whereas this same blood pressure for a taller 11-year-old boy is considered healthy. The majority of the papers included in this meta-analysis did not report BMI or blood pressure z-scores. Given the lack of standardized BMI and blood pressure data, our ability to accurately assess the direct linear relationships between BMI and blood pressure to measures of arterial stiffness is limited. Furthermore, as shown by Hvidt and colleagues, statistical differences observed for absolute and z-scores may not always be in agreement. As such, future studies should include BMI and blood pressure z-scores or control for age, sex, and height in the analyses.

Despite stringent selection criteria for this review, there are some methodological limitations in the application of these techniques for the assessment of arterial stiffness in children with obesity that should be discussed. In the presence of excess adiposity, echocardiographic methods of vascular assessment may be limited because of poor image quality. As such, investigations matching control subjects to their study population should consider this in recruitment, expecting some data may not be useable. It should also be noted that calculations of β stiffness are derived using changes in carotid or aortic diameter in relation to pressures obtained at the periphery (brachial artery). As amplification of pulse pressure between central and peripheral locations are known to be different, β stiffness may be overestimated as a result. Previous work by Colan et al. reported strong correlations between central aortic and brachial artery blood pressures (r=0.941–0.979) in infants and children, involving a wide range of pressure values. However, pulse pressure amplification may differ with obesity. In addition, as blood pressure and artery diameter measurements are not collected simultaneously, the utility of these measurements are limited by the assumption that there are no hemodynamic variations within this time period. Moreover, for PWV analysis, variability in the determination of length measurement for the carotid-femoral segment hampers the comparison between studies using different procedures for acquiring path length. Intuitively, with a high degree of central adiposity, the path length may be overestimated, artificially inflating the measurement of aortic PWV in obese individuals, and the acquisition of the femoral wave form may be challenging. Despite these limitations, PWV is considered the most favorable measure of arterial stiffness because of feasibility, reproducibility low cost of the measurement, and importantly, its association with adverse cardiovascular outcomes.

![Figure 4. Forest plot illustrating effect size for each of the 4 studies reporting aortic β stiffness index in children with obesity versus children with health body mass indexes (controls). Overall effect favored increased stiffness in obese (standardized mean difference = 1.017, 95% confidence interval [Cl]=0.419–1.615).](http://atvb.ahajournals.org/)

![Figure 5. Funnel plot of the standard error plotted against effect size (standardized mean difference) for pulse wave velocity (A), carotid β stiffness index (B), and aortic β stiffness index (C).](http://atvb.ahajournals.org/)
techniques of PWV assessment have not been rigorously compared, nor have any relationships between central PWV and carotid or aortic \(\beta\) stiffness been reported. Although these relationships are not clear, by assessing the mean difference between groups within each study and applying this value to the meta-analysis, we eliminate any direct comparisons between the actual values derived from these techniques.

The results of the present meta-analysis should be interpreted with caution. Although our data suggests a strong association between obesity and arterial stiffness in children and adolescents, adjustments for confounders, such as pubertal status, and standardized BMI and blood pressure scores was not possible, warranting further research to clarify this association. Measures of arterial stiffness are noninvasive, reproducible, and relatively inexpensive techniques. Although the prognostic significance of arterial stiffness has not been elucidated, it is a strong predictor of cardiovascular events in adults. Thus, in addressing the above mentioned confounders, future research may provide clarity to the association between arterial stiffness and obesity in children and provide evidence to support the use of such techniques in risk stratification and guiding clinical management of obese children to optimize cardiovascular outcomes.

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Disclosures

None.

References


Significance

This research represents the first systematic review of the literature as a means to evaluate the association between childhood obesity and noninvasive measures of arterial stiffness. The results of our meta-analysis indicate that childhood obesity is associated with greater arterial stiffness, and this relationship was apparent across the stiffness measures contained within this review. However, further research is needed to address confounders, such as body mass index and blood pressure z-scores and pubertal status that may affect this relationship in children. As central arterial stiffness has been linked with cardiovascular risk in adults, our results highlight the need for ongoing research to determine the prognostic significance in youth, as well as determining effective intervention strategies.
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Materials and Methods

Literature Search Strategy and Inclusion Criteria
We performed a keyword literature search for all scientific publications from January 1, 1950 to November 18, 2014 investigating the effects of childhood/adolescent obesity on arterial stiffness using electronic databases: MEDLINE, EMBASE, Cochrane Library, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED. The population search terms included: Child, Adolescent; combined with characteristic search terms: Overweight, Obese, Obesity; and descriptor search terms: Vascular Stiffness, Vascular Compliance, Vascular Elasticity, Vascular Resistance, Arterial Stiffness, Arterial Compliance, Arterial Elasticity, Arterial Resistance, Artery Stiffness, Artery Compliance, Artery Resistance, Pulse-Wave Velocity. The combination of these search terms resulted in the identification of 523 papers (Table 1).

All search results were downloaded to an online research management system (RefWorks, Bethesda, MD, USA) where data extraction began by removing duplicates, review papers, and letters to the editor (Figure 1). Papers were first inspected by title and abstract. The remaining papers (n=218) underwent a full text review to determine ultimate eligibility. For inclusion, papers had to meet the following criteria: 1) reported central PWV, aortic β-stiffness index, or carotid β-stiffness; 2) in children and/or adolescents (mean age < 19 yrs); and 3) classified children as obese. Due to the nature of our research question, the effect of obesity could only be assessed via a comparison of an obese group to that of a matched healthy BMI group. Exclusion criteria were papers without control groups, those reporting in adults or mixing adults in with the children, or those involving heart conditions or other chronic disease. During the full article review stage, articles that were excluded, including the reason for exclusion was recorded. Fifteen papers remained following this extraction process. No papers were added following cross-referencing from the bibliographies of these 15 publications or those of review papers on arterial stiffness and obesity. The screening process was conducted separately by two reviewers (A.T.C. and A.A.P.), with discrepancies addressed by consensus.

Study Quality Analysis and Data Extraction
All of the 15 manuscripts were available in English. An evaluation of the methodological quality of each article was completed using a modified Downs and Black (D&B) tool for non-randomized control trials. Higher points indicate a superior methodological quality. Typically the D&B includes 27 questions from which to evaluate each research article, however, given that by design all included studies in this systematic review were observational case-control studies (Level 3 Evidence), the D&B tool was modified to omit questions pertaining to interventions. The remaining questions included 1-3, 5-7, 10-13, 16, 18, 20-22, 25 and 27 resulting in a maximum of 17 points. Librarians from the University of British Columbia and all authors reached consensus to pursue this process for evaluation of study quality. Ranking scores were performed in duplicate after which any discrepancies were resolved by discussion. From each study, the following data was extracted: sex; mean age and standard deviation (SD); type of stiffness measurement; mode of acquisition; and research location (country).

Statistical Analysis
All statistical analyses were performed using Comprehensive Meta Analysis Software (Biostat Inc, Englewood, NJ, USA). Using a random effects meta-analysis model for each arterial stiffness measure (PWV, carotid β stiffness, and aortic β stiffness) calculating the standardized mean difference (SMD) and 95% confidence intervals (CI) for each study, the association of obesity with arterial stiffness was evaluated by calculating a pooled statistic, with statistical significance set at $P<0.05$. Odds ratios and 95% CI were also assessed for each stiffness measure. Heterogeneity was assessed using the Q statistic and quantified using $I^2$. The one-study-removed procedure was performed to assess sensitivity. A funnel plot of the standard error against effect size for each study was used to assess publication bias.
References
