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The impact of childhood obesity on morbidity and mortality in adulthood: a systematic review

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Abbreviations: BMI – body mass index; BMI-SDS – body mass index standard deviation score; CHD – coronary heart disease; CI – confidence interval; HR – hazard ratio; IOTF – International Obesity Task Force; OR – odds ratio

Abstract

The objective of this study was to evaluate the evidence on whether childhood obesity is a risk factor for adult disease, independent of adult body mass index BMI. Ovid MEDLINE (1948-May 2011), EMBASE (1980-2011 Week 18) and the Cochrane Library (1990-2011) were searched for published studies of BMI from directly measured weight and height in childhood (2-19 years) and disease outcomes in adulthood. Data were synthesized in a narrative fashion. 39 studies (n 181 – 1.1 million) were included in the review. There was evidence for associations between childhood BMI and type 2 diabetes (ORs for 1 BMI-SDS ranged 1.22-2.04), hypertension (1.35-3.75) and coronary heart disease (1.53-5.43). Few studies examined associations independent of adult BMI; these showed that effect sizes were attenuated after adjustment for adult BMI in standard regression analyses. Although there is a consistent body of evidence for associations between childhood BMI and cardiovascular outcomes, there is a lack of evidence for effects independent of adult BMI. Studies have attempted to examine independent effects using standard adjustment for adult BMI, which is subject to overadjustment and problems with interpretation. Studies that use more robust designs and analytical techniques are needed to establish whether childhood obesity is an independent risk factor for adult disease.

Introduction

Overweight and obesity in adulthood are associated with multiple co-morbidities, most notably type 2 diabetes, cardiovascular disease, and a number of cancers.¹⁻² Dramatic rises in childhood obesity prevalence over the last 30 years³ have brought increasing attention to the potential long-term health consequences of childhood obesity. However, our understanding of the associations of childhood obesity with long-term health is incomplete. In particular, due to the tracking of adiposity from childhood into later life,⁴ it remains unclear whether childhood obesity has an effect on adult health that is independent of adult weight status. Previous reviews have examined the relationship between childhood obesity and morbidity in adulthood,⁵ but have not considered whether the effects of childhood adiposity are independent of adult overweight.

The objective of this review was to systematically evaluate the current evidence on the contribution of childhood body mass index (BMI) to adult disease risk, independent of adult BMI. We paid particular attention to the methods used to assess these independent effects, and considered the strengths and limitations of these approaches.

Methods

We reviewed published studies investigating the associations between childhood BMI status and morbidity and mortality in adulthood, focusing on the methods used to assess independent associations. The outcomes of interest (type 2 diabetes, hypertension, coronary heart disease and stroke, asthma, osteoarthritis, gall bladder disease, cancers, and mortality) were selected based on previous reviews of the literature.⁶

Ovid MEDLINE (1948-May 2011), EMBASE (1980-2011 Week 18) and the Cochrane Library (1990-2011) were searched electronically for relevant publications. Reference lists from selected articles were hand-searched for additional studies.

Search terms used in MEDLINE were: 1. exp Child/ 2. exp Adolescent/ 3. juvenile 4. exp Infant/ 5. child\$ 6. adolescen\$ 7. infan\$ 8. teen\$ 9. P?ediatric\$ 10. Pediatrics/ 11. or/1-10. 12. obes\$ or obesity 13. exp Obesity/ 14. exp Overweight/ or exp Body Weight/ 15. BMI or body mass index or body-mass-index or weight-for-height 16. exp Body Mass Index/ 17. or/12-16. 18.asthm\$ or respiratory condition or exp Asthma/ 19. exp Hypertension/ or hypertension 20. cardiovascular disease or exp Cardiovascular Diseases/ 21. exp Diabetes Mellitus, Type 2/ or type 2 diabetes 22. osteoarthritis or exp Osteoarthritis/ 23. gall bladder disease or exp Gallbladder Diseases/ 24. cancer or exp Neoplasms/ 25. or/18-24. 26. exp Case-Control Studies/ 27. exp Cohort Studies/ 28. case control 29. cohort adj (study or studies) 30. Cohort analy\$ 31. Follow up adj (study or studies) 32. observational adj (study or studies) 33. Longitudinal 34. Retrospective 35. or/26-34. 36. 11 and 17 and 25 and 35.

Inclusion criteria: 1) Cohort or case-control designs (exposure and outcomes measured in the same individuals), 2) BMI from directly measured weight and height at one or more ages in childhood (mean age 2-12 years) or adolescence (13-19 years), 3) Childhood BMI status calculated using national or IOTF criteria,⁷ or BMI treated as a continuous measure, 4) Any of the outcomes of interest assessed in adulthood (≥ 19 years); and, 5) English language articles published after 1980.

Exclusion criteria: 1) Participants recruited for an obesity or health promotion intervention, 2) Participants from select clinical populations, e.g. preterm babies, childhood cancer survivors, 3) BMI from parent or self-reported height and weight in childhood; and, 4) Reporting of risk factors but no disease end-point, e.g. blood pressure but not hypertension. Abstracts were double screened (MHP

and CF) for retrieval of full-text articles, and inter-rater agreement was assessed using kappa coefficients (κ).⁸

Data were double-extracted by MHP and CF using a pre-designed form. The principal outcomes were measures of the association of adult disease risk with childhood BMI (regression or correlation coefficients) or BMI category/status (risk ratio, hazard ratio or odds ratio and confidence intervals), and these measures after accounting for adult BMI. Quality of observational studies was assessed for selection bias, comparability, measurement of outcomes, and adequacy of follow-up using a checklist adapted from the Newcastle-Ottawa Scale. Due to the diverse nature of outcomes, study designs and effect measures included in the selected studies, data were synthesised and presented in a narrative fashion. We evaluated the methods used to assess independent effects, and summarised their strengths and limitations. Publication bias was assessed using a funnel-plot in Stata 12. To assess potential measurement bias, results of studies using self-reported disease were compared with those using objective measures.

Results

The initial search yielded 7,890 results (Error! Reference source not found.). A total of 39 studies were included in the review; two of these were case-control studies,⁹⁻¹⁰ and the remaining were cohort studies. Inter-rater agreement was substantial (84%, $\kappa=0.62$). Sample sizes n ranged from 181¹¹ to 1.1 million¹². The majority of studies were from Western Europe (Denmark, Finland, Norway, Sweden, the UK, the Netherlands), and the US (including Hawaii). Two studies were conducted in Australia,¹³⁻¹⁴ and two in Israel.¹⁵⁻¹⁶ Mean ages at BMI measurement ranged from birth to 19 years. Full descriptions of included studies can be seen in

Table 1. Excluded studies are listed in Table S1.

Of the 39 included studies, ten reported on type 2 diabetes, five on hypertension, 15 on coronary heart disease (CHD), eight on stroke, two on asthma, three on cancers, two on colon cancer, one on kidney cancer, four on breast cancer, one on cervical cancer, one on ovarian cancer, and six on all-cause mortality. Associations between childhood BMI and adult disease outcomes are summarised by outcome in

Table 2.

Type 2 diabetes

There was consistent evidence that overweight in early life was associated with increased risk of type 2 diabetes in adulthood. Of 10 studies that analysed the relationship between BMI or BMI status in childhood (ages 0-18 years) and type 2 diabetes in adulthood, 9 reported a positive association (*n* ranged from 822¹⁷ to 37,674¹⁶). Odds ratios for one unit increase in BMI-SDS ranged from 1.22 (95% CI 1.10 to 1.36) at school entry (*n* 5,793),¹⁸ to 2.04 (1.7 to 2.4) at age 16 (*n* 10,683).¹⁹ One US study (*n* 181) found no evidence of an association between overweight at age 13-18 and diabetes at age 73.¹¹

When six studies using objectively assessed type 2 diabetes^{16-17, 20-23} were considered separately from those using self-reported data, all showed that increased BMI or overweight were associated with increased risk of type 2 diabetes in adulthood.

Three of the studies examined the effects of childhood obesity independent of adult BMI by adjusting for adult BMI in regression analyses. In a British cohort, associations between BMI-SDS in childhood and adolescence and self-reported type 2 diabetes at age 41 were attenuated to the null after adjustment for BMI at age 23 (*n* 10,683).¹⁹ For example, the odds ratio for one unit increase in BMI-SDS at age 11 was reduced from 1.78 (95% CI 1.5 to 2.1) to 1.06 (0.8 to 1.3). Similarly, in a study of BMI z-score at primary school entry and self-reported diabetes at age 46-50, OR per BMI-SDS at school entry decreased from 1.22 (95% CI 1.10 to 1.36) to 1.07 (0.96 to 1.19) after adjustment for adult BMI (*n* 5,793).¹⁸ The same effect was observed in an Israeli study; the HR for incident diabetes in adulthood was reduced from 2.76 (95% CI 2.12 to 3.58) to 1.01 (0.75 to 1.4) after the inclusion of BMI in adulthood in the regression model (*n* 37,674).¹⁶

Hypertension

Five studies reported on hypertension (*n* from 286²⁴ to 18,513¹⁵); all used an objective measure of hypertension as the outcome, and showed that increased BMI or overweight in early life (ages 1-19) was associated with increased risk of hypertension in adulthood (18-45 years). Odds ratios for obesity in childhood ranged from 1.35 (95% CI 1.13 to 1.64)²⁵ at age 7 to 3.75 (3.45 to 4.07) at age 16-19 y.¹⁵

Two of the five studies reported findings adjusted for adult BMI. In one study, individuals who had been overweight at age 8-15 years had five times the risk of hypertension in early adulthood compared to those who were normal weight (OR 5.1, 95% CI 1.4, 18.1); after adjustment for BMI at age 18-26, the effect size remained the same, but the confidence interval was wider and included OR=1.²⁴ In the other study, associations between BMI-SDS at ages 7, 11, and 16 and clinically assessed hypertension at age 45 were no longer observed after controlling for BMI at age 45 years.²⁵

Coronary heart disease

15 studies explored the relationship between BMI in childhood and objective measures of CHD events. Of these, 10 studies (*n* ranged from 2,990²⁶ to 1,145,467¹²) reported that increased BMI or overweight at ages 2-25 years was associated with increased risk of CHD in later life; half of these studies were in male study populations.^{12, 16, 27-29} Hazard ratios ranged from 1.53 for CHD mortality associated with high BMI at age 11²⁸ to 5.43 (95% CI 2.77 to 10.62) for incident CHD associated with high BMI at age 17.¹⁶ In one US study (*n* 181), higher BMI at ages 13-18 was associated with

increased risk of CHD morbidity and mortality in males but not females.¹¹ The remaining studies found no association between BMI at age 2-22 years and CHD.

Two of the studies of CHD looked at the independent effect of childhood obesity. In one study (*n* 37,674), the hazard ratio for incident CHD at age 25-45 for men with BMI in the top decile at age 17 (compared to the bottom decile) increased from 5.43 (95% CI 2.77 to 10.62) to 6.85 (3.3 to 14.2) after adjustment for BMI in adulthood.¹⁶ Another study (*n* 181), which reported an association between overweight in adolescence and CHD mortality among men, found that this association was attenuated to the null after adjustment for adult BMI.¹¹

Stroke

Of the 8 studies that reported on objectively measured stroke outcomes, two Swedish studies (*n* 46,156²⁹ and 1,145,467¹²) showed that overweight in late adolescence (ages 16-25) was associated with increased risk of stroke at ages 39-55. HRs ranged from 1.4 (95% CI 1.3 to 1.5) for overweight to 3.2 (2.4 to 4.3) for very obese children. A Norwegian study (*n* 226,678) reported an association between high BMI at age 14-19 and stroke mortality in males (RR 1.9, 95% CI 1.2 to 3.2) at ages up to 62 years³⁰; a further study (*n* 181) observed this association in males.¹¹ One Finnish study (*n* 12,439) reported an inverse relationship.³¹ Three British studies (*n* 2,990²⁶ to 14,561³²) found no evidence of an association between childhood BMI and stroke.

One small study (*n* 181), which reported an association between overweight in adolescence and stroke mortality, found that adjusting for adult BMI attenuated this effect to the null.¹¹

Asthma

Two studies focused on self-reported asthma as an outcome. One Australian study (*n* 753) showed that overweight at age 7 was associated with OR 3.1 (95% CI 1.3 to 7.3) for adult-onset asthma in women.¹⁴ Analysis of a British cohort (*n* 6,420) found no association between overweight at age 10 and asthma at age 26.³³

In the Australian study, the odds ratio was attenuated from 3.1 to 2.13 after adjustment for BMI in adulthood, and the 95% confidence interval included OR=1 (0.82 to 5.57).¹⁴

Cancer

Three studies reported on cancers from registry data; one study (*n* 2,347) showed that cohort members with BMI-SDS in the highest quartile at age 2-14 years had a 40% increase in risk of cancer.³⁴ In a Norwegian cohort, very high BMI at age 14-19 was associated with a 20% increase in risk of cancer mortality among women only.³⁰ Analysis of data from 78,612 Dutch men showed no association between BMI at age 18 and cancer mortality at ages 18-49.²⁷

Colorectal cancer mortality was associated with adolescent BMI (ages 13-19) in two studies (RR 2.1 to 9.1).^{11,30} In a Norwegian study (*n* 227, 221) high BMI at ages 14-19 was associated with kidney cancer among men (RR 2.6, 95% CI 1.5 to 4.7).³⁵ Of four publications that looked at breast cancer outcomes from registry data, one study of 117,415 Danish women showed that increased BMI at age 14 years was associated with a reduction in risk of breast cancer in adulthood (RR 0.97, 95% CI 0.96 to 0.98).³⁶ A case-control study of >10,000 women reported that the risk of pre-menopausal cancer was lower among women who were obese at age 18 (RR 0.6, 0.2 to 0.9), but there was no association with post-menopausal cases.⁹ The other studies found no evidence of an association. One study analysing cervical cancer mortality among Norwegian women showed that very high BMI at ages 14-

19 was associated with RR 1.9, 95% CI 1.1 to 3.2,³⁰ while a study of ovarian cancer in 111,883 women showed that high BMI at ages 14-19 was associated with 43-56% increase in risk of ovarian tumour.³⁷

Two studies of cancer outcomes examined the independent effect of childhood BMI. The US study which showed that adolescent overweight was associated with colorectal cancer mortality reported wide confidence intervals for the hazard ratio (*n* 181), which included HR=1 after adjustment for adult BMI.¹¹ The case-control study of breast cancer⁹ showed that women who were overweight at age 18, regardless of weight status in adulthood, did not have any difference in risk of pre- or post-menopausal breast cancer compared to those who were not overweight at age 18 or adulthood.

All-cause mortality

Six of the included studies reported on the relationship between BMI status in early life and all-cause mortality. Two studies from Norway (*n* 226, 678³⁰ and 227,003³⁸), one from Sweden (*n* 45,884 men),³⁹ one from the US (*n* 13,146),⁴⁰ and another from Britain (*n* 2,990)²⁶ showed that high BMI at ages 2-19 was associated with 40-60% increase in risk of all-cause mortality in adulthood.

In a small US cohort (*n* 181), an association was observed among men but not women¹¹; when this estimated was adjusted for adult BMI, there was no longer any strong evidence for an association.

Discussion

This review has shown that there is a consistent body of evidence for associations between childhood overweight, unadjusted for adult BMI, and cardiovascular outcomes and mortality in adulthood. However, few studies have assessed the independent effects of childhood overweight on adult disease, and the results of these have been inconclusive.

The finding that childhood overweight is associated with type 2 diabetes, hypertension, coronary heart disease, and mortality, unadjusted for adult BMI, is in line with a recently updated systematic review of overweight in childhood and mortality and adult morbidity.⁵ Evidence for stroke outcomes is mixed. A systematic review which explored the relationship between childhood obesity and asthma in adolescence concluded that obesity precedes, and is associated with, asthma⁴¹; however, based on the two studies included in this review, there is no strong evidence for an effect of childhood BMI on adult-onset asthma. There is limited evidence that childhood BMI is associated with increased risk of colorectal and kidney cancers. Three of four studies found no association between overweight in youth and breast cancer; one study showed that higher BMI in adolescence was associated with reduced risk of breast cancer,³⁶ as has been observed in studies using BMI from recalled height and weight in adolescence.⁴²⁻⁴³ High BMI in adolescence may be associated with cervical and ovarian cancers; however pooled analysis of data from six cohorts with recalled weight at age 18 or 20 found no association between BMI in early adulthood and ovarian cancer risk.⁴⁴ Inspection of a funnel-plot using effect sizes unadjusted for adult BMI revealed asymmetry, indicating the possible presence of publication bias.

This study has expanded on previous reviews⁵ by assessing the evidence for the effects of childhood overweight on adult disease, independent of adult BMI. A handful of studies have attempted to examine these independent effects by using standard adjustment for BMI or overweight in adulthood; most of these have shown that effect sizes were attenuated after adjustment. The results of these analyses are generally interpreted as evidence that unadjusted associations between childhood overweight and adult disease risk can be accounted for by adult BMI, and that childhood BMI has no

underlying effect on disease risk. However, adjusting for adult BMI in this way has methodological limitations. One problem is that adult BMI is likely to be on the causal path from childhood BMI to later disease; adjustment for adult BMI is likely to introduce overadjustment biases, which tend to pull effect estimates towards the null.⁴⁵ An effect called the ‘reversal paradox’ has been described in the literature, in which adjustment for variables on the causal pathway lead to artifactual associations between exposures and outcomes.⁴⁶⁻⁴⁷ Using simulations, Tu et al,⁴⁷ showed that a genuine positive association between birth weight and adult blood pressure could be attenuated after adjusting for current weight, and could even be reversed if correlations between variables were increased. Given the correlation between BMI in early and later life, particularly in those studies with closely spaced measurements, these effects are likely to be relevant to the study of childhood overweight and adult disease. Another issue with standard adjustment lies in the interpretation of results⁴⁸⁻⁴⁹; adjustment for adult BMI controls for adult body size, but also effectively adjusts for change in relative size between measurements, therefore this approach does not elucidate whether it is early life BMI or BMI gain which is associated with the outcome.⁴⁹ It is therefore difficult to conclude that childhood overweight has long-term effects on health based on the results of standard analyses.

A limitation of this review is that most of the included studies were conducted in Western Europe and North America, limiting the generalisability of our findings. Expansion of the search to include non-English language publications may have yielded studies from different settings. A wider limitation concerns the generalisability of evidence from cohorts which observe children who were living several decades ago. Contemporary child populations are experiencing more extreme obesity,⁵⁰ and children are becoming obese at younger ages than in previous generations.⁵¹ The effects of these characteristics of the obesity epidemic on long-term health cannot reliably be ascertained from studies of older cohorts, who are likely to have different characteristics and environments. Still, studying cohorts with long-term follow-up offers an expedient way of empirically assessing the long-term outcomes of childhood exposures. The findings of such studies are informative where we can reasonably assume that pathways to disease will not change dramatically across generations.

Given the high and rising prevalence of childhood overweight in all parts of the world, it is important to know whether childhood obesity has long-term effects on health. This review was unable to confirm the presence of long term health effects of childhood obesity, acting independently of its effects on adult BMI. It is conceivable that such effects exist but could not be detected in these studies due to limitations in statistical analysis and study design. The limitations in statistical analysis attributable to standard adjustments for adult BMI (explained above) could partially be addressed by more sophisticated statistical techniques (e.g. structural equation modelling⁵² and multilevel modelling⁵³) or alternative approaches to analyses developed specifically for use in life-course analyses (e.g. by analysis of different combinations of overweight over the life course⁵⁴⁻⁵⁵). However, given the high levels of correlatedness inherent in life-course data within cohort designs, more robust experimental designs may prove necessary to provide convincing evidence. True randomized trials may not be feasible because of a current lack of effective weight loss interventions and the need for long term follow up, but other pragmatic study designs (e.g. natural experiments, mendelian randomization) may be informative in the meantime. If it was found that childhood obesity had a direct effect on long term health, this would place a strong imperative on prevention and early treatment in childhood.

If on the other hand, more robust evidence failed to substantiate an independent effect of childhood obesity on adult health, this could indicate that the observed association is mediated entirely through adult obesity, or alternatively, that both childhood obesity and adult disease are shared consequences of risk factors operating from early life. There is evidence to suggest that certain patterns of growth,

particularly the combination of small size at birth and catch-up growth in later life, are associated with changes in body composition (increased adiposity and reduced lean mass⁵⁶⁻⁵⁸), and increased disease risk in later life.⁵⁹⁻⁶¹ Prenatal and postnatal exposures which manifest as growth patterns in early life may therefore be linked to structural and functional changes which program future disease risk.⁵⁹ Childhood obesity, measured using a summary measure such as BMI at a single stage of development, reflects only one aspect of body size, and in isolation does not capture the dynamic processes of growth over the life course which may have important implications for long-term health. Studies of childhood obesity and long-term health must be interpreted in light of these considerations.

At first glance, a lack of evidence for independent effects of childhood obesity might suggest that treating obesity in adulthood would be sufficient for reducing the excess health risk associated with it. However, given the intractable nature of established obesity and the emerging evidence on the potential biological and early developmental bases underlying this, promotion of healthy weight and the prevention of weight accumulation at all stages of the life-course is likely to prove the most effective option for individuals and from a policy perspective.

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Table and figure legends

Figure 1: Flow diagram of study selection process, from initial search to included studies

Table 1: Description of included studies, detailing the main exposures, outcomes, ages at measurement and main findings of each study included in the review

Table 2: Summary of included studies, detailing the available evidence for each disease outcome

Table 1: Description of included studies

Reference (study design)	Exposure measure(s)	Disease outcome(s)	Age at last follow-up	Population (n, sex, location, birth years)	Main effect size
Ahlgren 2004 ³⁶ (cohort)	BMI quintiles at age 14 y	Breast cancer (registry data)	Time to event	117,415 Women in Copenhagen, b.1930-75	Lower BMI at age 14 associated with increased risk of breast cancer: RR per 1 unit increase in BMI: 0.97 (95% CI 0.96, 0.98)
Al Mamun 2009 ¹³ (cohort)	BMI z-score at age 5 y; overweight & obesity (IOTF)	Type 1 and type 2 diabetes (self report)	21	2,639 (51% ♀) in Australia, b. 1981-84	1 unit increase in BMI z-score at age 5 associated with 60% increase in odds of diabetes (OR 1.61; 95% CI 1.24, 2.09); overweight/obesity vs non-obese: OR 2.60; 1.29, 5.22
Andersen 2010 ⁶² (cohort)	BMI at age 7 y	CHD – nonfatal and fatal (registry data)	Time to event after age 25	216,771 (49% ♀) Copenhagen, b.1936-76 & Helsinki, b.1924-44	Each unit increase in BMI at age 7 y associated with ~5-10% increase in odds of CHD event, after adjustment for birth weight
Baker 2007 ⁶³ (cohort)	BMI z-score at age 7-13 y	CHD – nonfatal and fatal (registry data)	Time to event	276,835 Men & women (50% ♀) in Copenhagen, Denmark, b. 1930-76	♂: 1 unit increase in BMI z-score associated with 5-17% increased odds of nonfatal event, 10-24% increase for fatal event ♀: 1 unit increase in BMI z-score associated with 2-11% increased odds of nonfatal event, 7-23% increase for fatal event
Barker 2002 ²⁰ (cohort)	BMI quartiles at age 11 y	Type 2 diabetes, hypertension, CHD (registry)	20+	13,517 Men & women in Helsinki, b. 1924-44	ORs for 1 unit increase in BMI at age 11 [Adjusted for age and sex]: <i>T2DM</i> 1.18 (1.13, 1.23); <i>Hypertension</i> 1.07 (1.04, 1.09); <i>CHD</i> 1.06 (1.03, 1.10)
Barker 2002b ⁶⁴ (cohort)	BMI Z-scores at ages 1-12 y	Hypertension (registry data)	38-39	6,730 Men & women (47% ♀) in Finland, b. 1934-44	From age 8, high BMI associated with hypertension; cumulative incidence 13.7% (11.2-16.2) among men with BMI <16 at age 12 vs 21.1% (18.4-23.8) among men with BMI >18
Bjorge 2004 ³⁵ (cohort)	BMI categories at age 14-19 (medium 25-74 th ; high -84 th ; v high ≥85 th centile, US ref.)	Kidney cancer (registry data)	Time to event; mean age 45 y	227,221 Men & women (49% ♀) in Norway, b. 1943-1950s	♂: Very high BMI at age 14-19 y associated with 2.6 times risk of renal cancer compared to medium BMI category: RR 2.64 (95% CI 1.48, 4.70) ♀: No evidence of association between BMI category at age 14-19 y and renal cancer
Bjorge 2008 ³⁰ (cohort)	BMI categories at age 14-19 (medium 25-74 th ; high -84 th ; very high ≥85 th centile, US ref.)	Mortality: cause-specific and all-cause (registry data)	Time to event up to 2005; mean age 40 - 43 y	226,678 Men & women (49% ♀) in Norway, b. 1943-1950s	Highest BMI category vs. medium [RR (95% CI)]. <i>All-cause mortality</i> : ♂: 1.4 (1.3, 1.6); ♀: 1.4 (1.2, 1.5) <i>Cancer (all)</i> : ♂: 1.2 (0.9, 1.5); ♀: 1.2 (1.1, 1.5) <i>Ischemic heart disease</i> : ♂: 2.9 (2.3, 3.6); ♀: 3.7 (2.3, 5.7) <i>Cerebrovascular diseases</i> : ♂: 1.9 (1.2, 3.2); ♀: 1.5 (0.9, 2.6)
Burgess 2007 ¹⁴ (cohort)	BMI z-score quartiles at age 7 y; overweight and obesity (IOTF) vs non-obese	Incident asthma [adult-onset: age >21 y] (self reported)	32	753 Men & women (52% ♀) in Tasmania, Australia, b. 1961	♂: No evidence of association between BMI z-score quartile or overweight at age 7 and asthma at age 32 ♀: Each increase in BMI z-score quartile at age 7 associated with OR 1.73 (95% CI 1.17, 2.17); overweight at age 7 OR 3.05; 1.28, 7.29
Chu 1991 ⁹ (case-control)	Overweight (BMI >85 th centile) at age 18 y	Breast cancer	20-54	4,742 cases; 5,698 controls. Women in USA b. 1926-1962	No evidence of association between BMI category and post-menopausal breast cancer risk; RR pre-menopausal breast cancer for obese women 0.6 (0.2, 0.9), no association with overweight

De Stavola 2004 ⁶⁵ (cohort)	BMI-SDS at ages 2, 4, 7, 11 and 15 y	Breast cancer (registry data)	53	2,187 Women in UK, b. 1946	No evidence of association between BMI-SDS at any age and breast cancer
Engeland 2003 ³⁷ (cohort)	BMI categories at age 14-19 (medium 25-74 th ; high -84 th ; v high \geq 85 th centile, US ref.)	Ovarian tumour (registry data)	Time to event, up to age 100 y or 2001	111,883 Women in Norway, b. 1943-61	Being in high and very high BMI categories in adolescence associated with increased risk of ovarian cancer compared with medium BMI category. High: RR 1.43 (1.00, 2.04); Very high: RR (1.56 (1.04, 2.32)
Engeland 2003 ³⁸ (cohort)	BMI categories at age 14-19 (85 th -94 th , \geq 95 th vs. reference 25 th -75 th centile)	All-cause mortality (registry data)	Time to event, mean 31.5 years follow-up)	227,003 men and women in Norway, b. 1948-68	Obesity (BMI >95 th centile) at age 14-19 was associated with increased risk of all-cause mortality in adulthood (RR in men 1.82; 95% CI 1.48, 2.43, RR in women 2.03; 95% CI 1.51, 2.72)
Eriksson 1999 ²⁸ (cohort)	BMI categories at age 11 (BMI \leq 15.5; -16.5; -17.5; >17.5)	CHD deaths (registry data)	Deaths during 1971-95	3,641 Men in Finland, b. 1924-33	BMI at age 11 positively associated with risk of CHD death. Compared to baseline group (BMI \leq 15.5) at age 11 y: BMI 15.5-16.5: HR=1.28; BMI 16.5-17.5: HR=1.35; BMI >17.5: HR=1.53
Eriksson 2001 ⁶⁶ (cohort)	BMI z-score; BMI categories at age 6 (BMI \leq 13.6; -14.2; -14.8; -15.4; >15.4)	CHD hospitalizations & deaths (registry)	Events during 1971-97	4,630 Men in Finland, b. 1934-44	No evidence of association between BMI z-score and CHD
Eriksson 2003a ²¹ (cohort)	BMI at ages 1-12 y	Type 2 diabetes (registry data)	Diagnoses 1964-98 at age >40 y	8,760 Men & women (47% ♀) in Finland, b. 1934-44	Cumulative incidence of T2DM positively associated with BMI at each age from 4 years onwards
Falkstedt 2007 ²⁹ (cohort)	BMI category in late adolescence (BMI <18.5; -20.9; -22.9; -24.9; -29.9; \geq 30)	CHD and stroke, fatal and nonfatal (registry data)	40-55	46,156 Men in Sweden, b. 1949-51	<i>CHD</i> : BMI \geq 30 kg/m ² at age 18-20 years associated with 4 times risk compared to BMI 18.5-20.9 (HR 4.3; 95% CI 3.1-5.9). <i>Stroke</i> : HR in highest BMI category=2.4 (1.3, 4.5); lowest risk in BMI category 21.0-22.9 (HR 0.9; 95% CI 0.7, 1.1).
Field 2005 ²⁴ (cohort)	BMI z-scores and centiles (US ref.) at age 8-15 y	Hypertension (self report of medication or clinical assessment)	18-26	286 Men & women in Boston USA, b. 1963-73; results reported for male subjects only	Compared to reference group (BMI <75 th centile in childhood) individuals with BMI 75 th -84 th centile had 3 times risk of hypertension in adulthood (OR=3.6; 95% CI 0.7, 18.2); individuals with BMI \geq 85 th centile had 5 times risk (OR=5.1; 95% CI 1.4, 18.1).
Forsen 2004 ⁶⁷ (cohort)	BMI z-score at age 11 y	CHD – hospital admissions and deaths (registry)	27-64	4,130 Women in Finland, b. 1934-44	No evidence of association between BMI z-score and CHD risk. Compared to baseline group BMI <15.9 kg/m ² , HR for CHD among BMI >18.4 was 1.79 (0.89, 3.60).
Gunnell 1998 ²⁶ (cohort)	BMI categories at ages 2-14 (<25 th ; 25-49 th ; 50 th -75 th ; >75 th centile, UK90 ref.)	Mortality – all cause, CVD, IHD, stroke (registry data)	Up to July 31, 1995	2,990 Men & women (51% ♀) in Britain, b. 1922-37	BMI in 50-75 th centile vs. 25 th -49 th centile: <i>All cause</i> HR 1.4 (1.1, 1.8), <i>CV</i> HR 1.6 (1.1, 2.5), <i>IHD</i> HR 2.1 (1.3, 3.6). BMI >75 th centile vs. 25 th -49 th centile: <i>All cause</i> HR 1.6 (1.1, 2.3). No evidence of association with stroke mortality.
Hoffmans 1989 ²⁷ (cohort)	BMI at age 18 y and BMI categories (\leq 18.9; -19.9; -24.9; \geq 25 kg/m ²)	Mortality – CHD and cancer (death certificates)	18-49 (32 years follow-up)	78,612 Men in the Netherlands, b. 1932	Compared to reference group with BMI 19-19.9 kg/m ² <i>CHD mortality</i> : BMI 20-24.9 associated with 30% increase in risk (HR 1.31; 1.02, 1.67); BMI \geq 25 HR 2.42 (1.36, 4.30). <i>Cancer mortality</i> : No association with BMI category.

Hypponen 2003 ¹⁹ (cohort)	BMI-SDS tertiles at ages 7, 11, 16, 23 y	Type 2 diabetes (self-reported)	41	10,683 Men & women in Britain, b. 1958	Compared to ref. group (BMI-SDS in middle tertile): <i>Age 7</i> : Upper tertile OR 3.97 (95% CI 1.7, 9.1); 1 unit increase in BMI-SDS OR 1.44 (1.2, 1.7). <i>Age 11</i> : Upper tertile OR 3.59 (1.7, 7.5); BMI-SDS OR 1.78 (1.5, 2.1). <i>Age 16</i> : Upper tertile OR 4.18 (2.1, 8.4); BMI-SDS OR 2.04 (1.7, 2.4).
Israeli 2007 ¹⁵ (cohort)	Overweight (BMI 25-30 kg/m ²) and obesity (>30) at ages 16.5-19	Hypertension (medical history or clinical assessment)	26-45	18,513 Men in Israel, recruited to Israeli Defense Forces 1976-96	Adjusted for age and blood pressure at baseline, compared to normal weight, overweight in adolescence associated with hypertension risk (OR 1.75; 95% CI 1.66, 1.86); obesity associated with nearly 4 times risk (OR 3.75; 3.45, 4.07).
Jeffreys 2004 ³⁴ (cohort)	BM-SDS at ages 2-14 y	Cancers: All, breast, colon, prostate, lung; cases and mortality (registry)	Cases up to Dec 2001, deaths to Jan 2003	2,347 Men & women in Britain, b. 1922-37	<i>All cancers</i> : Compared to lowest BMI-SDS quartile, being in highest quartile associated w/ 40% increase in risk (OR 1.43; 95% CI 1.01, 2.04); 1 unit increase in BMI-SDS OR 1.14 (1.00, 1.29); stronger association w/ cancers related to smoking. No association w/ other cancers
Lawlor 2005 ⁶⁸ (cohort)	BMI z-score at primary school entry; BMI z-score quartiles; IOTF categories	CHD and stroke hospital admissions and mortality (registry data)	Follow-up began on January 1, 1981	11,106 Men & women in Scotland, b. 1950-56	<i>For CHD, stroke and CHD/stroke</i> : No evidence of association with BMI z-score quartile at school entry; no evidence of association with overweight/obese status.
Lawlor 2006a ¹⁸ (cohort)	BMI z-score at primary school entry	Diabetes diagnosis at age >20 y (self-reported)	46-50	5,793 Men & women in UK, b. 1950-56 (singleton births only)	Each unit increase in BMI z-score at school entry associated with 22% increase in risk of diabetes in adulthood (OR 1.22; 95% CI 1.10, 1.36)
Lawlor 2006b ³² (cohort)	BMI z-score in childhood and adolescence; IOTF overweight & obesity	IHD and stroke (registry data)	Up to 30 Nov 2004	2,586 men&women in GB b.1922-37; 1,420 men b.1936-69; 10,555 men&women b.1948-68	Pooled results: no evidence of an association between BMI z-score in childhood and risk of mortality from IHD or stroke
Le Marchand 1988 ¹⁰ (case-control)	BMI tertiles at age <25 y	Breast cancer (registry data)	29-65	3,208 Women in Hawaii, b. 1918-43	No evidence of association between BMI tertile at age <25 y and breast cancer risk
Li 2007 ²⁵ (cohort)	BMI-SDS at ages 7, 11, 16; overweight and obesity (IOTF)	Hypertension (clinical assessment or medication)	45	9,297 Men & women (50% ♀) in Britain, b. 1958	BMI-SDS at all ages positively associated w/ hypertension: <i>Age 7</i> , OR 1.10 (1.04, 1.17); <i>Age 11</i> , OR 1.22 (1.15, 1.28); <i>Age 16</i> , OR 1.27 (1.20, 1.34) Overweight/obese associated w/ increased risk of hypertension: <i>Age 7</i> , OR 1.35 (1.13, 1.64); <i>Age 11</i> , OR 1.66 (1.39, 1.97); <i>Age 16</i> , OR 1.96 (1.64, 2.35)
Magnussen 2010 ²² (cohort)	BMI Z-scores at ages 9-18 y; overweight and obesity (IOTF)	Type 2 diabetes (clinical assessment)	24-41	1,781 Men & women (56% ♀) in US & Finland	BMI≥75 th centile in childhood RR 3.4 (95% CI 1.8-6.4) [adjustment for other MetS components, RR 3.0; 1.6-5.7] IOTF overweight/obesity RR 3.4 (1.7-6.8)
Morrison 2010 ¹⁷ (cohort)	BMI at age 12.4±3.3 (Princeton Follow-up Study) 10.0±0.5 (National Growth & Health Study)	Type 2 diabetes (clinical assessment or self-report)	PFS: 38.6±3.6 NGHS: 19.1±0.7	PFS: 822 men & women (53% ♀) in the US b. 1960s NGHS: 1,067 women in the US	PFS: BMI in top fifth centile at baseline associated with 4-fold increase in risk of T2DM (OR 4.00; 95% CI 1.28, 12.5) NGHS: no evidence that BMI at baseline associated with T2DM in stepwise logistic regression model

Must 1992 ¹¹ (cohort)	BMI categories at ages 13-18 y (overweight: BMI>75 th centile; lean: 25 th - 50 th centiles, US ref.)	Mortality; Morbidity: CHD, angina, diabetes, athero-sclerosis, stroke, hip fracture, cancer, arthritis (self-report)	73±1	181 Men & women (55% ♀) in the US, b. 1914-16	♀- no evidence of association between overweight in adolescence and mortality ♂- overweight in adolescence associated with all-cause mortality (HR 1.8; 1.2, 2.7); CHD mort. (HR 2.3; 1.4, 4.1); stroke mort. (HR 13.2; 1.6, 108.0); colorectal cancer mort. (HR 9.1; 1.1, 77.5) No evidence of association between overweight in adolescence and angina, diabetes, atherosclerosis, stroke, colorectal cancer or stroke; CHD risk increased in men (HR 2.8; 1.1, 7.2)
Neovius 2009 ³⁹ (cohort)	BMI categories at age 16-20 y (under-, normal, overweight, obese; WHO)	Mortality (registry data)	Follow-up to Sept 2007	45,884 men in Sweden, b. 1949-51	Overweight (HR 1.33; 95% CI 1.15, 1.53) and obesity (HR 2.14; 95% CI 1.61, 2.85) associated with increased risk of death (adjusted for muscular strength, age socioeconomic status and smoking).
Nieto 1992 ⁴⁰ (cohort)	Quintiles of relative weight derived internally at age 5-18	Mortality (death certificates)	Follow-up to June 1985	13,146 men and women (50.3% ♀) in the US, b. 1915-40	Relative weight in highest quintile (prepubertal and postpubertal) associated with increased risk of mortality (OR 1.5; 95% CI 1.0, 2.4)
Nguyen 2008 ²³ (cohort)	BMI at ages 4-18 y	Type 2 diabetes (clinical assessment)	19-44	1,988 Men & women (57% ♀) in the US, b. late 1950s-1990	Each unit increase in BMI since childhood associated with increased risk of adult diabetes (β 0.09; 0.06, 0.12)
Osmond 2007 ³¹ (cohort)	BMI at ages 1-11 y	Stroke - hospitalization or death (registry data)	59-69	12,439 Men & women (48% ♀) in Finland	Each unit increase in BMI associated with reduced risk of all stroke at ages 2 (HR 0.84; 0.77, 0.92) and 7 y (HR 0.85; 0.76, 0.94) [same pattern with hemorrhagic and thrombotic stroke]; no evidence for association with BMI at age 11 y
Shaheen 1999 ³³ (cohort)	BMI and BMI quintiles at age 10 y	Asthma in the previous year (self reported)	26	6,420 Men & women (55% ♀) in Britain, b. 1970	BMI at age 10 y not associated with asthma at age 26 y
Silventoinen 2009 ¹² (cohort)	BMI categories at conscription (under-, normal, overweight, obese, very obese; WHO)	CHD and stroke – hospitalization and mortality (registry data)	39-44 (follow-up to end 2006)	1,145,467 Men in Sweden, b. 1951-76	Hazard ratios (reference group: normal weight) <i>CHD</i> : Overweight 1.74 (1.64, 1.84); Obese 2.50 (2.22, 2.81); Very obese 3.23 (2.54, 4.10) <i>Stroke</i> : Overweight 1.37 (1.26, 1.47); Obese 2.08 (1.78, 2.42); Very obese 3.20 (2.40, 4.26)
Tirosh 2011 ¹⁶ (cohort)	BMI percentile at age 17 y	Type 2 diabetes and coronary heart disease (clinical)	25-45 (mean age 30.6±5.3)	37,674 Men in Israel Defense Forces (IDF) Medical Corps	HR for incident diabetes in adulthood for top decile of BMI in adolescence vs bottom decile: 2.76 (2.12, 3.58) HR for incident CHD: 5.43 (2.77, 10.62)

♂=male; ♀=female; b.=born; ref.=reference population; BMI=body mass index kg/m²; CHD=coronary heart disease; HR=hazard ratio; OR=odds ratio; RR=risk ratio; 95% CI=95% confidence interval; IOTF=International Obesity Task Force definition of childhood overweight/obesity; WHO=World Health Organization definition of overweight/obesity

Table 2: Summary of included studies

Outcome	Number of studies	Summary–unadjusted for adult size	Summary–adjusted for adult size	Description
Type 2 diabetes	10	+++++++?	???	9 studies ^{13, 16-23} : increased BMI/overweight in childhood and adolescence associated with increased risk 1 study: no evidence of association ¹¹ 3 studies: adjustment for adult body size → no association
Hypertension	5	+++++	??	5 studies ^{11, 15-16, 18, 20, 23-25, 64} : increased BMI/overweight in childhood/adolescence associated with increased risk 2 studies: adjustment for adult BMI → no association
Coronary heart disease	15	+++++++???? + (♂)	+?	10 studies ^{12, 16, 20, 26-30, 62-63} : increased BMI/overweight in childhood and adolescence associated with increased risk of CHD (nonfatal and fatal) in adulthood 1 study ¹¹ : Positive association in men only 4 studies ^{32, 66-68} : no evidence of association 1 study: adjustment for adult BMI → increased HR 1 study: adjustment for adult BMI → no association
Stroke	8	+++ -??? + (♂)	?	2 studies ^{12, 29} : increased BMI/overweight in adolescence associated with increased risk of stroke in adulthood 1 study ³⁰ : higher BMI in adolescence associated with increased risk of death from cerebrovascular diseases 1 study ¹¹ : positive association in men only 1 study ³¹ : increased BMI associated with reduced risk 3 studies ^{26, 32, 68} : no evidence of association 1 study: adjustment for adult BMI → no association
Asthma	2	? + (♀)	?	1 study ¹⁴ : increased BMI in childhood associated with increased risk of asthma in women only 1 study ³³ : no evidence of association 1 study: adjustment for adult BMI → no association
All cancers	3	+? + (♀)	n/a	1 study ³⁴ : Higher BMI-SDS in childhood associated with increased odds of cancer (cases and mortality) 1 study ³⁰ : higher BMI in adolescence associated with increased risk of cancer mortality in women only 1 study ²⁷ : no evidence of association
Colon cancer	2	++	?	2 studies ^{11, 30} : Higher BMI in adolescence associated with increased risk of colorectal cancer mortality 1 study: adjustment for adult BMI → no association
Kidney cancer	1	+ (♂)	n/a	1 study ³⁵ : High BMI in adolescence associated with increased risk of renal cancer in boys
Breast cancer	4	—??	?	1 study ³⁶ : lower BMI at age 14 y associated with increased risk; 1 study ⁹ : obesity associated with reduced risk of pre-menopausal breast cancer 2 studies ^{10, 65} : no evidence of association 1 study: adjustment for adult overweight → no association
Cervical cancer	1	+	n/a	1 study ³⁰ : Higher BMI in adolescence associated with increased risk of cervical cancer mortality
Ovarian cancer	1	+	n/a	1 study ³⁷ : High BMI in adolescence associated with increased risk of ovarian cancer
All-cause mortality	6	+++++ + (♂)	?	5 studies ^{26, 30, 38-40} : increased BMI in childhood/adolescence associated with increased risk of mortality 1 study ¹¹ : association in men only 1 study: adjustment for adult BMI → no association

+ indicates positive association between BMI/weight status and disease; – indicates negative association; ? indicates no association; ♂=male; ♀=female; n/a=not available

