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Dear Professor York,

Thank you for the opportunity to submit a revised version of the MS entitled
“Childhood predictors of cardiovascular disease in adulthood. A systematic review
and meta-analysis”.

The comments from referee 1 have been very helpful in improving the clarity of the
MS, and our response is attached.

We confirm that this work is original and has not been published elsewhere.
We report the results of a systematic review and meta-analysis examining the ability
of anthropometric measures of obesity in childhood to predict dysglycemia and adult
atherosclerotic cardiovascular disease (ACVD).

To our knowledge, this is the first analysis of longitudinal studies, investigating the
ability of Body Mass Index, weight gain, skinfold thickness, and waist circumference
to predict the risk of ACVD,

The paper should be of interest to readers in the areas of obesity, cardiovascular
disease risk, cardiac and vascular function.

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Thank you for your consideration.

Sincerely,
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1 Childhood predictors of cardiovascular disease in adulthood. A systematic review and
2 meta-analysis

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23
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42 Abstract

43 Childhood obesity predicts the risk of adult adiposity, which is associated with the

44 earlier onset of cardiovascular disease [adult atherosclerotic cardiovascular disease,

45 ACVD: hypertension, increased carotid intima media thickness (CIMT) stroke,

46 ischemic heart disease (IHD)] and dysglycemia. Because it is not known whether

47 childhood obesity contributes to these diseases, we conducted a systematic review of

48 studies that examine the ability of measures of obesity in childhood to predict

49 dysglycemia and ACVD.

50 Data sources were: Web of Science, MEDLINE, PubMed, CINAHL, Cochrane,

51 SCOPUS, ProQuest, and reference lists. Studies measuring BMI, SF, and WC were

52 selected; of 1954 studies, 18 met study criteria.

53 Results: Childhood BMI predicted CIMT: OR, 3.39 (95% CI, 2.02 to 5.67, $P < 0.001$)

54 and risk of impaired glucose tolerance in adulthood, but its ability to predict ACVD

55 events (stroke, IHD; OR, 1.04; 95% CI, 1.02 to 1.07; $P < 0.001$) and hypertension (OR,

56 1.17, 95% CI 1.06 to 1.27, $P = 0.003$), was weak-moderate. BMI was not predictive

57 of systolic BP ($r = -0.57$, $P = 0.08$) and weakly predicted diastolic BP ($r = 0.21$, $P = 0.002$).

58 SF in childhood weakly predicted CIMT in female adults only ($r = 0.09$, $P < 0.05$).

59 Conclusion: Childhood BMI predicts the risk of dysglycemia and abnormal CIMT in

60 adulthood but its ability to predict hypertension and ACVD events was weak and

61 moderate respectively. SF was a weak predictor of CIMT in female adults.

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70 INTRODUCTION

71 Obesity has become increasingly prevalent worldwide in both children and adults ^{1,2}.
72 It is detected by specific cut-offs in anthropometric measures - the most popular of
73 which is the body mass index (BMI) ^{3,4}. Although used less often in clinical practice,
74 measures of adiposity such as waist circumference (WC) and skin fold thickness (SF)
75 are thought to be more predictive of adiposity-related comorbid conditions - perhaps
76 because they more closely correlate with the presence of excess body fat ^{5,6}.
77 Irrespective of how it is measured, adult obesity is associated with dysglycemia and
78 an increased incidence of atherosclerotic cardiovascular disease (ACVD) and type 2
79 diabetes (T2D) ^{1, 7}, which together are responsible for over half of all deaths from
80 non-communicable diseases worldwide ⁸. Although the relationship between adult
81 obesity and ACVD risk factors is convincing ⁹, the association of anthropometric
82 measures of obesity in childhood with disease in adulthood remains uncertain ¹⁰. This
83 is despite the fact that increased adiposity in childhood is predictive of overweight
84 adults ¹¹, and that ACVD risk factors are more prevalent in obese children than those
85 of normal weight ^{12, 13}. The predictive ability of anthropometry in childhood ^{19, 20} may
86 relate to the method used to determine obesity. For instance, in children, BMI
87 explains just 40% of the variance in insulin resistance ^{14,15}, whereas WC appears more
88 predictive of insulin resistance and dyslipidaemia ^{16,17}. SF has been reported to
89 increase the sensitivity of WC to detect dysglycemia by up to 15% ¹⁸. To investigate
90 this, we systematically reviewed and pooled data from longitudinal studies that
91 examined the association between anthropometric measures of childhood adiposity
92 and adult ACVD, prediabetes and type 2 diabetes.

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94

95 **METHODS**

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97 We conducted a systematic review and meta-analysis of longitudinal cohort studies of
98 anthropometric measures of obesity (Body Mass Index-BMI, skinfold thickness-SF,
99 and waist circumference-WC) in childhood and the relationship to the risk of ACVD
100 and dysglycemia in adulthood. We followed the Meta-analysis of Observational
101 Studies in Epidemiology guidelines for meta-analyses and systematic reviews of
102 observational studies (MOOSE)²¹.

103 **Search Strategy**

104 We used a systematic approach for searching the literature with specific eligibility
105 criteria. We searched 7 electronic databases: Web of Science, MEDLINE, PubMed,
106 CINAHL, Cochrane, SCOPUS and ProQuest from inception through September 2014
107 to identify appropriate literature. We also searched the bibliographies of the included
108 studies to identify any other relevant articles. Our search strategy utilized medical
109 subject headings (MeSH)/ index terms across databases including the terms: BMI,
110 change in BMI, skinfold, waist circumference, cerebrovascular disease, stroke,
111 hypertension, ischemic heart disease, coronary artery disease, vascular dysfunction,
112 carotid intima media thickness, dysglycemia, impaired fasting glucose, impaired
113 glucose tolerance, type 2 diabetes, adult, and child. The full search strategy is
114 provided in the supplemental data and on the international prospective register of
115 systematic reviews (PROSPERO, registration number CRD42014014392).

116 **Study selection (figure 1)**

117 All relevant abstracts were downloaded into an online reference management system
118 (RefWorks; ProQuest LLC). Using a screening tool, two reviewers (O.A, C.B.)
119 independently evaluated and screened all citations and abstracts for eligibility. Studies

120 included were longitudinal studies of healthy children recruited between 2 and 18
121 years of age, where BMI, change in BMI, SF or WC were used as predictors of blood
122 pressure, ACVD (carotid intima media thickness, hypertension or events including
123 cerebrovascular disease/stroke ischemic heart disease or vascular dysfunction) or
124 dysglycemia (impaired fasting glucose, impaired glucose tolerance or T2D) in
125 adulthood (defined as ≥ 18 years). Although not considered direct measures of
126 adiposity, because of the link between pubertal timing and obesity²², studies of peak
127 height and weight velocity were included. No limits were placed on the searches in
128 terms of sample size, duration of follow-up, region/country/language of publication.
129 Studies were excluded if the participants were part of an intervention program, if
130 outcomes were self-reported, if anthropometric measures were classified using
131 arbitrary cut-off points, or if children with a diagnosis of malignancy, diabetes,
132 hypertension, preterm birth or low birth weight were included. A third reviewer
133 compared the entered data and resolved inconsistencies by referring to the full text
134 article (M.W.).

135 **Data extraction**

136 For each study we extracted baseline characteristics of the participants (age, gender
137 and birth cohort) and study characteristics (location, length of follow-up,
138 anthropometric measure [BMI, SF, PHV, PWV, and WC] and outcome measure).
139 Data were directly extracted from the article or from figures. Multiple attempts were
140 made to contact authors in order to obtain for data missing from published results.

141 **Study Quality Assessment**

142 Study quality was assessed using the Newcastle-Ottawa Scale (NOS)²³ for cohort
143 studies. This scale assigns ‘star ratings’ based on several criteria including:

- 144 • The representativeness of the study population compared to the community
145 average
- 146 • Demonstration that the outcome of interest was not present at the start of the
147 study,
- 148 • How the outcome was assessed, and
- 149 • Whether follow-up was of sufficient duration for outcomes to occur.

150 **Statistical Analysis**

151 The data analysis was performed using the Mantel-Haenszel method by meta-analysis
152 software ‘Comprehensive Meta-Analysis 2.0’ (Biostat, Englewood, NJ, United
153 States). For each study, we calculated the odds ratio (OR) or means for the primary
154 outcome measure of adiposity. The ORs and means were presented with 95%
155 confidence intervals (CIs), with a P-value < 0.05 considered significant. We estimated
156 the degree of heterogeneity among the trial results using the χ^2 statistic (with a P-
157 value < 0.10 considered significant) and the I^2 test (25%, 50%, and 75% represent
158 low, moderate and high heterogeneity, respectively). Whenever significant
159 heterogeneity ($P < 0.1$ or $I^2 > 50\%$) was detected, we used the random effects model
160 to combine the effect sizes of included studies; otherwise, the fixed effects model was
161 utilized. Subgroup analyses were performed for systolic and diastolic blood pressure,
162 but not for those investigating peak height and weight velocity to avoid data dredging;
163 more so there were no other studies found with similar outcomes making it impossible
164 to conduct further quantitative analysis of these studies. We assessed the presence of
165 publication bias with a funnel plot of standard error by log odds ratio (see Figure 1).
166 Large studies appear at the top of the graph and cluster near the mean effect size. The
167 absence of significant publication bias is indicated by a symmetrical distribution
168 around the combined effect size.

169 RESULTS AND DISCUSSION

170 The search identified 1954 citations (1934 from database searches and 20 from
171 reference lists) from which 18 studies were found relevant to this review. The
172 selection process has been represented using a PRISMA flow diagram (Figure 2)
173 Most of the studies were conducted in industrialized countries: six in North America
174 ²⁴⁻²⁹, five in Finland ³⁰⁻³⁴, four in the United Kingdom ³⁵⁻³⁸, one each in India ³⁹,
175 Denmark ⁴⁰, and The Netherlands ⁴¹. Of the total of 317,133 adults studied, the
176 majority were white Caucasian. The mean age at which baseline childhood data was
177 collected was 10y, and mean follow-up was 25 years. Table 1 shows the
178 characteristics of each study; Five studies were excluded from the meta-analysis
179 because the method of statistical analysis (rank correlation coefficients which cannot
180 be converted to odds ratio) precluded inclusion ²⁶, the study subjects were classified
181 based on BMI category/glycemic function in childhood ^{24, 30, 33}, or because there were
182 insufficient studies within a subgroup for adequate comparison ³³. As further analysis
183 of these studies could not be undertaken, a qualitative summary of the results was
184 prepared; these studies were not included in any statistical analyses.

185

186 *Childhood predictors for adult atherosclerotic cardiovascular disease and/or*

187 *dysglycaemia*

188 Studies used one or more of the following: BMI, standardized BMI scores, change in
189 BMI, SF, or combination of BMI and skin folds (SF) ²⁸ as childhood predictors, with
190 the exception of Tzoulaki *et al* ³³ in which peak height velocity (PHV) and peak
191 weight velocity (PWV) were used as childhood predictors.

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194 **Outcome measures**

195 Seven studies assessed the presence of ACVD by carotid intima media thickness
196 (CIMT)^{26,28,29 31,32, 38, 41}, three studied the incidence of ACVD events^{34, 36, 40}, while
197 five examined blood pressure (BP) or the presence of hypertension^{25, 27, 33, 35, 37}.
198 Hypertension was defined as at least one of the following: prescription for blood
199 pressure lowering medication, systolic BP (SBP) ≥140 mmHg, and diastolic BP
200 (DBP) ≥90 mmHg. Of the three studies that investigated the incidence of dysglycemia
201 ^{24, 33, 39}, two used both impaired glucose tolerance (IGT) and T2D^{24, 39} and one
202 studied the association with T2D alone³³. IGT and T2D were defined by either the
203 American Diabetes Association (ADA; 1997)^{24, 33} or the WHO (1998)³⁹ criteria.

204 **Study Quality and Publication Bias**

205 Study quality was assessed using appropriate elements of the Newcastle-Ottawa scale
206 ²³ (Table 2). All the studies scored at least four ‘stars’ out of a possible six indicating
207 good methodological quality. We assessed the presence of publication bias with a
208 funnel plot of standard error by log odds ratio (Figure 1). The absence of significant
209 publication bias is indicated by a symmetrical distribution around the combined effect
210 size.

211 **Meta-analysis**

212 Figure 3 provides the forest plot with pooled estimates and 95% CI values for the
213 ability of childhood BMI to predict outcomes (detailed below). Table 3 provides the
214 relative weight of each study.

215

216 **BMI/SF and CIMT**

217 Childhood BMI was predictive of CIMT in adulthood (OR, 3.5; 95% CI, 1.1 – 11.1, P
218 = 0.034) even after adjusting for adult BMI. With the variability across the studies

219 exceeding what would be expected based purely on sampling error (I^2 98.9%, $n=6$
220 studies), random effects analysis was conducted. Two studies were not included in the
221 quantitative analysis because the statistical method of analysis used was not
222 compatible for meta-analysis^{26 27}. Field *et al*²⁷ found that a 1- standard deviation
223 increase in SF in childhood was associated with 16 μ m increase in CIMT in adulthood
224 while Davis *et al*²⁶ found very weak correlations between BMI/SF in childhood and
225 adult CIMT in females (BMI: spearman rank correlation r_s 0.18, $P < 0.001$, SF r_s
226 0.09, $P < 0.05$).

227 **BMI and AVCD events**

228 Childhood BMI had a negligible ability to predict the development of ACVD events
229 in adulthood, (OR, 1.04; 95% CI, 1.02 to 1.07; $P < 0.001$). None of the studies
230 however, made statistical adjustment for the effect of BMI in adulthood. The
231 variability across the studies did not exceed what would be expected based on
232 sampling error (I^2 11.2%, $n=3$ studies).

233 **BMI, blood pressure and hypertension**

234 After statistical adjustments were made for the impact of adult BMI, childhood BMI
235 was weakly predictive of adult diastolic blood pressure (mean, 0.25; 95% CI, 0.003 to
236 0.386; $P=0.046$) but not systolic blood pressure (mean, -0.57, 95% CI, -1.22 to 0.07;
237 $P=0.082$). Due to the presence of moderate variability across the studies for diastolic
238 pressure (I^2 53%), random effects analysis was conducted. BMI in childhood
239 predicted the risk of adult hypertension (OR, 1.17, 95% CI 1.06 to 1.27, $P = 0.003$)³⁵,
240⁴⁰, while Tzoulaki *et al*³³ found no relationship between peak weight velocity in
241 childhood and adult hypertension.

242 **BMI and dysglycemia**

243 Nguyen *et al*²⁴ found that neither BMI nor childhood weight gain predicted the risk
244 of adult diabetes. However the odds ratios of developing prediabetes in adulthood
245 using baseline BMI and change in BMI in childhood were 1.44 and 1.85 respectively.
246 By contrast, the odds ratios of adult prediabetes for those at the top decile for fasting
247 insulin and HOMA-IR (insulin resistance) in childhood were 2.85 and 2.55
248 respectively. Conversely, Fall *et al*³⁹ found that those who gained weight in
249 childhood were more likely to develop IGT/T2D in adulthood (regression coefficient
250 1.25, P=0.01) as did Koskinen *et al*³⁰, who found that overweight youths without the
251 metabolic syndrome were 3.9 times more likely to develop T2D in adulthood,
252 compared to those of with the metabolic syndrome but of normal weight. None of
253 these studies made statistical adjustments for the effect of adult BMI.

254 **Discussion**

255 This systematic review and meta-analysis indicates that childhood BMI predicts the
256 risk of prediabetes and CIMT in adulthood. There was a modest predictive effect of
257 childhood BMI and adult hypertension

258 The ability of childhood BMI to predict adult ACVD events was weak. This could be
259 explained by the relatively slow progression of atherosclerosis in healthy young adults
260 or to a later change in environment or habits – for instance the uptake of cigarette
261 smoking, a significant risk factor, tends to occur no earlier than adolescence⁴²; the
262 smoking-related formation of focal plaques in coronary vessels is more predictive of
263 ischemic cardiovascular events than CIMT⁴³. BMI cannot discriminate fat from lean
264 mass, and the latter has a significant influence CIMT⁴⁴; this might explain why some
265 individuals with an abnormal CIMT and high BMI do not develop AVCD⁴⁵.

266 Although weight gain in childhood predicted T2D in adulthood, BMI predicted
267 prediabetes only. BMI is a weaker discriminator of visceral fat than measures such as

268 WC and this may impact on the ability of BMI to predict metabolic risk⁴⁶. Visceral
269 fat is associated with increased release of free fatty acids (delivered to the liver) and
270 pro-inflammatory cytokines, which lead to worsening insulin resistance⁴⁷. T2D
271 occurs once beta-cell function is no longer able to compensate for this insulin
272 resistance. Inter-individual differences in beta-cell function and/or mass may
273 therefore account for the ability of childhood BMI to predict adult prediabetes rather
274 than T2D. A longer duration of follow-up than that reported in the included studies,
275 may be required for T2D to develop.

276 Childhood BMI weakly predicted adult hypertension but did not predict adult systolic
277 blood pressure. This may relate to the relatively low tracking of systolic blood
278 pressure measurements during childhood⁴⁶.

279 In most of the included studies, statistical adjustments were not made for the
280 confounding effect of adult BMI on the risk of ACVD events or dysglycemia¹⁰. In
281 the studies that did^{32, 35, 40}, there was a partial attenuation in the effect sizes seen,
282 indicating that adult BMI may have a confounding effect on the outcomes studied.

283 Also, other potential confounders like ethnicity, socioeconomic status, birth order,
284 and so forth that were not measured, introduce further bias in the estimated effect
285 sizes described; less prominent if there is significant correlation between them, more
286 so otherwise (unmeasured confounders) The weak/modest effect sizes seen in all the
287 outcomes might also be related to the short length of follow up between childhood
288 and adulthood (25 years). For instance, the average age at which a man in a
289 westernized country is diagnosed with an acute coronary event is 65y and just 4-10%
290 of cases of myocardial infarction occur before the age of 45y⁴⁸. A longer duration of
291 follow-up would mean the accrual of more ACVD and diabetes events. More events

292 may increase the power to determine the effect of childhood anthropometric measures
293 in predicting adult disease.

294 The strengths of this systematic review and meta-analysis relate to the wide variety of
295 anthropometric measures of adiposity studied, and the use of a wide range of outcome
296 measures. We performed comprehensive searches of multiple databases and ensured
297 independent study selection and dual data extraction. Although performing a meta-
298 analysis of observational epidemiological studies is often difficult due to incomplete
299 and unstandardized reporting of studies, the quality of the included studies was good,
300 and random effect analysis was conducted where significant inter-study variations
301 was present. Limitations of this review may be that searches were limited to studies
302 published in English; few studies examined SF and WC and so more studies are
303 required to confirm the applicability of these measures of adiposity in predicting the
304 risk of adult ACVD and dysglycemia. Finally, statistical methods like meta-regression
305 which may be helpful in explaining the cause of heterogeneity, was limited by the
306 number of studies in each subgroup.

307 This systematic review found that anthropometric measures of obesity in childhood
308 predicted CIMT and prediabetes in adulthood. Childhood obesity did not predict
309 ACVD event rates in adults. Whether this relates to inherent inaccuracies of the
310 methods used to measure childhood obesity or to a lack of pathophysiologic effect of
311 childhood obesity requires further study. The prevention and reduction of childhood
312 obesity should remain a priority for public health promotion programs.

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Table 1. Description of included studies

Author, yr of publication	Participants	Country	Type of study	Age in childhood ^a	Age adulthood ^a	N	Predictor	Outcome	Results
Cardiovascular disease									
Field, AE. 2005 ²⁷	1963-70 cohort	USA	Prospective	11.7 (1.8)	22.1 (1.8)	269	BMI	Htn	1unit ↑in BMI=0.5mmHg ↑in SBP in males.
Hardy, R. 2004 ³⁵	1946 Birth cohort	England	Prospective	7 (2-15)	43	1241	BMI	Htn/BP	Negative correlation but not significant
Lauer, RM. 1989 ²⁵	Muscatine study	USA	Prospective	11 (7-18)	26-30	339	BMI	Htn/BP	In females, R=0.3 for SBP, 0.34 for DBP; in males: 0.29 and 0.14
Li, L. 2007 ³⁷	1958 Birth cohort	England	Prospective	11 (7-16)	45	7344	BMI	Htn/BP	No significant association after adjusting for adult BMI
Tzoulaki, I. 2010 ³³	1966 Birth cohort	Finland	Prospective	2	31	3246	PWV	Htn/Bp	No significant association after adjusting for adult BMI
Tzoulaki, I. 2010 ³³	1966 Birth cohort	Finland	Prospective	2	31	3069	PHV	Htn/BP	r=1.57 P 0.001 after adjusting for adult BMI
Baker, JL. 2007 ⁴⁰	1930-76 cohort	Denmark	Retrospective	11 (7-13)	25-60	276835	BMI	CVD	RR 1.14 in males, 1.10 in females
Eriksson, JG. 2001 ³⁴	1934-44 cohort	Finland	Retrospective	11	27-63	4574	BMI	CVD	Slight increase in HR 1.03 P 0.0005
Lawlor, DA. 2005 ³⁶	1950 birth cohort	Scotland	Retrospective	4.9 (0.7)	36	11106	BMI	CVD	No increase in HR
Davis, PH. 2001 ²⁶	Muscatine study	USA	Prospective	8-18	33-42	725	SF	CIMT	P=0.04 in males, 0.09 in females
Freedman, DS. 2004 ²⁹	BHS 1959-1968	USA	Prospective	11 (3)	35 (3)	513	SF	CIMT	1 unit ↑ in SSF=16μm ↑ in CIMT
Freedman, DS. 2004 ²⁹	BHS 1959-1968	USA	Prospective	11 (3)	35 (3)	513	BMI	CIMT	1 unit ↑ in BMI=14μm ↑ in CIMT P=0.03 after adjusting for adult BMI
Davis, PH. 2001 ²⁶	Muscatine study	USA	Prospective	8-18	33-42	725	BMI	CIMT	P=0.09 in males, P=0.18 in females
Freedman, DS. 2009 ²⁸	BHS 1959-1968	USA	Prospective	10 (3)	36 (4)	1142	BMI	CIMT	1 unit ↑in BMI=16μm ↑in CIMT after adjusting for adult BMI
Juonala, M. 2006 ³¹	YFS	Finland	Prospective	12 (3-18)	33	408	BMI	CIMT	r=0.05(ns) after adjusting for adult BMI
Oren, A. 2003 ⁴¹	ARYA	Netherlands	Prospective	12-16	28.4 (1.6)	750	BMI	CIMT	r=0.9 after adjusting for adult BMI
Oren, A. 2003 ⁴¹	ARYA	Netherlands	Prospective	12-30	28.4 (1.6)	750	BMI Δ	CIMT	r 11.8 P 0.01
Raitakari, OT. 2003 ³²	YFS	Finland	Prospective	14.9 (2.4)	31.7 (5)	1170	BMI	CIMT	Small association: r: 0.009, P=0.007
Wright, CM. 2001 ³⁸	1947 Birth cohort	England	Prospective	9, 13 (9y data)	50	412	BMI	CIMT	r=-0.02 in women, -0.1 in men after adjusting for adult BMI
Dysglycemia									
Nguyen, QM. 2010 ²⁴	BHS 1981-2000	USA	Prospective	11.6 (3.6)	28.3 (5.1)	1120	BMI Δ	IGT	OR 1.44 P<0.05 for developing IGT
Nguyen, QM. 2010 ²⁴	BHS 1981-2000	USA	Prospective	11.6 (3.6)	28.3 (5.1)	1120	BMI	IGT	OR 1.85 P<0.01 for developing IGT
Koskinen, J. 2014 ³⁰	YFS	Finland	Prospective	16.2 (5.3)	32-46	1330	BMI	T2D	Obesity associated with 3.9 fold increase in risk of T2D
Nguyen, QM. 2010 ²⁴	BHS 1981-2000	USA	Prospective	11.6 (3.6)	28.3 (5.1)	1120	BMI Δ	T2D	Not predictive
Nguyen, QM. 2010 ²⁴	BHS 1981-2000	USA	Prospective	11.6 (3.6)	28.3 (5.1)	1120	BMI	T2D	Not predictive
Fall, CH. 2008 ³⁹	1969-1972 cohort	India	Prospective		29.2 (1.3)	1492	BMI Δ	T2D/IGT	OR 1.25 P 0.01 for developing IGT/T2D

^a mean age in years, standard deviation (sd) stated where available, age range stated otherwise. PWV: Peak weight velocity, PHV: peak height velocity, BMI: Body mass index (kg/m2), SF: Skin fold thickness; WHR: waist-hip ratio; BP: blood pressure; Htn: Hypertension, defined as systolic ≥140mmHg and/or diastolic ≥90mmHg; IGT and T2D: defined according to ADA criteria in 2 studies (14,15) and 1999-WHOcriteria in one study(16). CIMT: carotid intima media thickness; r: regression coefficient; HR: Hazard ratio; OR: Odds ratio; *P*: Spearman rank correlation; ns: P >0.05; N refers to number of participants in adulthood. YFS: Young Finns Study; ARYA: Atherosclerosis Risk in Young Adults study; BHS: Bogalusa Heart Study

Table 3. Relative weights of studies

Table 4. Quality assessment based on the Newcastle-Ottawa Quality Assessment Scale

Author, yr of publication	Representative ^a	Data source ^b	Adjusts for adult measure ^c	Assessment of Outcome ^d	Follow up ^e	Adequacy of follow up ^f
Baker, JL. 2007 ⁴⁰		*		*	*	*
Davis, PH. 2001 ²⁶	*	*		*	*	*
Eriksson, JG. 2001 ³⁴		*		*	*	*
Fall, CH. 2008 ³⁹	*	*		*		*
Field, AE. 2005 ²⁷		*		*	*	*
Freedman, DS. 2004 ²⁹	*	*	*(for BMI not SF)	*	*	*
Freedman, DS. 2009 ²⁸	*	*	*	*	*	*
Hardy, R. 2004 ³⁵	*	*		*	*	*
Juonala, M. 2006 ³¹	*	*	*	*	*	*
Koskinen, J. 2014 ³⁰	*	*		*	*	*
Lauer, RM. 1989 ²⁵	*	*		*	*	*
Lawlor, DA. 2005 ³⁶	*	*		*	*	*
Li, L. 2007 ³⁷	*	*	*	*	*	*
Nguyen, QM. 2010 ²⁴	*	*		*	*	*
Oren, A. 2003 ⁴¹	*	*	*	*	*	*
Raitakari, OT. 2003 ³²	*	*	*	*	*	*
Tzoulaki, I. 2010 ³³	*	*	*	*	*	
Wright, CM. 2001 ³⁸	*	*	*	*	*	*

a Truly representative or somewhat representative = * rating ; b Secure record linkage = * rating; c Study controls for corresponding adult anthropometric measure = * rating
d Independent blind or record linkage = * rating; e Was follow up long enough (16 years) for outcomes to occur=* rating; f All subjects accounted for/those lost to follow up unlikely to introduce bias/small number lost (<30%)/description provided for those lost = * rating

Figure 1. Publication Bias

Large studies appear at the top of the graph and cluster near the mean effect size.

Publication Bias

120x87mm (300 x 300 DPI)

Figure 2.
Study selection process

Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement*. PLoS Med 6(6) e1000097

Study Selection

159x145mm (300 x 300 DPI)

Table 2. Meta-Analysis

Meta Analysis

276x158mm (150 x 150 DPI)