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Efficacy of anthropometric measures for Identifying Cardiovascular Disease Risk in Adolescents: Review and Meta-Analysis

Short title: Anthropometric indices & CVD risk in adolescents

Michael Lichtenauer[1*], Sean D. Wheatley[2* ‡], Marrissa Martyn-St James[3], Michael J. Duncan[4], Fernanda Cobayashi[5], Gabriela Berg[6], Carla Musso[7], Mabel Graffigna[8], Jimena Soutelo[9], Pascal Bovet[10], Anastasios Kollias[11], George S. Stergiou[11], Evangelos Grammatikos[12], Claire Griffiths[2], Lee Ingle[13*] Christian Jung[14*]

[1] Clinic of Internal Medicine II, Department of Cardiology, Paracelsus Medical University of Salzburg, Austria

[2] School of Sport, Carnegie Faculty, Leeds Beckett University, UK

‡ Corresponding author: Sean Wheatley, Fairfax Hall, Headingley Campus, Leeds, LS6 3QS, UK

Email: S.D.Wheatley@leedsbeckett.ac.uk

Telephone: 07891 732561

[3] School of Health & Related Research, University of Sheffield, UK

[4] Faculty of Health and Life Sciences, Coventry University, UK

[5] Public Health Nutrition Program, School of Public Health, University of São Paulo, São Paulo, Brazil

[6] Lipids and Atherosclerosis Laboratory, Faculty of Pharmacy and Biochemistry, University of Buenos Aires, Buenos Aires, Argentina

[7] Endocrine Division, Milstein Hospital, Buenos Aires, Argentina

[8] Endocrinology Division, Carlos Durand Hospital, Buenos Aires, Argentina

[9] Endocrinology Service, Churruca Visca Hospital, Buenos Aires, Argentina

[10] University Institute of Social and Preventive Medicine, Lausanne, Switzerland and Ministry of Health, Victory, Republic of Seychelles

[11] Hypertension Center STRIDE-7, National and Kapodistrian University of Athens, School of Medicine, Third Department of Medicine, Sotiria Hospital, Athens, Greece

[12] Second Department of Pediatrics, P & A Kyriakou Children Hospital, Athens, Greece

[13] Department of Sport, Health & Exercise Science, University of Hull, UK

[14] University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Medical Faculty, Division of Cardiology, Pulmonology and Vascular Medicine, Düsseldorf, Germany

* contributed equally

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ABSTRACT

BACKGROUND: To compare the ability of body mass index (BMI), waist circumference (WC) and waist to height ratio (WHtR) to estimate cardiovascular disease (CVD) risk levels in adolescents.

METHODS: A systematic review and meta-analysis was performed after a database search for relevant literature (Cochrane, Centre for Review and Dissemination, PubMed, British Nursing Index, CINAHL, BIOSIS citation index, ChildData, metaRegister).

RESULTS: 117 records representing 96 studies with 994,595 participants were included in the systematic review, 14 of which (13 studies, n=14,610) were eligible for the meta-analysis. The results of the meta-analysis showed that BMI was a strong indicator of systolic blood pressure, diastolic blood pressure, triglycerides, high-density lipoprotein cholesterol and insulin; but not total cholesterol, low-density lipoprotein or glucose. Few studies were eligible for inclusion in the meta-analysis considering WC or WHtR ($n \leq 2$). The narrative synthesis found measures of central adiposity to be consistently valid indicators of the same risk factors as BMI.

CONCLUSION: BMI was an indicator of CVD risk. WC and WHtR were efficacious for indicating the same risk factors BMI performed strongly for, though there was insufficient evidence to judge the relative strength of each measure possibly due to heterogeneity in the methods for measuring and classifying WC.

INTRODUCTION

Levels of adiposity, one of the key modifiable risk factors associated with the development of cardiovascular disease (CVD) risk in adolescents (1), have reached concerning levels; with over a third of 10-11 year old children already being classified as overweight (OW) or obese (Ob) in the UK (2). The ability to identify individuals with the highest disease risk is important in order to effectively target interventions. Thus, valid methods of assessing whether someone is normal weight (NW), OW or Ob are essential. Anthropometric measures provide the most appropriate methods for doing this due to their relative ease, speed, and low cost (3, 4). There are however multiple anthropometric adiposity indexes which have been proposed for this purpose. Research is required to elucidate which of these is most efficacious for identifying individuals with increased CVD risk factor levels.

Body mass index (BMI) is the most commonly used measure of adiposity. Although BMI is a good indicator of general health in adolescents (5) it does have limitations, including the inability to differentiate between individuals with different fat distributions. Studies have demonstrated that participants with greater abdominal adiposity may have higher risk than those with gluteo-femoral obesity (6, 7). The use of measures of central obesity such as waist circumference (WC) and waist-to-height ratio (WHtR) may therefore be important. Furthermore, it has been demonstrated that the extent of the obesity epidemic differs when different adiposity indexes are used; with BMI potentially underestimating the extent of the issue (8, 9). With such variation in the reported prevalence of obesity when different methods are used it is clear that establishing which of these measures is most appropriate for identifying sub-optimal health is important.

The purpose of the current review and meta-analysis was to investigate whether adiposity status classified using BMI is an indicator of CVD risk factors in adolescents (aged 11-19 years) and to establish whether indicators of central adiposity (WC and WHtR) are more efficacious for this purpose.

METHODS

Search Strategy

Systematic searches of the following electronic databases were performed up to the end of September 2012: The Cochrane Library, the Centre for Review and Dissemination, PubMed, the British Nursing Index, CINAHL Plus, the BIOSIS citation index, ChildData, and the metaRegister of clinical trials. The primary search terms used were variants of "adolescent/adolescence", "obesity" and "cardiovascular OR cardiovascular risk"; for example the search terms for the PubMed search were "(((obesity) AND cardiovascular) AND risk) AND (adolescence OR adolescent)".

Study selection

Studies were included after the primary database search if, after scrutiny of the title and abstract, the study reported at least one adiposity measure and at least one cardiovascular disease risk factor in adolescents (11-19 years of age). All observational studies were eligible for inclusion in the review; including cross-sectional studies, cohort studies (prospective or retrospective) and case control studies.

Studies that considered adiposity based on BMI, WC and/or WHtR were eligible for inclusion. The outcomes for the review were cardiovascular disease (CVD) risk factors, specifically: systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), fasting glucose (plasma or serum), and/or fasting insulin (plasma or serum). A summary of studies included in this meta-analysis is shown in Table 1 (n = 13 data sets representing 14 identified records) (10-22).

Quality Assessment

As no universally recognised quality assessment tool exists for observational studies (23) relevant items were taken from both the Newcastle-Ottawa scale (24) and the Cochrane Collaboration's tool for assessing risk of bias (25). Each item was judged as high, medium or low risk based on the following criteria: Low risk, if the study was judged to be "low" risk in all categories; medium risk, if the study was judged to be "medium" risk for one to three categories; high risk, if the study was judged to be "high" risk for ≥ 1 category and/or

"medium" risk for ≥ 4 categories. Table 2 shows details of the quality assessment of studies included in the meta-analysis (n = 13).

Analysis

All studies identified for inclusion were tabulated and reported in a narrative synthesis. Where appropriate outcome data were available from the included studies meta-analysis was undertaken using RevMan software (Version 5.2. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration) for analysis. To be included in the meta-analysis it was required that the study compared CVD risk factors between adiposity groups classified using the IOTF BMI classification criteria (26), the British WC adiposity status classification methods (27), and/or using WHtR groups of <0.5 (NW) and ≥0.5 (OW/Ob) (28). Where studies did not categorise participants into adiposity classifications based on these methods study authors were contacted to request outcome data according to these categories, or raw data to be converted by one author (SW).

As the outcomes of the review were continuous, meta-analysis of pooled between-group differences were calculated in RevMan using a mean difference with 95% confidence intervals (95%CI). Statistical heterogeneity was assessed using the I-squared (I^2) statistic. For all comparisons a random-effects model was applied. Between-group differences (estimated in RevMan as Z-scores) were considered significant at $P < 0.05$.

The following between-group comparisons were made according to adiposity classification: "underweight (UW)/NW" with "OW", "UW/NW" with "OW/Ob", "UW/NW" with "Ob". Sensitivity analyses were defined a priori to assess the impact of study quality (with overall high-risk studies excluded), study type (cross-sectional, case control or cohort) and country.

RESULTS

Study selection

The study selection process is reported in the PRISMA diagram (29) in Figure 1. Following de-duplication 11,859 citations were identified. Of these 10,325 were excluded at the title and/or abstract stage. 1,534 articles were obtained for further screening. Of these 1,357 were excluded. Details of these excluded studies and reasons for exclusion are reported in supplementary table S1. 96 studies (117 citations) were included in the systematic review, of which 13 (14 citations) provided data for the meta-analysis. Details of the included studies are presented in Table 1**Error! Reference source not found.** for those included in the meta-analysis and in a supplementary table 2 for those included in the narrative synthesis.

Risk of bias and quality assessment

Of the 13 studies included in the meta-analysis, 4 were classified as high risk of bias, 9 were classified as medium risk and none were classified as low risk (see Table 2).

Meta-analysis results

No studies were identified that had data available in the required format for inclusion in the meta-analysis which measured SBP, DBP, glucose or insulin when classifying adiposity status using WC or WHtR. OW and Ob participants were combined due to the greater availability of data in this format.

SBP was significantly lower in UW/NW participants than OW/Ob participants (-6.81mmHg, 95%CI -8.71 to -4.90; Figure 2a). A similar pattern was observed for DBP, with significant differences between UW/NW participants and OW/Ob participants (-3.53mmHg, 95%CI -5.17 to -1.53; Figure 2b)**.**

TC was not significantly different between adiposity groups (mean difference in UW/NW v OW/Ob -0.18mmol$\cdot L^{-1}$, 95%CI -0.37 to 0.02); though there was divergence in the direction of the mean differences between sexes (males had higher TC in the UW/NW group whilst for females the values were lower in the UW/NW group; results not presented). Sensitivity analyses with high risk studies excluded led to the results for this comparison becoming more clearly non-significant (Figure 2c). Results for WC and WHtR in relation to TC were similar to those observed for BMI (mean difference in UW/NW v OW/Ob 0.03mmol$\cdot L^{-1}$, 95%CI -0.10 to 0.15 and -0.15mmol$\cdot L^{-1}$, 95%CI -0.36 to 0.06 respectively).

Triglyceride concentration was significant different between UW/NW and OW/Ob participants when classified by BMI (mean difference in UW/NW v OW/Ob -0.19mmol·L^{-1}, 95%CI -0.24 to -0.14; Figure 2d). Using WC (see Supplementary table 1) or WHtR (see Supplementary table 2) the difference in TG was significant between NW and OW/Ob participants in the whole sample and in males but there were not sufficient studies to assess this validly in females.

HDL-c concentration was significantly higher in UW/NW than OW/Ob participants when BMI was used (mean difference 0.10mmol·L^{-1}, 95%CI 0.06 to 0.14; Figure 2e). For WC adiposity classifications HDL-c was significantly higher in NW participants than OW/Ob participants (Figure 2f). For all participants and for male participants, HDL-c was significantly different in those with a WHtR <0.5 (NW) compared to those with WHtR ≥0.5 (OW/Ob) (mean differences 0.14mmol·L^{-1} for all participants and 0.18mmol·L^{-1} for males) (Figure 2g).

LDL-c concentrations were significantly different between BMI classification groups when all participants were combined (mean difference between UW/NW and OW/Ob -0.11mmol·L^{-1}, 95%CI -0.21 to -0.01; P=0.04). Sensitivity analyses with high risk studies excluded resulted in the outcomes becoming non-significant for all participants and more clearly non-significant within male and female sub groups (Figure 2h).

There was no significant difference between UW/NW and OW/Ob participants' glucose levels (mean difference -0.06mmol·L^{-1}, 95%CI -0.18 to 0.06), nor was there any difference by sex. Insulin concentrations were significantly different between UW/NW and OW/Ob participants using BMI (mean difference -29.38pmol·L^{-1}, 95%CI -42.06 to -16.71; Figure 2i).

Narrative Synthesis Results

Of the 117 studies included, 115 presented relevant results using BMI (98%), 31 presented relevant results using WC (26%) and six presented relevant results using WHtR (5%).

44/51 studies (86%) found BMI to be related to SBP (or SBP to be significantly different between adiposity classification groups) with SBP increasing as BMI or BMI category increased. For DBP, 34/45 studies (76%) found the same. 21/21 studies (100%) that looked at hypertension without differentiating between SBP and DBP found a significant relationship and/or difference; with BP increasing as BMI did. 13/16 studies (81%) found SBP increased as WC did. 3/3 studies (100%) found a relationship/difference for WHtR. For DBP, 11/13

(85%) found an increase in this variable along with an increase in WC. 2/2 studies (100%) found a positive association between WHtR and DBP.

When multiple adiposity classification methods were included, 9/17 studies (53%) could not differentiate between the abilities of BMI and WC for indicating elevated BP, two could not differentiate between the abilities of all three adiposity indexes whilst the only study to compare just BMI and WHtR again could not find a difference between the efficiency of either measure.

None of the adiposity indexes were consistently effective for predicting TC levels. 19/43 studies (44%) found a relationship between BMI and TC. For WC, 7/12 (58%) studies found a significant relationship. Only 2 studies considered TC alongside WHtR; one of which found a significant relationship. Of the 12 studies that considered two of these measures, one study found BMI to be superior to WC for indicating heightened TC levels, whilst all others showed no clear difference. There was no clear difference in the efficacy of any of the adiposity measures in either of the studies comparing all three.

38/49 studies (78%) showed BMI to be related to TG concentration. 11/14 studies (79%) demonstrated the same for WC. 2/3 studies (67%) found WHtR to be an indicator of elevated TG. There was little evidence of any superiority of BMI or WC for indicating TG concentration in studies that used both of these measures. There was no difference in the ability of BMI, WC or WHtR in the three studies that included all of these adiposity measures.

37/50 studies (74%) found either a significant relationship between BMI and HDL-c or showed that HDL-c levels were significantly different between adiposity classification groups when BMI was used. WC was also consistently linked with HDL-c with 14/15 (93%) studies showing this. Only three studies considered WHtR and HDL-c, with two of them (67%) showing a significant relationship/difference. 4/12 studies (33%) that looked at the relationship of both WC and BMI with HDL-c found that WC was associated.

22/36 studies (61%) found a significant association between LDL-c and BMI. For WC 5/8 studies (63%) found a significant ability to identify individuals with increased LDL-c. For WHtR 2/3 (67%) supported this assertion.

10/28 studies (36%) found a significant relationship between glucose and BMI (or a significant difference between adiposity classification groups). 3/6 studies (50%) found a positive association between glucose and WC. 1/2 studies (50%) found this with WHtR. No study showed a superiority of BMI or WC for indicating fasting glucose levels when only

these two indexes were used, whilst the only study that compared all three found none of them to be related to glucose thus no measure was superior.

Of the 28 studies looking at the association between insulin and BMI (or the difference in insulin between adiposity groups classified using BMI) 27 (96%) found a positive association. All of the studies using WC (9/9) found a positive association whilst the only study that used WHtR also found a positive association. There was no evidence for the superiority of any of the adiposity variables for predicting CVD risk.

DISCUSSION

The results from the meta-analysis showed BMI to be a strong indicator of heightened SBP, DBP, TG, HDL-c and insulin; with significant differences in the pooled analyses between most adiposity classification groups for these variables and a consistent direction of differences apparent in associated Forest plots. For TC, LDL-c and glucose the majority of inter-classification comparisons were non-significant, suggesting that BMI was not a strong indicator of these CVD risk factors. These findings are not unexpected as other research has also not found a strong association between adiposity and TC or LDL-c in adolescents (30, 31). This lack of relationship may be in part due to the influence of pubertal development on these factors (32), or may be a reflection of limitations of using TC and LDL-c as markers of health due to possible heterogeneity in their make up (i.e. both include sub-fractions with different roles in the development of CVD risk) (33-36).

The outcomes of the current review were similar to those presented in a similar review which considered the association of BMI with CVD risk in 5-15 year olds (5). The primary difference between the two studies' findings was that in the current review there was no difference in TC or LDL-c concentration between adiposity classification groups, unlike the previous study [7] where differences existed between the Ob and NW groups (though not between OW and NW participants) of 0.15 and 0.18 $mmol \cdot L^{-1}$ respectively. Friedemann and colleagues (5) also found a significant sex difference for glucose between NW and both OW and Ob participants. The magnitude of differences between adiposity classification groups(5) was similar for SBP (+4.54 and +7.49 mmHg versus NW in OW and Ob respectively), DBP (+2.57 and +4.06 mmHg) and insulin (+21.82 and +48.47 $pmol \cdot L^{-1}$) to those observed in the current study. For HDL-c (-0.17 and -0.22 $mmol \cdot L^{-1}$ versus NW in OW and Ob respectively) and TG (+0.21 and +0.26 $mmol \cdot L^{-1}$) the differences were smaller in the current study, though in the same direction.

Due to the low number of studies that used WC and, particularly, WHtR it is difficult to draw strong conclusions regarding whether these methods were as effective as, or superior to, BMI for indicating CVD risk in adolescents. It is possible that this is in part due to the absence of internationally recognised WC cut-points, which introduces heterogeneity within the methods and precludes the valid pooling of data. The limited data available for the meta-analysis found both WHtR and WC to be statistically significant indicators of TG and HDL-c in the pooled analysis, though not for TC or LDL-c. The narrative synthesis outcomes suggested

WC was a useful indicator of SBP (81% of studies supported this), DBP (85%), TG (79%), HDL-c (93%) and insulin (100%); but not TC (58%), LDL-c (63%) or glucose (50%); similar to the results observed for BMI. Comparable outcomes were seen for WHtR, though the validity of these findings is questionable due to the small number of studies included. The 95%CI of all similar analyses between adiposity indexes overlapped in the meta-analysis, suggesting there was no statistically significant difference in the ability of each adiposity index to identify CVD risk. In the studies that directly compared two or more of the adiposity indexes in the descriptive review no measure consistently proved superior for any of the CVD risk factors. These findings are similar to those of a study with older adolescents, which found that BMI performed equally well as an indicator of CVD risk as WC and WHtR in 19-20 year olds in the Seychelles (37); providing some support for this conclusion. Without the research base to fully assess the suggestion that WC or WHtR may be superior indicators of CVD health in adolescents it cannot be recommended that either of these measures be used to replace (or be applied alongside) BMI as a public health tool.

Heterogeneity, particularly that due to differences in methods and participant characteristics, is much greater between observational studies than between randomised control trials (38, 39), introducing barriers to the validity of pooling data. The use of descriptive analyses based on systematic methods and analysis of patterns through using Forest plots, alongside consideration of sources of heterogeneity (38), may be more important and appropriate than reliance on single figure outputs of pooled analysis. Within the current study several of the sub-analyses had high heterogeneity based on the I^2 statistic (40). For TG the I^2 values for the entire population were higher than they were for each sex, suggesting the variation was due to an effect of sex. Variation in the ages of the participants included in each analysis is potentially a particularly important source of heterogeneity, for example there were studies that had included 12-17 year olds (41) and 14-19 year old (42). Studies often fail to report maturation, socio-economic status and ethnicity, all of which are factors which could influence the results and thus introduce heterogeneity. The lack of reporting of such details precludes the running of sensitivity analyses to fully assess their influence.

Despite the limitations of pooling observational data the validity of the observed outcomes in the current study are supported by alternative methods. Firstly, there was consistent agreement between the meta-analyses and descriptive analysis results. Furthermore, the forest plots demonstrated a consistent finding for all variables where the adiposity index was

adjudged to be a positive indicator. Forest plots were not presented by Friedemann and colleagues (5) (whose study exhibited comparable heterogeneity between studies) in their review; thus this can be considered a comparative strength of the current review. Finally, dose-responses, a key indicator of causality (43), was also observed; with risk increasing as adiposity status increased.

LIMITATIONS

The lack of a fully validated quality assessment tool for observational studies may reduce the validity of the portion of the study considering the relative risk of bias associated with each paper. Overall the method applied was similar to that used in another recent review (5) and is considered appropriate. Further, the search strategy could also be considered a limitation. The inclusion of more specific terms may have produced further relevant results, and may have increased the number of studies identified evaluating markers of central obesity in particular. Based on the large number of studies identified and considered it is likely that the identification of papers was comprehensive and the review was valid. Despite these limitations the current review still provides valuable information to inform future research and practice.

FUTURE RECOMMENDATIONS AND CONCLUSIONS

In both meta-analyses and descriptive analyses, BMI was consistently an indicator of SBP, DBP, TG, HDL-c and insulin; but not of TC and LDL-c or glucose. There was limited research available for either the meta-analysis or descriptive analysis for the consideration of WC and WHtR in relation to these risk factors in adolescents. The data available from both of these analyses suggested that measures of central adiposity were valid indicators of the same risk factors as BMI. Further research is needed to fully address this question and, importantly, to reach agreement regarding the method for measuring adiposity status by WC. Meta-analyses of studies using alternative analytical techniques, such as the pooling of results of correlation analyses or utilising odds ratios where cut points for elevated levels of CVD risk are applied, may also help to address these questions.

The findings of the current study, and all other meta-analyses using observational data, need to be considered in the context of major limitations of using such analyses with this type of

study. This is largely due to the large heterogeneity likely to be present in such study populations and methods. The agreement between the meta-analysis findings with those of the descriptive review, as well as the consistency of findings observed when analysing Forest plots, combined with evidence of a dose-response relationship suggests that the conclusions reached in the current study were appropriate.

Figure Legends

Figure 1: PRISMA diagram showing the study selection process.

Figure 2: (a) Meta-analysis comparing systolic blood pressure (in mmHg) between underweight/normal weight and overweight/obese participants classified using IOTF BMI criteria. (b) Meta-analysis comparing diastolic blood pressure (in mmHg) between underweight/normal weight and overweight/obese participants. (c) Meta-analysis comparing total cholesterol concentration (in $mmol \cdot L^{-1}$) between underweight/normal weight and overweight/obese participants, with high risk studies removed. (d) Meta-analysis comparing triglyceride concentration (in $mmol \cdot L^{-1}$) between underweight/normal weight and overweight/obese participants. (e) Meta-analysis comparing high-density lipoprotein cholesterol concentration (in $mmol \cdot L^{-1}$) between underweight/normal weight and overweight/obese participants. (f) Meta-analysis comparing high-density lipoprotein cholesterol concentration (in $mmol \cdot L^{-1}$) between normal weight and overweight/obese participants classified using waist circumference. (g) Meta-analysis comparing high-density lipoprotein cholesterol concentration (in $mmol \cdot L^{-1}$) between normal weight (<0.5) and overweight/obese (≥0.5) participants classified using waist to height ratio. (h) Meta-analysis comparing low-density lipoprotein cholesterol concentration (in $mmol \cdot L^{-1}$) between underweight/normal weight and overweight/obese participants, with high risk studies removed. (i) Meta-analysis comparing insulin concentrations (in $pmol \cdot L^{-1}$) between underweight/normal weight and overweight/obese participants.

Table 1: Summary of studies included in the meta-analysis (n = 13 data sets representing 14 identified records).

Table 2: Quality assessment of studies included in the meta-analysis (n = 13).

Supplementary Table 1: Mean differences in triglyceride levels between normal weight and overweight/obese groups when waist circumference was used as an adiposity index.

Supplementary Table 2: Mean differences in triglyceride levels between normal weight (<0.5) and overweight (≥0.5) groups defined using waist to height ratio.

Supplementary Table 3: Summary of included Studies.

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