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Is body mass index before middle age related to coronary heart disease risk in later life? Evidence from observational studies

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Abstract

Objective—Although obesity beginning early in life is becoming more common, its implications for coronary heart disease (CHD) risk in later life remain uncertain. We examined the relationship of body mass index (BMI) before 30 years of age to CHD risk in later life.

Design—Systematic review of published studies relating BMI between age 2-30 years to later CHD risk. Studies were identified using Medline (1950 onwards), Embase (1980 onwards) and Web of Science (1970 onwards) databases (to November 2007).

Measurements—Relative risks (RR) of CHD associated with a 1 standard deviation (SD) increase in BMI (most based on a narrow age-range at measurement) were extracted by 2 authors independently, and combined using random-effect models.

Results—Fifteen studies provided seventeen estimates (731,337 participants, 23,894 CHD events) of the association of early BMI to later CHD outcome. BMI in early childhood (2 to 6 years, 3 estimates) showed a weak inverse association with CHD risk (RR 0.94, 95% CI 0.82-1.07). BMI in later childhood (7 to <18 years, 7 estimates) and BMI in early adult life (18-30 years, 7 estimates) were both positively related to later CHD risk (RR 1.09, 95% CI 1.00-1.20; RR 1.19, 95% CI 1.11-1.29 respectively). However, there was considerable statistical heterogeneity between study estimates. Results were unaffected by adjustment for social class and/or cigarette smoking, blood pressure and/or total cholesterol, in studies with available data. Gender and year of birth (1900-1976) had little effect on the association.

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Contributors

CGO, PHW, DGC, CO, JRE contributed substantially to the conception and design of this paper. QC, AKW, SJK carried out the literature search, CGO and LO extracted data and carried out the statistical analyses. The paper was critically appraised by all authors for intellectual content; CGO drafted the paper and will act as guarantor. The guarantor accepts full responsibility for the integrity of the work as a whole. All authors had access to the data, and approved the final version to be published.

Competing interests

None to declare

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Conclusions—BMI is positively related to CHD risk from childhood onwards; the associations in young adults are consistent with those observed in middle age. Long-term control of BMI from childhood may be important to reduce the risk of CHD.

Keywords

Body mass index; coronary heart disease; child/children; adolescent; young adults

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Introduction

Obesity is a major public health problem and is increasing in prevalence in both the developed and developing world.1-3 The increase in the prevalence of obesity is occurring not only in adults, but also in children and adolescents, in whom relative increases in obesity prevalence are particularly striking.4 As a consequence, long-term overweight from childhood and early adult life onwards is becoming increasingly common.5 It is well established that overweight and obesity in middle age are associated with coronary heart disease,6;7 which is a major cause of morbidity and mortality worldwide.8 Two recent reviews of the strength of the prospective relationship between adiposity in adult life (measured as body mass index [BMI]) and CHD risk have suggested that a 1 kg/m^2 higher BMI is associated with increases in CHD risk of approximately 7% 9;10 and 5%.7 The association is largely independent of confounding by cigarette smoking 9 but is partly mediated by blood pressure and blood lipids.7 However, the long-term implications of overweight and obesity in childhood and early adult life for CHD in adult life remain unclear. The results of individual studies relating BMI in early life to later CHD risk have been inconsistent, particularly in the first decade.11-13 To date, no systematic assessment of published evidence on the relation of BMI in early life to CHD risk, taking account of the age of BMI measurement, differences in the size and statistical power of different studies, the degree of adjustment for potential confounding or mediating variables and the possibility of publication bias, has been undertaken. We have therefore carried out a systematic review of published evidence on the relation of BMI in childhood, adolescence, and early adulthood (from 2 to 30 years) to CHD risk in later life. The results are set in context of the reported strength of the relation of BMI in middle age to CHD risk from analyses based on 57 prospective cohort studies.10

Methods

Rationale

Apart from age and gender, the main potential confounders of the association between BMI and CHD in adults include the presence of pre-existing disease and cigarette smoking.14 However, the impact of cigarette smoking on the adult BMI-CHD association is very limited 9 and the impact of pre-existing CHD of limited relevance in children and young adults. In the present review, our primary aim was therefore to examine the unconfounded associations between BMI, measured at ages between 2 and 30 years, and later CHD risk. Because confounding by cigarette smoking and pre-existing CHD is likely to be of limited relevance in younger populations, the main analysis has been based either on unadjusted or (where available) age-adjusted and (where appropriate) age and gender - adjusted associations. Importantly, analyses adjusted for body weight or BMI at another age are potentially misleading15 and have been excluded from consideration. For the primary analyses, crude or age-adjusted estimates were obtained from published reports or, where not available from published reports, directly from study authors. For secondary analyses, the impact of potential confounders (particularly cigarette smoking and socioeconomic status) and

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potential mediators (blood pressure and blood lipids) have been examined using published data where available.

Studies that measured BMI in children and young adults (to 30 years) with CHD outcome in later life

Eligible studies were those that examined the association of measures of BMI in childhood or early adulthood (average age of BMI assessment between 2 and 30 years of age) with coronary heart disease (CHD), either fatal, non-fatal or both in population-based samples which were not specifically restricted to participants with specific BMI levels. Studies with outcomes including, but not exclusively based on CHD (for example all cardiovascular events) were excluded. No other specific exclusion criteria were imposed. We searched Medline (1950 onwards), Embase (1980 onwards) and Web of Science (1970 onwards) databases for published papers, letters, abstracts and review articles. References were identified using combined text words, MESH and subject headings (for Medline and Embase respectively) - see Appendix. The electronic search, which was restricted to studies carried out on human subjects, written in English language (completed by QC, AKW, SJK in November 2007), yielded 2103 unduplicated references; a review of abstracts showed that 31 were potentially relevant (Figure 1).9;12;13;16-43 Manual searches of citations from these papers identified a further 3 papers - 34 papers in total.44-46 Two papers known to the authors published after the search was completed (as of December 2007) were also included, 11;47 one of which replaced an abstract identified in the review referring to the same study. 11;16 Twenty studies were excluded; one was a review article,9 6 studies used a population examined in other reports,24-26;28-30 11 did not examine the association between early measures of adiposity (BMI) and CHD outcomes in later life,17-20;31;35-37;39;41;42 one study considered cardiovascular disease mortality rather than CHD as an outcome,22 and another study only followed overweight children into adulthood 21 (Figure 1). Hence, 15 studies (including 731,337 participants) were considered further. 11-13;23;27;32-34;38;40;43-47 A paper presenting findings from 2 historic cohorts provided unique data for one cohort (Christ's Hospital),38 and replaced data previously published from another study.34

Data extraction

The relative risk of CHD (morbidity and/or mortality, with combined events where possible) per 1 kg/m^2 increase and per SD increase in BMI was extracted from each study (Table 1) along with other study characteristics, by 2 authors independently (CGO, LO) using a predefined variable list. Any discrepancies in study estimates extracted by the authors were resolved and agreed. For 12 studies hazard ratios from proportional hazards models provided estimates of relative risks;11-13;23;27;32-34;38;38;40;46;47 for the remaining 3 studies odds ratios provided relative risk estimates.43-45 In two of those studies, the proportion of cases were around 10% or less,43;45 in the third the proportion was 20%.44 Odds ratios will be approximately synonymous with hazard ratios in the 2 former studies when the proportion of cases are 10% or less.43;45 In studies which presented the relations between early life BMI at more than one age point in the same individuals to later CHD,11;12;23 estimates for the youngest age-group were extracted (except where estimates from the same individuals could be included in separate age groups).12 Both combined gender and gender-specific estimates were extracted where available. Published studies presented results with various levels of adjustment, ranging from crude associations to adjustment for measures of body size in infancy, socio-economic status (in childhood and/or adulthood), education and cardiovascular risk factors (Table 1). Crude or age-adjusted associations could be obtained for the majority of studies, with most having a narrow age range at which BMI was measured. The main analysis was based on crude or, where available, age-adjusted estimates of relative risk; analyses adjusted for BMI at another age-point were excluded from analysis.

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In two studies in which published estimates were only available adjusted for BMI at another point in early life (in one study the relation of BMI at 2 years to adult CHD was adjusted for BMI at 11 years,12 and in another the association between BMI at 7 years to adult CHD was adjusted for ponderal index at birth)23 unadjusted estimates were sought and obtained directly from the authors (Eriksson, Osmond).12;23 In addition, two other types of adjusted relative risks were sought. The first group included adjustment for potential confounding factors (including socioeconomic status and cigarette smoking, but excluding blood pressure and blood lipids and BMI in later life). The second group included relative risks adjusted for potential cardiovascular mediators of adiposity effects (blood pressure and blood lipids but excluding BMI in later life).

Statistical analysis

Statistical analysis was carried out using STATA/SE software (Stata/SE 9.2 for Windows, StataCorp LP, College Station, TX, USA). The relative risks of CHD for both a 1 kg/m^2 and SD increase in BMI were used as the main outcomes, with their variances. The latter was used as the principal outcome because the SD of BMI increased with age. When relative risks were presented for BMI groups (often quintiles), rather than for BMI as a continuous variable, estimates were derived using log-linear dose response regression.48 The assumption of log linearity is supported by the findings of earlier studies 9;11 and was verified in the present analyses by plotting relative risks across BMI groups for relevant studies to check the shape of the associations. In one study, the effect was estimated from the published relative risk comparing heavier versus normal weight percentiles, by scaling the relative risk by the inverse of the difference in BMI between percentile groups.40

Heterogeneity in the relative risk of coronary outcome between studies was examined using the I^2 index, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance.49 Cochran's Chi-Square (Q-test) was used to provide a formal statistical test of heterogeneity.49 Small study bias (the tendency of small, non statistically significant studies not to be published) was assessed using funnel plots, Begg tests and Egger tests.50-52 Trim and fill analysis (based on a random-effects meta-analytic point estimate) was also performed, in order to formally identify funnel plot asymmetry.53 Relative risks were generally heterogeneous and were therefore combined using random effect models (using the METAN command) throughout. Because of concerns that the BMI-CHD association may alter with age, meta-analyses were carried out stratified by age-group at which BMI was measured (<7, 7 to <18, 18 to 30 years); the age 7 cut point was decided a posteriori, the age 18 cut point a-priori. In one study with a broad age range when BMI was measured (2-15 years), estimates were obtained directly from study authors in those age 2 to <7 years, and 7 to 15 years.33 Supplementary analyses examined the influence of study size (to further examine for the presence of small study bias), definitions of coronary outcome (fatal and / or non-fatal), and method of BMI ascertainment (direct measurement vs. recall). Meta-regression (METAREG command using the residual maximum likelihood method, which gave similar findings to the Monte Carlo 'permute' option) was used to examine the influence of the following factors (defined *a priori*) using a test for trend: age at BMI assessment, mean BMI, year of birth, duration of follow up, number of events, and study size (all fitted univariately as continuous variables, with a constant term). A post estimation command (LINCOM) was used after the meta-regression to further examine the effect of age at BMI measurement, in order to estimate the age at which the BMI-CHD association becomes positive. Meta-regression was also used to examine the influence of gender, the definition of coronary outcome (CHD morbidity, CHD hospitalization or death, and CHD death) and whether estimates were crude or adjusted, treated as categorical variables.

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Results

Study characteristics

Relative risks of CHD morbidity or mortality per SD rise in BMI were extracted from all 15 studies that met the inclusion criteria (731,337 individuals, of whom 23,894 had a CHD outcome, Table 1). One study with a wide age-range at recruitment (2 to 15 years) provided 2 estimates for young and older children.33 A second cohort study provided data from the same children for two different age groups at 2 years and 11 years of age.12 The remaining 13 studies provided single estimates.11;13;23;27;32;34;38;40;43-47 Hence, in total there were 17 estimates from 15 studies. Three study estimates were available for BMI at a mean age of less than 7 years,12;13;33 7 study estimates were available between 7 to <18 years (including 2 studies which also measured BMI in the youngest age group), 11;12;23;33;38;40;47 and 7 study estimates from 18 to 30 years.27;32;34;43-46 Estimates for both genders combined were obtained directly from two studies,13;34 by combining data for males and females in a further three studies (using fixed-effect models),11;40 or directly from the authors in 2 studies.12;33 Of the remaining studies, 7 had estimates for males 23;27;32;38;43-45 and one for females.46 Twelve studies were based in Northern Europe 11;12;23;27;44;45;47 (including 5 from the UK),13;33;34;38;43 and 3 from North America. 32;40;46 Eleven studies measured BMI directly,11-13;23;27;33;34;38;40;44;47 while 4 studies relied on participants recalling their weight after approximately 20 to 40 years (either at 18,43;46 20 45 or 25 years of age).32

Association between a 1 kg/m^2 increase in BMI and CHD risk

Age-adjusted or crude relative risks of CHD outcome per 1 kg/m^2 rise in BMI are shown in Figure 2 and Table 1. Almost all studies showed positive associations with CHD risk. The exceptions were 2 studies in the youngest age-groups, which showed a clear inverse association at 2 years 12 and a weak inverse association at 5 years, 13 and one study in early adulthood where a modest inverse association was apparent.38 Between 7 and less than 18 years of age (7 observations), a 1 kg/m^2 increase in BMI was associated with a 5% increase in the risk of CHD (relative risk 1.05 (95% CI 1.01, 1.09); between 18 and 30 years of age (7 observations) a 1 kg/m^2 increase in BMI was associated with a 8% increase in the risk of CHD (relative risk 1.08 (95% CI 1.05, 1.11). Although the direction of associations were similar for almost all studies, there was considerable heterogeneity in the estimates from different studies; even within age-groups most of the variation between studies could not be attributed to chance (I^2 values >70%, Table 2). In a meta-regression analysis based on studies of BMI from 7 years and over, there was little evidence to suggest that the association increased in strength with age (0.3%, 95% CI -0.2, 0.7% per year P=0.18). A bubble plot showing the logged relative risk of CHD per 1kg/m^2 rise in BMI by age at BMI measurement (with the bubble size for each study related to the inverse of the variance) is available from the website (supplemental Figure 1).

The SD of BMI increased with age during childhood, from 1.6 kg/m^2 under age 7 to 2.5 kg/m^2 at 18 to 30 years (Table 2). Because the implications of a unit increase in BMI represents a different shift in the BMI distribution at different ages, our main analyses focus on the effect of a 1 SD increase in BMI on CHD risk.

Association between a 1 SD increase in BMI and CHD risk

The relations of a 1 SD increase in BMI to CHD risk in age-adjusted or crude analyses are shown in Figure 3. Almost all studies in both children and adults showed positive associations with CHD risk. The exceptions are again the studies in the youngest children, which show a clear inverse association at 2 years 12 and a small inverse association at 5 years,13 and a study where BMI was measured at 17 years of age which showed a weak

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inverse relationship.38 There was evidence of marked heterogeneity in the effect of an SD increase in BMI across age groups (I^2=79%, 95% CI 32 to 93%, df 2, P<0.001), and from 7 years of age onwards (I^2=92%, 95% CI 89 to 95%, df 13, P<0.001). Combined estimates by age-groups (Table 2) showed positive associations between an SD increase in BMI and risk of CHD outcome from 7 years of age. BMI at 7 to <18 years of age (7 estimates) and 18 to 30 years (7 estimates) were both positively related to CHD risk (RR 1.09, 95%CI 1.00,1.20; RR 1.19, 95%CI 1.11, 1.29 respectively). Although heterogeneity was marginally reduced in these age-groups compared to all ages, considerable heterogeneity was still apparent (I^2 values >60%, Table 2). A bubble plot showing the natural log of the relative risk of CHD per 1 SD rise in BMI by age at which BMI was measured (with the bubble size for each study related to the inverse of the variance) is available from the website (supplemental Figure 2). The Figure suggests a log-linear trend between BMI and CHD outcome with age; a meta-regression showing a 1.3% increase (95% CI 0.4 to 2.2%, P=0.005) per year. The modelled relative risk crossed the line of unity at 6.0 years of age (relative risk 1.00, 95% CI 0.91,1.09).

Analyses of potential confounding and mediating factors—Adjustment for social class and/or cigarette smoking (examined in 4 studies)33;34;38;46 had little or no effect on relative risk estimates (1.13, 95% CI 0.98, 1.30 before adjustment, 1.13, 95% CI 1.03, 1.25 after adjustment), although effect estimates were marginally more homogeneous after adjustment (I^2 from 81% before to 60% after adjustment). Similarly, adjustment for factors including blood pressure and/or total cholesterol (examined in 3 studies)27;32;44 had little or no effect on relative risk estimates (1.25, 95% CI 1.15, 1.35 before adjustment, 1.25, 95% CI 1.17, 1.33 after adjustment), but estimates were less heterogeneous after adjustment (I^2 from 68% to 46%).

Tests for publication and small study bias and sensitivity analyses—In analyses based on SD increases in BMI, forest plots (Supplemental Figure 3), Begg and Egger tests (although of limited power), showed no evidence of publication or small study bias (P=0.8, P=0.3 respectively). Trim and fill analysis did not reveal any evidence of funnel plot asymmetry (with no theoretical missing studies being identified). Meta regressions (excluding the 3 observations where BMI was measured at less than 7 years) and sensitivity analyses, showed no appreciable effect of gender (11 observations in males versus 5 in females), year of birth, period of follow-up, method of BMI ascertainment, age at outcome (all P-values >0.1). The relative risks did not differ appreciably between different CHD outcomes (P=0.8) and did not differ between 10 studies with direct ascertainment of early life BMI and 4 studies in which BMI was recalled over an extended period (P=0.5). Relative risks were also unrelated to the follow-up rates achieved in the prospective studies.

Discussion

The results of this systematic review and meta-analysis of published studies suggest that BMI from about 7 years of age shows a consistently positive relation to risk of CHD. There is appreciable heterogeneity between study estimates. Limited published data suggest that the positive BMI-CHD association is not materially affected by adjustment for potential confounding factors (cigarette smoking and social class) or for potential mediators (blood pressure or blood cholesterol). In the first years of life, BMI appears to show a weak inverse association with CHD risk.

Strengths and weaknesses

A major strength of this review is that it included data from all studies identified that examined the relation between BMI from early childhood to the third decade of life. There

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was no evidence of small study or publication bias. For most studies, information on BMI in early life was ascertained by direct measurement and there was no apparent difference in the results of the limited number of studies using recalled BMI. Analyses are based on the assumption of a log-linear association between BMI and CHD risk, which is consistent with methods used in other studies,9;11 and supported by inspection of the data from studies where the risk of CHD could be examined across several BMI groups.27;32;43;46 Although the use of BMI as a measure of adiposity has been criticised,54 the measurement is very strongly positively correlated with DXA-measured fat mass both in children and adolescents 55-57 and in adults58 and is by far the most widely reported measure of adiposity available in epidemiological studies.59 While the findings are applicable to populations in Northern Europe and Northern America, no studies from low / lower middle income countries were included in the review. Further data from these latter countries are needed.

Interpretation

The results of this study suggest that BMI assessed at any point between about 7 years and 30 years of age is positively related to CHD risk. Does this positive association reflect a causal association between BMI in early life and later CHD? The estimates from different studies show appreciable statistical heterogeneity, but little biological heterogeneity; estimates of association are consistently positive and broadly similar in strength. Evidence on confounding by cigarette smoking and social class was available from 4 studies. 33;34;38;46 Adjustment for these variables, which appeared to be well measured in these studies, had little effect on relative risk estimates. This does not suggest that the BMI-CHD association is appreciably confounded by cigarette smoking and social class, though the wide confidence limits around the estimates make the finding, which is consistent with observations on BMI in adults,9 a provisional one. Evidence from 3 studies 27;32;44 shows little evidence that the BMI-CHD relationship is appreciably mediated by blood pressure and/or blood cholesterol. However, the extent of these adjustments was limited with only one of the three studies being able to adjust for both factors. Hence, further studies are needed to examine whether the early BMI-later CHD association is mediated through established cardiovascular risk factors, particularly blood pressure and lipids.

The strengths of association between BMI and CHD risk, both when measured in absolute terms (a 1 kg/m^2 increase) and as an SD increase, increase slightly with age and are very consistent with those observed in middle age. In the present review, a 1 kg/m^2 increase in BMI measured between 7 to 30 years of age is associated with a relative risk of CHD rising from about 1.05 to 1.08. A recent systematic review and meta-analysis based on 57 prospective cohort studies (with over 10,000 CHD events in 894,576 participants) showed that a 1 kg/m^2 increase in BMI in middle age was associated with a relative risk of CHD of 1.07 (95% CI 1.06, 1.08);10 the results of an earlier review (12,112 events, 267,984 participants) also suggested a corresponding estimate of 1.07.9 Corresponding comparisons of the strength of associations for SD increases at different ages suggest that per SD increases in CHD risk go up from 1.09 in children over 7 years to about 1.19 in young adults and to about 1.23 in middle age (assuming an SD of about 3.5 kg/m^2 in middle age).9 The continuity of these associations between childhood, early adult life and middle age suggests that the relationship between BMI and CHD risk is developing well before middle age.7 Assuming that these associations are causal, and that one-fifth of the population with the lowest BMI are unexposed to risk, the population attributable risk fraction for CHD is approximately 10% for childhood obesity and 20% for obesity in early adult life. The strength of these associations is therefore sufficiently large to be of potential public health importance.

There is strong biological plausibility for the importance of BMI early in life for later CHD risk. A higher body mass index is associated from childhood onwards with unfavourable

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levels of established cardiovascular risk factors, particularly blood pressure, blood lipids and other components of the metabolic syndrome,60-62 and with direct effects on arterial structure or function63;64 and the development of early atherosclerotic changes.65 However, a central question is whether the association between early BMI and CHD risk entirely reflects the influence of early BMI on BMI attained in middle-age. Analyses examining the effect of adjustment for adult BMI on the association between early BMI and CHD risk have been reported for only 2 studies and were inconclusive.15;43 In one very large study of 115,818 participants, the positive relation of BMI at 18 years to later CHD risk (relative risk 1.23 95%CI 1.15, 1.32) was abolished after adjustment (RR 0.99, 95% CI 0.92,1.07). In a second, smaller study with BMI measurements at 13 to 18 years, the relation of a 1 SD increase in BMI with CHD (1.92, 95% CI 1.07, 3.61) was reduced by almost a half (1.55, 95% CI 0.78, 3.07), but remained statistically significant.15 However, the validity of the conclusions of such analyses have been questioned.15 Reliable assessment of the independent contribution of early BMI to CHD risk is likely to require longitudinal observational studies with multiple repeated assessments of BMI over the life course, analysed to examine the influence of the duration as well as the extent of obesity on CHD risk. Studies examining the extent to which the risks of CHD associated with raised BMI can be reversed by weight loss in middle age, a question which currently remains unanswered,66 will also help to address this issue.

The weak inverse relationship observed in this review between BMI in early childhood and CHD does not appear to reflect changes in the validity of BMI as a measure of adiposity, which remains high in early childhood.55 The finding that BMI in early childhood might be inversely related to CHD risk, though based on limited evidence, is entirely consistent with the large body of literature showing that low weight and weight-for-length at birth and in infancy are inversely related to CHD risk.67;68 Although the precise mechanisms underlying this association have not been resolved, undernutrition in fetal life and infancy have been implicated.69 The observations that the BMI-CHD association may be inverse in early childhood but positive from later childhood onwards, imply that there must be a reversal of the direction of the BMI-CHD association from inverse to positive, probably within the first decade of life. This conclusion is consistent with observations from the Helsinki Birth Cohort Studies, in which subjects who developed CHD had a lower than average BMI up to the age of 2 years, but then showed a progressive reversal, with higher than average BMI being associated with CHD risk by the end of the first decade.12 Thus the reported inconsistency in findings for BMI during the first decade13 is likely to reflect a change in the pattern of relationships with increasing age. These different patterns may well reflect the different implications of higher BMI at different ages.70 Gains in weight and body mass index during infancy and early childhood predominantly reflect lean body mass/ muscle mass development (associated with better adult outcomes); whereas higher BMI later in childhood mainly reflects gain in fat mass (associated with worse adult outcomes).71

Further evidence on the impact of early life and later life obesity, to establish whether the effects are cumulative, and whether there are particularly adverse consequences from the combination of obesity both in early life and later life will require data from long-term studies with multiple BMI measurements. Although existing longitudinal studies of CHD can provide important information on these issues, most are based in populations which at the time of study had relatively low rates of overweight and obesity in childhood and early adult life. New cohort studies, particularly in populations with high rates of early life obesity (now occurring both in high income and low income countries), will be needed to resolve these issues. In the meantime, there is a strong presumption that early life obesity is likely to have adverse effects for cardiovascular disease, as well as for other chronic diseases, making primary prevention of obesity from early childhood onwards an important public health priority.

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Main conclusions

Higher levels of BMI may be related to increased levels of CHD risk from early childhood onwards. Although the independent contribution of early obesity to CHD risk has still to be established, the control of obesity from childhood onwards may be an important priority for long-term CHD prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix: Search strategies used

Medline

(((Coronary Heart Disease) OR (Ischaemic heart disease) OR (Ischemic heart disease) OR (Cardiovascular Disease) OR (Cardiovascular mortality) OR (Myocardial infarction)).tw) AND (((Child) OR (Childhood) OR (Children) OR (Adolescent) OR (Adolescence) OR (Teenage$) OR (Early adulthood) OR (Young adults)).tw)

AND ((Body Mass Index).tw) OR (((Coronary Disease/) OR (Cardiovascular Diseases/) OR (Myocardial Infarction/) OR (Myocardial Ischemia/))

AND ((CHILD/) OR (ADOLESCENT/)) AND (Body Mass Index/))

Embase

(((Coronary Heart Disease) OR (Ischaemic heart disease) OR (Ischemic heart disease) OR (Cardiovascular Disease) OR (Cardiovascular mortality) OR (Myocardial infarction)).tw) AND (((Child) OR (Childhood) OR (Children) OR (Adolescent) OR (Adolescence) OR (Teenage$) OR (Early adulthood) OR (Young adults)).tw)

AND ((Body Mass Index).tw) OR (((Coronary Artery Disease/) OR (Cardiovascular Disease/) OR (Heart Infarction/) OR (Heart Muscle Ischemia/))

AND ((CHILD/) OR (ADOLESCENT/)) AND (Body Mass/)))

Web of Science

(((Coronary Heart Disease) OR (Ischaemic heart disease) OR (Ischemic heart disease) OR (Cardiovascular Disease) OR (Cardiovascular mortality) OR (Myocardial infarction))

AND ((Child) OR (Childhood) OR (Children) OR (Adolescent) OR (Adolescence) OR (Teenage) OR (Early adulthood) OR (Young adults))

AND ((Body Mass Index)))

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Key

$=wildcards, tw=text words, upper case words and / denote MESH (for Medline) and subject (for Embase) headings. Note, Web of Science searches are text word only.

Reference List

1. Seidell JC, Flegal KM. Assessing obesity: classification and epidemiology. Br.Med.Bull. 1997; 53:238–52. [PubMed: 9246834]
2. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech.Rep.Ser. 2000; 894:1–253.
3. de Onis M, Blossner M. Prevalence and trends of overweight among preschool children in developing countries. Am.J.Clin.Nutr. 2000; 72:1032–9. [PubMed: 11010948]
4. Ebbeling CB, Pawlak DB, Ludwig DS. Childhood obesity: public-health crisis, common sense cure. Lancet. 2002; 360:473–82. [PubMed: 12241736]
5. Reilly JJ, Methven E, McDowell ZC, et al. Health consequences of obesity. Arch.Dis.Child. 2003; 88:748–52. [PubMed: 12937090]
6. Kushner RF. Body weight and mortality. Nutr Rev. 1993; 51:127–36. [PubMed: 8332284]
7. Bogers RP, Bemelmans WJ, Hoogenveen RT, et al. Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons. Arch.Intern.Med. 2007; 167:1720–8. [PubMed: 17846390]
8. Rogers, A.; Vaughan, P. The World Health Report 2002: Reducing Risks, Promoting Healthy Life. Geneva, Switzerland: World Health Organization; 2003.
9. Whitlock G, Lewington S, Mhurchu CN. Coronary heart disease and body mass index: a systematic review of the evidence from larger prospective cohort studies. Seminars in Vascular Medicine. 2002:369–81. vasc. [PubMed: 16222627]
10. Whitlock G, Lewington S, Sherliker P, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009; 373:1083–96. [PubMed: 19299006]
11. Baker JL, Olsen LW, Sorensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. N.Engl.J Med. 2007; 357:2329–37. [PubMed: 18057335]
12. Barker DJ, Osmond C, Forsen TJ, et al. Trajectories of growth among children who have coronary events as adults. New England Journal of Medicine. 2005; 353:1802–9. [PubMed: 16251536]
13. Lawlor DA, Leon DA. Association of body mass index and obesity measured in early childhood with risk of coronary heart disease and stroke in middle age: findings from the aberdeen children of the 1950s prospective cohort study. Circulation. 2005; 111:1891–6. [PubMed: 15837941]
14. Manson JE, Stampfer MJ, Hennekens CH, et al. Body weight and longevity. A reassessment. JAMA. 1987; 257:353–8. [PubMed: 3795418]
15. Tu YK, West R, Ellison GT, et al. Why evidence for the fetal origins of adult disease might be a statistical artifact: the “reversal paradox” for the relation between birth weight and blood pressure in later life. Am.J Epidemiol. 2005; 161:27–32. [PubMed: 15615910]
16. Baker J, Olsen L, Sorensen T. Excess childhood body mass index at age 7 years is associated with coronary heart disease (CHD) in adulthood among 201,670 Danish schoolchildren. Obesity Research. 2005; 13:A98.
17. Carnethon MR, Gidding SS, Nehgme R, et al. Cardiorespiratory fitness in young adulthood and the development of cardiovascular disease risk factors. JAMA. 2003; 290:3092–100. [PubMed: 14679272]
18. Cook S. The metabolic syndrome: antecedent of adult cardiovascular disease in pediatrics. Journal of Pediatrics. 2004; 145:427–30. [PubMed: 15480357]
19. Cox BD, Whichelow M. Ratio of waist circumference to height is better predictor of death than body mass index. BMJ. 1996; 313:1487. [PubMed: 8973270]
20. Dietz WH. Childhood weight affects adult morbidity and mortality. Journal of Nutrition. 1998; 128(Suppl):414S.

Europe PMC Funders Author Manuscripts

21. DiPietro L, Mossberg HO, Stunkard AJ. A 40-year history of overweight children in Stockholm: life-time overweight, morbidity, and mortality. International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity. 1994; 18:585–90. [PubMed: 7812410]
22. Dyer AR, Stamler J, Garside DB, et al. Long-term consequences of body mass index for cardiovascular mortality: the Chicago Heart Association Detection Project in Industry study. Annals of Epidemiology. 2004; 14:101–8. [PubMed: 15018882]
23. Eriksson JG, Forsen T, Tuomilehto J, et al. Catch-up growth in childhood and death from coronary heart disease: longitudinal study. BMJ. 1999; 318:427–31. [PubMed: 9974455]
24. Eriksson JG, Forsen T, Tuomilehto J, et al. Early growth and coronary heart disease in later life: longitudinal study. BMJ. 2001; 322:949–53. [PubMed: 11312225]
25. Eriksson JG, Forsen TJ. Childhood growth and coronary heart disease in later life. Annals of Medicine. 2002; 34:157–61. [PubMed: 12173685]
26. Eriksson JG. Growth and coronary heart disease in adult life. Cardiovascular Reviews & Reports. 2002; 23:557–60.
27. Falkstedt D, Hemmingsson T, Rasmussen F, et al. Body mass index in late adolescence and its association with coronary heart disease and stroke in middle age among Swedish men. Int.J Obes. (Lond). 2007; 31:777–83. [PubMed: 17060924]
28. Forsen T, Osmond C, Eriksson JG, et al. Growth of girls who later develop coronary heart disease. Heart (British Cardiac Society). 2004; 90:20–4. [PubMed: 14676233]
29. Frankel S, Elwood P, Sweetnam P, et al. Birthweight, body-mass index in middle age, and incident coronary heart disease. Lancet. 1996; 348:1478–80. [PubMed: 8942776]
30. Frankel S, Elwood P, Sweetnam P, et al. Birthweight, adult risk factors and incident coronary heart disease: The Caerphilly study. Public Health. 1996; 110:139–43. [PubMed: 8668758]
31. Garces C, Lasunscion MA, Ortega H, et al. Metabolic factors in school children population associated with adult cardiovascular mortality. Four provinces study. Medicina Clinica. 2002; 118:767–70. [PubMed: 12049691]
32. Galanis DJ, Harris T, Sharp DS, et al. Relative weight, weight change, and risk of coronary heart disease in the Honolulu Heart Program. American Journal of Epidemiology. 1998; 147:379–86. [PubMed: 9508105]
33. Gunnell DJ, Frankel SJ, Nanchahal K, et al. Childhood obesity and adult cardiovascular mortality: a 57-y follow-up study based on the Boyd Orr cohort. American Journal of Clinical Nutrition. 1998; 67:1111–8. [PubMed: 9625081]
34. Jeffreys M, McCarron P, Gunnell D, et al. Body mass index in early and mid-adulthood, and subsequent mortality: a historical cohort study. International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity. 2003; 27:1391–7. [PubMed: 14574351]
35. Juonala M, Raitakari M, Viikari SA, et al. Obesity in youth is not an independent predictor of carotid IMT in adulthood. The Cardiovascular Risk in Young Finns Study. Atherosclerosis. 2006; 185:388–93. [PubMed: 16045913]
36. Kittleson MM, Meoni LA, Wang NY, et al. Association of childhood socioeconomic status with subsequent coronary heart disease in physicians. Archives of Internal Medicine. 2006; 166:2356–61. [PubMed: 17130389]
37. Lawlor DA, Ronalds G, Clark H, et al. Birth weight is inversely associated with incident coronary heart disease and stroke among individuals born in the 1950s - Findings from the Aberdeen children of the 1950s prospective cohort study. Circulation. 2005; 112:1414–8. [PubMed: 16129799]
38. Lawlor DA, Martin RM, Gunnell D, et al. Association of body mass index measured in childhood, adolescence, and young adulthood with risk of ischemic heart disease and stroke: findings from 3 historical cohort studies. American Journal of Clinical Nutrition. 2006; 83:767–73. [PubMed: 16600926]
39. Maffeis C, Tato L. Long-term effects of childhood obesity on morbidity and mortality. Hormone Research. 2001; 55:42–5. [PubMed: 11408761]

Europe PMC Funders Author Manuscripts

40. Must A, Jacques PF, Dallal GE, et al. Long-term morbidity and mortality of overweight adolescents. A follow-up of the Harvard Growth Study of 1922 to 1935. New England Journal of Medicine. 1992; 327:1350–5. [PubMed: 1406836]
41. Power C, Hypponen E, Smith GD. Socioeconomic position in childhood and early adult life and risk of mortality: a prospective study of the mothers of the 1958 British birth cohort. American Journal of Public Health. 2005; 95:1396–402. [PubMed: 15985645]
42. van Dam RM, Willett WC, Manson JE, et al. The relationship between overweight in adolescence and premature death in women. Annals of Internal Medicine. 2006; 145:91–7. [PubMed: 16847291]
43. Yarnell JW, Patterson CC, Thomas HF, et al. Comparison of weight in middle age, weight at 18 years, and weight change between, in predicting subsequent 14 year mortality and coronary events: Caerphilly Prospective Study. Journal of Epidemiology & Community Health. 2000; 54:344–8. [PubMed: 10814654]
44. Hoffmans MD, Kromhout D, Coulander CD. Body Mass Index at the age of 18 and its effects on 32-year-mortality from coronary heart disease and cancer. A nested case-control study among the entire 1932 Dutch male birth cohort. J Clin Epidemiol. 1989; 42:513–20. [PubMed: 2738614]
45. Rosengren A, Wedel H, Wilhelmsen L. Body weight and weight gain during adult life in men in relation to coronary heart disease and mortality. A prospective population study. Eur.Heart J. 1999; 20:269–77. [PubMed: 10099921]
46. Willett WC, Manson JE, Stampfer MJ, et al. Weight, weight change, and coronary heart disease in women. Risk within the 'normal' weight range. JAMA. 1995; 273:461–5. [PubMed: 7654270]
47. Bjorge T, Engeland A, Tverdal A, et al. Body mass index in adolescence in relation to cause-specific mortality: a follow-up of 230,000 Norwegian adolescents. Am J Epidemiol. 2008; 168:30–7. [PubMed: 18477652]
48. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. Stata Journal. 2007; 6:40–57.
49. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat.Med. 2002; 21:1539–58. [PubMed: 12111919]
50. Light, RJ.; Pillemar, DB. Summing Up: The Science of Reviewing Research. Cambridge, MA, USA: Harvard University Press; 1984.
51. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994; 50:1088–101. [PubMed: 7786990]
52. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315:629–34. [PubMed: 9310563]
53. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000; 56:455–63. [PubMed: 10877304]
54. Williams SR, Jones E, Bell W, et al. Body habitus and coronary heart disease in men. A review with reference to methods of body habitus assessment. Eur.Heart J. 1997; 18:376–93. [PubMed: 9076375]
55. Lindsay RS, Hanson RL, Roumain J, et al. Body mass index as a measure of adiposity in children and adolescents: relationship to adiposity by dual energy x-ray absorptiometry and to cardiovascular risk factors. J Clin Endocrinol.Metab. 2001; 86:4061–7. [PubMed: 11549626]
56. Demerath EW, Schubert CM, Maynard LM, et al. Do changes in body mass index percentile reflect changes in body composition in children? Data from the Fels Longitudinal Study. Pediatrics. 2006; 117:e487–e495. [PubMed: 16510627]
57. Taylor RW, Jones IE, Williams SM, et al. Body fat percentages measured by dual-energy X-ray absorptiometry corresponding to recently recommended body mass index cutoffs for overweight and obesity in children and adolescents aged 3-18 y. Am J Clin Nutr. 2002; 76:1416–21. [PubMed: 12450911]
58. Shaw KA, Srikanth VK, Fryer JL, et al. Dual energy X-ray absorptiometry body composition and aging in a population-based older cohort. Int.J Obes.(Lond). 2007; 31:279–84. [PubMed: 16788568]

Europe PMC Funders Author Manuscripts

59. Gallagher D, Visser M, Sepulveda D, et al. How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups? Am J Epidemiol. 1996; 143:228–39. [PubMed: 8561156]

60. Berenson GS, Srinivasan SR, Wattigney WA, et al. Obesity and cardiovascular risk in children. Ann.N.Y.Acad.Sci. 1993; 699:93–103. [PubMed: 8267341]

61. Freedman DS, Dietz WH, Srinivasan SR, et al. The relation of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa Heart Study. Pediatrics. 1999; 103:1175–82. [PubMed: 10353925]

62. Raitakari OT, Porkka KV, Rasanen L, et al. Clustering and six year cluster-tracking of serum total cholesterol, HDL-cholesterol and diastolic blood pressure in children and young adults. The Cardiovascular Risk in Young Finns Study. J Clin Epidemiol. 1994; 47:1085–93. [PubMed: 7722541]

63. Whincup PH, Gilg JA, Donald AE, et al. Arterial distensibility in adolescents: the influence of adiposity, the metabolic syndrome, and classic risk factors. Circulation. 2005; 112:1789–97. [PubMed: 16172286]

64. Raitakari OT, Juonala M, Viikari JS. Obesity in childhood and vascular changes in adulthood: insights into the Cardiovascular Risk in Young Finns Study. Int.J Obes.(Lond). 2005; 29(Suppl 2):S101–S104. [PubMed: 16385760]

65. McGill HC Jr. McMahan CA, Herderick EE, et al. Obesity accelerates the progression of coronary atherosclerosis in young men. Circulation. 2002; 105:2712–8. [PubMed: 12057983]

66. Eilat-Adar S, Eldar M, Goldbourt U. Association of intentional changes in body weight with coronary heart disease event rates in overweight subjects who have an additional coronary risk factor. Am J Epidemiol. 2005; 161:352–8. [PubMed: 15692079]

67. Huxley R, Owen CG, Whincup PH, et al. Is birth weight a risk factor for ischemic heart disease in later life? Am J Clin Nutr. 2007; 85:1244–50. [PubMed: 17490959]

68. Barker DJ, Winter PD, Osmond C, et al. Weight in infancy and death from ischaemic heart disease. Lancet. 1989; 2:577–80. [PubMed: 2570282]

69. Barker, DJ. Mothers, babies and health in later life. 2nd ed.. London, United Kingdom: Churchhill Livingstone; 1998.

70. Deurenberg P, Weststrate JA, Seidell JC. Body mass index as a measure of body fatness: age- and sex-specific prediction formulas. Br.J Nutr. 1991; 65:105–14. [PubMed: 2043597]

71. Yliharsila H, Kajantie E, Osmond C, et al. Body mass index during childhood and adult body composition in men and women aged 56-70 y. Am J Clin Nutr. 2008; 87:1769–75. [PubMed: 18541567]

72. Engeland A, Bjorge T, Sogaard AJ, et al. Body mass index in adolescence in relation to total mortality: 32-year follow-up of 227,000 Norwegian boys and girls. Am.J.Epidemiol. 2003; 157:517–23. [PubMed: 12631541]

73. Rasmussen F, Johansson M, Hansen HO. Trends in overweight and obesity among 18-year-old males in Sweden between 1971 and 1995. Acta Paediatr. 1999; 88:431–7. [PubMed: 10342544]

74. Must A, Willett WC, Dietz WH. Remote recall of childhood height, weight, and body build by elderly subjects. Am J Epidemiol. 1993; 138:56–64. [PubMed: 8333427]

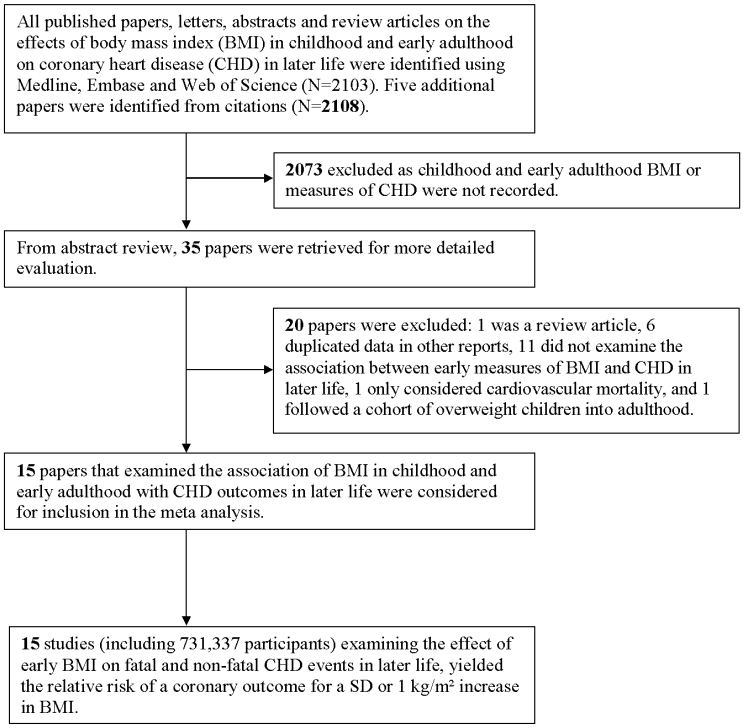

Figure 1.
Flow diagram showing the number of studies included and excluded from the meta analysis

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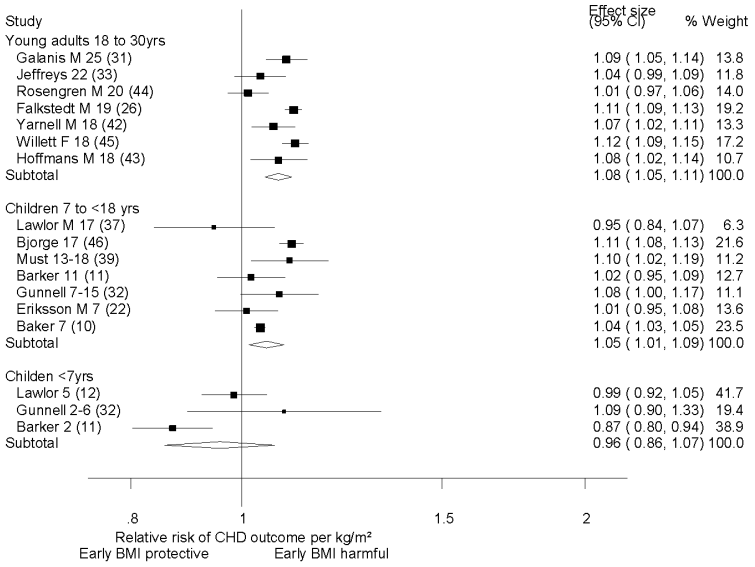

Figure 2.

Relative risk (95% CI) of coronary outcome for a 1 kg/m^2 increase in BMI (including studies with repeat measures of BMI). Box area of each study is proportional to the inverse of the variance, with horizontal lines showing the 95% CI. First author is indicated on the y-axis, for males (M), females (F), mean age in ascending order of BMI assessment (years); with reference citation in parenthesis.

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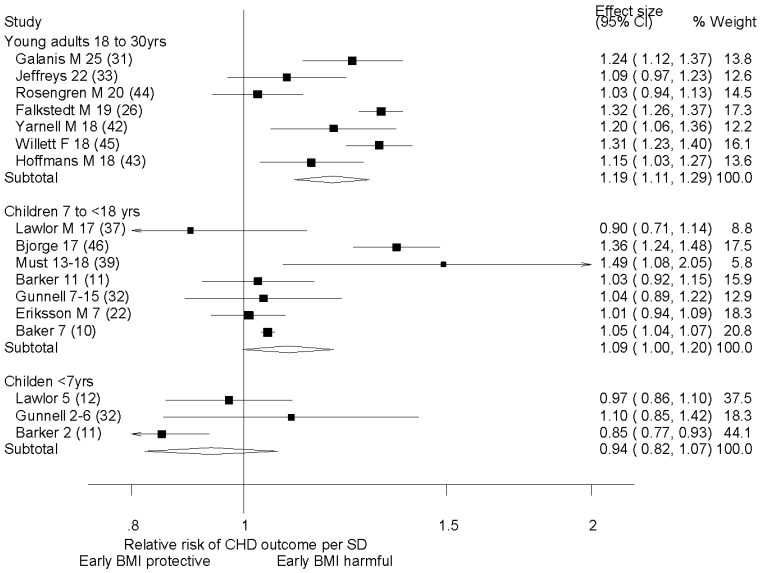

Figure 3.

Relative risk (95% CI) of coronary outcome for a SD increase in BMI (including studies with repeat measures of BMI). Box area of each study is proportional to the inverse of the variance, with horizontal lines showing the 95% CI. First author is indicated on the y-axis, for males (M), females (F), mean age in ascending order of BMI assessment (years); with reference citation in parenthesis.

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Table 1

Studies that provided data for inclusion in the meta-analysis in alphabetical order

Study	Source	Birth year	Age BMI measured in years, mean BMI (SD) kg/m^2	Age at outcome in years	Outcome measured	No. with outcome / total no. used in analysis (FU rate %)	RR (95%CI) per SD	RR (95%CI) per 1 kg/m^2	RR adjustments
Baker et al 11	Copenhagen School Health Records linked with the National Registers, Denmark	1930 to 1976	7, 15.5 (1.3)[a]	25 to 60	Fatal and non-fatal CHD	16133 / 276835 (99%)	1.05 [a] (1.04,1.07)	1.04 [a] (1.03,1.05)	None stated
Barker et al 12	Born at the Helsinki University Central Hospital, Finland	1934 to 1944	2, 16.6 (1.2) 11, 16.9 (1.8)	27 to 64	Hospitalization or death due to CHD	444 / 8760 (100%)	0.85 (0.77,0.93) 1.03 (0.92,1.15)	0.87 (0.80,0.94) 1.02 (0.95,1.09)	None [b] None [b]
Bjorge et al 47	Norwegian Health Survey, Norway	1946 to 1958	17, 21.2 (2.9)72	61 (FU 35)	Fatal IHD	870 / 226678 (85%)	1.36 [f] (1.24,1.48)	1.11 [f] (1.08,1.13)	None
Eriksson et al 23	Males born at the Helsinki University Central Hospital, Finland	1924 to 1933	7, 15.4 (1.1)	38 to 71	Hospitalization or death due to CHD	M 310 / 3641 (92%)	1.01 (0.94,1.09)	1.01 (0.95,1.08)	None [b]
Falkstedt et al 27	Males conscripted to military service, Sweden	1949 to 1951	19, 21.1 (2.6)73	40 to 55	Fatal and non-fatal CHD	M 1452 / 46156 (96%)	1.32 [c] (1.26,1.37) 1.29 [c] (1.23,1.35)	1.11 [c] (1.09,1.13) 1.10 [c] (1.08,1.12)	None Socioeconomic position (based on occupation and educational level) and crowded housing in childhood, smoking status (non-smoker, current and amount) and BP at 18-20 yrs, CHD mortality of parents under age 65 years, socioeconomic position in adulthood
Galanis et al 32	Honolulu Heart Program	1900 to 1919	25, 22 (2.4) BMI at 25 recalled at age 55	55 to 78 (FU 23)	Fatal and non-fatal CHD	M 479 / 6176 (83%)	1.24 [c] (1.12,1.37) 1.28 [c] (1.15,1.42)	1.09 [c] (1.05,1.14) 1.11 [c] (1.06,1.16)	None Age, smoking status at 25 yrs (never, former, current and amount), weight change between 25 to

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Study	Source	Birth year	Age BMI measured in years, mean BMI (SD) kg/m^2	Age at outcome in years	Outcome measured	No. with outcome / total no. used in analysis (FU rate %)	RR (95%CI) per SD	RR (95%CI) per 1 kg/m^2	RR adjustments
									54 yrs, and 54 to 59 yrs, SBP (mean of 3) and non-fasting TC at 59 yrs
Gunnell et al 33	Carnegie (Boyd Orr) Survey of Family Diet and Health, UK	1922 to 1937	2 to 6, 15.8 (1.2) 7 to 15, 16.3 (1.6) 2 to 15, 16.1 (1.5)	59 to 72 *d* (FU 57)	IHD mortality	75 / 1118 202 / 1529 277 / 2647 230 / 2586 (80%)	1.10 (0.85,1.42) 1.04 (0.89,1.22) 1.06 (0.92,1.22) 1.13 (0.99,1.28) 1.14 (1.00,1.30)	1.09 (0.90,1.33) 1.08 (1.00,1.17) 1.10 (1.02,1.19) 1.08 (0.99,1.18) 1.09 (1.00,1.19)	None *b* None *b* None *b* None Age, sex, head of household social class at 2 to 15 yrs
Hoffmans et al 44	Male military records, Netherlands *i*	1932	18, 20.8 (1.8)	38 to 49 *d* (FU ≥20)	CHD mortality	M 648 / 3234 (93%)	1.15 *c* (1.03,1.27) 1.15 *c* (1.03,1.28)	1.08 *c* (1.02,1.14) 1.08 *c* (1.02,1.15)	None Health score, education level, regional origin, resting heart rate (4 levels), SBP and DBP (to the nearest 5 mmHg)
Jeffreys et al 34;38	Glasgow Alumni Cohort, UK	1928 to 1950	22, 19.4 (1.4)	68.4	IHD mortality	280 / 10555 (69%)	1.09 (0.97,1.23) 1.10 (0.98,1.24)	1.04 (0.99,1.09) 1.04 (0.99,1.10)	None Age, sex, father's social class, smoking (yes/no)
Lawlor et al 13	Aberdeen Children of the 1950's, UK	1950 to 1956	4.9, 16.5 (1.9) *a*	25 to 53 *d*	Hospitalization or death due to CHD	302 / 11106 (91%)	0.97 *a* (0.86,1.10)	0.99 *a* (0.92,1.05)	None
Lawlor et al 38	Male Christ's Hospital cohort, UK	1927 to 1956	17, 21.6 (1.9)	48 to 77 *d*	IHD mortality	73 / 1420 (45%)	0.90 (0.71,1.13) 0.92 (0.73,1.17)	0.95 (0.84,1.07) 0.96 (0.85,1.09)	None Age, social class based on father's occupation
Must et al 40;74	Harvard Growth Study, USA	1915	13 to 18, 22.8 (4.1)a	73 (FU 55)	CHD mortality	70 / 342 (67%)	1.49 *e, a* (1.08,2.05)	1.10 (1.02, 1.19)	None
	Males only (no SS associations in females)					M 31 / 155 *h*	1.92 *e* (1.07,3.61) 1.55 *e* (0.78,3.07)	1.31 (1.03, 1.71) 1.20 (0.90, 1.60)	None Adult BMI at 53 years of age
Rosengren et al 45	Gothenburg men's study, Sweden	1915 to 1925	20, 22.4 (2.2) BMI at 20 recalled at age 52	71 (FU 19.7 from age 52)	Fatal coronary disease	M 686 / 6874 (94%)	1.03 *f* (0.94,1.13)	1.01 *f* (0.97,1.06)	None

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Study	Source	Birth year	Age BMI measured in years, mean BMI (SD) kg/m^2	Age at outcome in years	Outcome measured	No. with outcome / total no. used in analysis (FU rate %)	RR (95%CI) per SD	RR (95%CI) per 1 kg/m^2	RR adjustments
Willett et al 46	Female registered nurses, USA	1939 to 1964	18, median 21 (2.5) [g] BMI at 18 recalled at age 34 to 59	44 to 69 [d] (FU 14)	Nonfatal and fatal CHD	F 1044 / 115818 (80%)	1.31 [f](1.23,1.40) 1.23 [f](1.15,1.32)	1.12 [f](1.09,1.15) 1.09 [f](1.06,1.12)	Age Age, smoking (past, never, current and amount), menopausal state (including postmenopausal medications), parental history of MI (<60 years of age)
							0.99 [f](0.92,1.07)	1.00 [f](0.97,1.03)	As above with adjustment for BMI at 43 years
Yarnell et al 43	Male Caerphilly Prospective Study, UK	1921 to 37	18, 22.3 (2.8) BMI at 18 recalled at age 27 to 41	59 to 73 [d] (FU 14)	Coronary event	M 382 / 2335 (93%)	1.20 [f](1.06,1.36)	1.07 [f](1.02,1.11)	Age, smoking, social class

Abbreviations: RR relative risk, SD standard deviation, SS statistically significant, CHD coronary heart disease, IHD ischaemic heart disease, BMI body mass index, SD standard deviation, TC total cholesterol, SBP systolic blood pressure, DBP diastolic blood pressure, FU follow-up after BMI measured (years), M male, F females

[a] Data for males and females combined using weighted means and SDs, or using fixed effects estimates for RR.

[b] Estimates provided by the author

[c] RR estimated from published RR by BMI groups using log-linear dose response regression; dose BMI in each group calculated from simulated data with normal distribution using sample mean (SD)

[d] Age at outcome estimated from period of follow-up after age BMI measured, or calculated from years between measurement and follow-up

[e] RR estimated from published RR for normal weight percentiles in BMI versus overweight / heavier percentiles

[f] RR estimated from published RR by percentile BMI groups (tertiles,[45;47] quintiles[43;46]) using log-linear dose response regression

[g] SD calculated from difference in BMI per unit change in Z value for given percentiles

[h] Estimated numbers used in the analysis

[j] Nested case control study design, remaining studies are cohort

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Table 2

Association of a 1 SD and 1 kg/m^2 rise in BMI to risk of CHD outcome in later life, by age group at BMI measurement

Age group (years)	Number of estimates	No. with outcome / total no. used in analysis	Effect of a 1 kg/m^2 increase in BMI	I^2 (95% CI) index for heterogeneity for a 1 kg/m^2 increase in BMI	Weighted mean BMI (SD)	Effect of a SD increase in BMI	I^2 (95% CI) index for heterogeneity for a SD increase in BMI
<7	3	821 / 20984	0.96 (0.86, 1.07)	74% (12, 92%)	16.5 (1.6)	0.94 (0.82, 1.07)	61% (0, 89%)
7 to <18	7	18102 / 519205	1.05 (1.02, 1.09)	79% (56, 90%)	17.9 (2.0)	1.09 (1.00, 1.20)	85% (72, 92%)
18 to 30	7	4971 / 191148	1.08 (1.05, 1.11)	75% (47, 89%)	21.1 (2.5)	1.19 (1.11, 1.29)	82% (63, 91%)