Change in body mass index from childhood onwards and risk of adult cardiovascular disease

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Abstract

Childhood obesity adversely affect the structure and function of the cardiovascular system, but the relationship between excessive weight gain during childhood and adult cardiovascular disease (CVD) is not fully understood. This review summarizes evidence for associations of change in body mass index (BMI) from childhood onwards with CVD outcomes. We found that excessive gain in BMI from childhood onwards was consistently associated with presence of CVD risk factors, with increased risks of coronary heart disease, and there were suggestions of associations with stroke and heart failure, but a lack of evidence precludes firm conclusions. These results indicate that the risk of CVD may be traced back to child ages and highlights the importance of early strategies for preventing excessive weight gain in childhood.

Keywords: Body Mass Index, Cardiovascular disease, Children, Growth, Obesity, Overweight.

Introduction

The epidemic of childhood overweight and obesity constitutes a major global health problem as worldwide 50 million girls and 75 million boys were classified as obese in 2016 [1]. Of great concern is that excess weight in childhood has serious health consequences appearing at both child and adult ages [2-4]. In particular, excess childhood body mass index (BMI; kg/m^2) is linked to cardiovascular disease (CVD) risk factors already during childhood [2] and there is evidence for links to adult CVD as well. Based on 17 studies, two meta-analyses demonstrated that higher BMIs in childhood are associated with significantly increased risks of coronary heart disease (CHD), covering stable angina and acute myocardial infarction in most studies [3,5]. Although earlier reviews and studies reported limited evidence supporting an association between childhood BMI and risks of stroke [3,4,6,7], we recently showed that children with an above-average BMI at each age from 7 to 13 years have increased risks of early (<55 years) but not late ischemic stroke [8]. Additionally, high childhood BMI has been positively associated with heart failure, CHD mortality and CVD mortality [9-12].

Taken together there is strong evidence that obesity at one age in childhood increases the risk of CVD in adulthood. However, from a public health perspective, early adverse BMI trajectories are important to understand as they may reveal potential intervention targets. This raises the questions of whether cardiovascular health is worsened by excessive BMI increases during childhood and if it can be improved or restored by weight loss during childhood and through to adulthood. The aim of this review is to summarize the current evidence for associations of change in BMI during childhood and from childhood to adulthood with CVD outcomes, and to discuss the potential biological mechanisms underlying these associations.

Methodology

In this narrative review we include topics of excessive gain in BMI (covered by "BMI", "overweight," "obesity", "childhood growth", "trajectory", "BMI change" and "BMI increase") and CVD (defined as "coronary heart disease", "stroke", "heart failure" and "atrial fibrillation"). Studies on associations between change in BMI or weight status during childhood (<16 years) or from childhood to adulthood and any CVD outcome were included.

As children age, they increase in BMI as depicted in growth charts. To standardize body size measures across age, BMI standard deviation scores (SDS) are used. Tracking in growth means that a child stays on a centile or BMI SDS over time, and deviations in BMI SDS over time equates to centile crossing. Most studies express excess gain per BMI SDS; an increase of 1 BMI SDS is equivalent to moving from the 50^{th} to the 84.1^{st} or from the 84.1^{th} to the 97.7^{st} BMI percentile of a growth chart. Childhood overweight and obesity are generally classified by excess BMI, but unlike in adults, cut-offs differ by age, sex and depend on the reference used. A standardized definition of childhood overweight and obesity does not exist. We extracted results for growth adjusted for baseline BMI, if available, rather than adjusted for attained BMI.

BMI changes and cardiovascular risk factors

Numerous studies have examined associations between changes in BMI from childhood onwards and CVD risk factors. Due to the volume of literature, only selected studies that we consider as representative of this area are described (for a list of additional studies see **Appendix S1)**.

BMI changes during childhood and adolescent cardiovascular risk factors

Results from a contemporary prospective study in the UK showed that children who had a greater BMI SDS increase between ages 9-12 and 15-16 years had a greater odds of adverse levels of CVD risk factors at 15-16 years [13]. Similarly, obese adolescents who had excessive increases in BMI SDS across ~20 months had decreases in insulin sensitivity and higher levels of 2-hour plasma glucose, triglycerides, and decreased HDL cholesterol compared to baseline levels [14]. In contrast, a reduction in the degree of obesity led to improvement in these CVD risk factors [14]. Similarly, children in the UK who changed from overweight to normal-weight by adolescence improved their levels of CVD risk factors compared with children who developed or remained overweight [13]. Supporting the reversibility of CVD risk factors, several exercise interventions showed improvements in blood pressure, flow-mediated dilation and carotid intima media thickness (cIMT) [15].

BMI changes during childhood and adult cardiovascular risk factors

Excessive increases in BMI during childhood are consistently related to CVD risk factors including elevated systolic blood pressure, higher levels of fasting insulin and lipids in young adulthood in studies from the US [16] and the Netherlands [17], and to CVD risk factors in midlife in studies from Iceland [11] and the UK [18]. The timing of when the excessive BMI gain during childhood is most harmful for CVD risk factors in young adulthood is largely unknown, although one study suggested that it was from 2-6 years rather than from birth to 2 or from 6-18 years [17].

BMI changes from childhood to adulthood and adult cardiovascular risk factors

A seminal study from the 1960s on schoolchildren in Hagerstown, USA, found that individuals who developed overweight after childhood had a higher prevalence of hypertension than those who were

overweight at both child and adult ages [19]. These results set forth the idea that the pattern of change in BMI from childhood rather than just the level of adult overweight may be important for CVD risk.

Results from the Bogalusa Heart study support that change in BMI from child to adult ages is associated with adult CVD risk factors. It found that a below-average BMI in childhood combined with obesity in adulthood was associated with the same high level of CVD risk factors as observed for the pattern of being obese at both ages [20]. Encouragingly, remitting from overweight in childhood was associated with a level of CVD risk factors similar to the pattern of having normal weight at both time points [20].

Supporting this, a study using data from 4 prospective studies [21], showed that the development of obesity (i.e. weight gain) from childhood to adulthood is as detrimental as persistent obesity for the risk of hypertension, dyslipidemia and cIMT and that remission of obesity mitigates the adverse effects of childhood obesity on these outcomes [21]. Similarly, in a study in which child-to-adult BMI trajectories were modeled, participants in the Cardiovascular Risk in Young Finns Study who had a BMI trajectory that reached or persisted at high adult BMI levels had an increased risk of an adverse cardiometabolic profile in adulthood (24-49 years) than the normal stable group [22]. Importantly, participants who remitted from a high childhood BMI did not have increased risks of adverse levels of dyslipidemia and hypertension, however, they still had a higher risk of an increased cIMT.

BMI changes and adult CVD events

We identified eight studies on BMI changes during childhood (<16 years) and CVD events in adulthood [8,11,23-28] and six studies on BMI changes from childhood through adulthood and CVD events [7,9,10,29-31].

BMI changes during childhood and adult CVD events

Four Finnish studies [23-26] and one Icelandic study [11] using data on individuals born in the 1920s-1940s consistently found that increases in BMI SDS were positively associated with risks of CHD in adulthood (**Table 1**). They reported hazard ratios (HRs) ranging from 1.20 to 1.52 per BMI SDS change at different ages from birth to 12 years [23-26]. When examining the mean change in BMI per year from 8 to 13 years, they found the risk of CHD was about double in the highest gaining group versus the lowest [11] (Table 1). When looking even earlier in life, a combination of having a low ponderal index (kg/m^3) at birth [23] or a low BMI at 2 years [26] in combination with a high BMI at age 11 yielded a greater risk of CHD than children who started life as heavy and had a low BMI at 11 years. These results indicate that those who experienced the greatest relative increase had the highest risk.

The literature on BMI changes during childhood and stroke outcomes is more limited than for CHD [8,11,27]. Of the three identified studies, neither a study from Finland [27] or Iceland [11] supported an association, whereas a larger one from Denmark did [8] (Table 1). In the Danish study, a 0.5 unit increase in BMI SDS between 7 and 13 years was associated with 8-10% increased risk of early stroke (≤55 years) in men and women who had an above-average BMI at 7 years. The associations were weaker for late stroke (>55 years) [8].

Few studies investigated associations with heart failure or composite measures of CVD. A Finnish study reported a significant and positive association between excess gain in BMI from 2 to 11 years of age and heart failure, but the HR was not reported [28]. One study from Iceland found that the risk of adult fatal CVD events (diagnoses were not specified) was about the double in children with the highest versus the lowest BMI gain during childhood [11] (Table 1).

BMI changes from childhood to adulthood and adult CVD events

We identified two studies examining the association between BMI changes from childhood to adulthood and CHD [29,30]. In participants from 3 British birth cohorts, compared to being never overweight in childhood, adolescence and adulthood, those who increased from non-overweight in childhood to overweight from adolescence onwards or by adulthood had almost a 4-fold increased risk of CHD, whereas those who had been overweight in childhood and/or adolescence only did not have an increased risk (**Table 2**). In two large US cohorts of men and women, those with moderate or marked increases in body-adiposity trajectories from 5 to 55 years had significantly increased risks of CHD than those who had a stable pattern of a lean body shape [30] (**Table S1**).

Of the two studies on BMI change and stroke, one in Swedish men found that per BMI SDS increase from 8 to 20 years the risk of any type of stroke increased by 21% [7] (Table 2). Results were similar for ischemic stroke and intracerebral hemorrhage [7]. Further, men who remitted from overweight at age 8 by age 20, had a similar risk of stroke as men who had normal-weight at both ages, whereas men who developed overweight had an increased risk (Table S1) [7]. In contrast, in a large US study, an increasing body-adiposity trajectory from child to adult ages was not associated with the risk of stroke among men, whereas it was in women (Table 2) [30]. The only study we identified on heart failure using a Swedish male cohort found that increases in BMI from 8 to 20 years were non-linearly associated with the risk of heart failure; there was a markedly increased risk in the highest quintile of BMI change [10] (Table 2).

Three studies assessed the association between BMI change from childhood to adulthood and CVD morbidity [30,31] or CVD mortality [9]. Despite using different definitions of CVD, all provide evidence that a greater BMI increase is associated with increased risks of CVD (Table 2, Table S1). In a Swedish male cohort, per increase in BMI SDS from 8 to 20 years, risks of CVD mortality increased by 21% (Table 2). Men who had overweight at 8 years, but not at 20 years, had a similar

risk of CVD mortality as men who had normal-weight at both ages, whereas men who developed overweight had an increased risk (Table S1) [9]. A similar pattern was found in the US study [31], although the data are challenging to interpret as confidence intervals were not provided.

Discussion

The main finding of this review is that children who gain excess BMI during childhood and from childhood to adulthood have increased risks of CHD, which may be mediated by CVD risk factors. Although some studies support an association with stroke, the evidence is inconsistent, and the association may differ by age at diagnosis. Evidence for an association with heart failure and composite measures of CVD morbidity and mortality is limited (only 2 and 3 studies on each), but generally support an association.

For many CVD outcomes, the risks increased across the entire range of BMI change and were not limited only to children who gained enough to be classified as overweight or obese at a later timepoint [7,8,10,12]. Although the associated risks are high, as a cautionary note, an excess increase of one BMI SDS is a substantial increase and most children do not change that much [8]. Only for heart failure in men was a threshold effect identified; risks were observed only among men who gained more than 8.3 BMI units from 8 to 20 years [10]. More studies are needed to replicate these findings.

The findings from this review suggest that the CVD consequences of childhood obesity may be reversible if a child normalizes his or her weight status before adulthood. Similarly, we have shown that childhood overweight at age 7 years is associated with increased risks of adult type 2 diabetes only if it continues until puberty or later ages [32]. Thus, it is possible that there are favorable BMI trajectories that can attenuate the association of excess child BMI with CVD risk.

The association between excess BMI gain in childhood and adult CVD outcomes is likely complex and multifactorial in etiology. It may involve genetic, environmental, and early life determinants, some operating already in utero. Childhood overweight and obesity has appreciable short-term effects on the cardiovascular system, which may be mediated through various adipocytokines, including leptin, resistin, adiponectin, interleukin-6, and tumor necrosis factor-a [33]. Clustering of traditional CVD risk factors that accompany childhood obesity such as insulin resistance, hypercholesterolemia, diabetes, and high blood pressure may be mediators of the development of CHD, stroke, and heart failure in adulthood. Evidence suggests that excess BMI gain in childhood or the presence of higher levels of CVD risk factors inherent to obesity may promote early key steps in the development of CVD *e.g.* impaired endothelial function, diminished arterial distensibility, and adverse changes in cIMT as shown in this review. Moreover, excess gain in BMI during childhood may have direct adverse effects on cardiac structure and function, including larger atrial and ventricular dimensions, increased left ventricular mass, altered left ventricular geometry, and subclinical myocardial dysfunction, which in turn increases the likelihood of CVD outcomes [34]. Thus, it is plausible that these early life determinants may act alone or interact with each other, accentuating the atherosclerotic process and lowering the threshold for plaque rupture and thrombosis in adulthood.

Heavy children often remain overweight or obese as adults, but the likelihood strongly depends on several factors. The risk of persistence is higher with more severe overweight and obesity in childhood, with increasing childhood age, and if it is assessed at younger adult ages [35,36]. Thus, the long-term consequences of childhood obesity on the risk of adult CVD may at least partly be associated with adult obesity. Based on studies that adjusted for adult BMI, two reviews concluded that adult BMI matters more than child BMI for CVD, and that it is the tracking of childhood obesity that accounts for the risk [4,37]. Although these types of analyses are intuitively appealing they often

address a different question than expected since it is not possible to derive the independent effects of child BMI (starting level), change and adult BMI (ending level) from a single regression model [38]. These reviews were based on studies that used a parameterization of the model in which child BMI was adjusted for adult BMI. In other words, it investigates the effect of a one SDS difference in BMI between two children who attain the same BMI as adults. These models often yield regression coefficients <1, because inherently the child with the lower BMI increased more to end up at the same adult BMI level as the child who had a higher BMI. Thus these models do not show the effect of body size at one point in time, and they ignore the starting level of BMI in childhood [38]. Additionally, these models and the reviews did not examine the effects of remission from obesity. Studies included in our review demonstrate that remission from overweight during childhood or before adulthood can reduce risks of CVD, thus highlighting that BMI trajectories are suitable targets for preventive interventions. Despite high degrees of BMI tracking during childhood, large changes can occur [39]. As newer analytic models are used [22,30], it may become easier to identify life-course body-size patterns and thus better capture the long-term cumulative risk than simple cross tabulations of child and adult BMI.

Although studies on childhood BMI changes and CVD risk factors are plentiful, hence precluding us from doing an exhaustive review, studies on childhood BMI changes and adult CVD events are still scarce. Additionally, many are small, and publication bias cannot be precluded. Moreover, the studies are diverse in population, calendar time, design, methods and definitions of CHD and CVD are not standardized, limiting direct comparisons. Further, few studies included information on body size at more than one time point at child or adult ages [29,30]. As with all long-term follow-up studies, many of the cohorts were born a long time ago. Since then, many cohort studies with an abundance of information including repeated measures of body size have been initiated. Future studies should follow these contemporary cohorts for the association between early

BMI gain and CVD outcomes. Potential threshold effects of excess BMI gain and differences by sex may be important research areas, as major differences between men and women exist in epidemiology, clinical presentation, pathophysiology, treatment, and outcome of CVD, but these were rarely investigated in the studies included in this review. Additionally, future studies should examine effects of childhood BMI gain on other important outcomes such as atrial fibrillation, venous thromboembolism, valvular heart diseases and peripheral artery disease.

Conclusions

Current evidence supports an association between excess gain in BMI during childhood and from child to adult ages and presence of CVD risk factors and increased risks of CHD. Studies also indicate that excess BMI gain from childhood onwards is associated with ischemic stroke, heart failure, and composite measures of CVD morbidity and mortality although there are few studies in these areas. Underlying mechanisms may include clustering of cardiovascular risk factors, structural changes in cardiac structure and function and tracking of BMI to adulthood. As remission from overweight may reduce CVD risks, the rationale for early strategies to prevent weight gain in childhood is compelling.

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Table 1. Studies on growth during childhood and adult cardiovascular disease

Year	Study [reference]	Country	Birth years	Women, N included/ N outcomes	Men, N included/N outcomes	Growth pattern	Outcome	Adjustment	Main findings (adjusted models if available)
1999	Helsinki Birth Cohort [23]	Finland	1924-33	None	3,641/310	BMI at 11 y adjusted for PI at birth	Fatal CHD	Length of gestation	HR=1.22 (1.10-1.36)
2001	Helsinki Birth Cohort [24]	Finland	1934-44	None	4,630/357	Change in BMI-SDS age 1-12 y	CHD	None	HR=1.20 (1.08-1.33)
2004	Helsinki Birth Cohort [25]	Finland	1934-44	4,130/	None	Change in BMI-SDS age 3-12 y	CHD	1. None 2. Birth length, education	1. HR=1.56 (1.27-1.92) 2. HR=1.52 (1.23-1.89)

2005	Helsinki Birth Cohort [26][2]	Finland	1934-44	4,130/87	4,630/357	BMI-SDS at 11 y adjusted for BMI-SDS at 2 y	CHD	None	Women: HR=1.35 (1.02-1.11) Men: HR=1.14 (1.00-1.31)
2007	Helsinki Birth Cohort [27]	Finland	1934-44	5,950/174	6,489/333	BMI-SDS at 11 y adjusted for BMI-SDS at 2 y	Any stroke	None	HR=1.04 (0.94 to 1.15)
2010	Helsinki Birth Cohort [28]	Finland	1934-44	6,370/49	6,975/138	BMI-SDS at age 11 y adjusted for BMI-SDS at 2 y	Chronic heart failure	None	HR>1, P=0.001
2014	The Longitudi-nal Rey-kjavik Study [11]	Iceland	1921-35	945/90	979/202	BMI velocity from 8-13 years (mean change in kg/m^2 per year). Comparison: Highest versus lowest tertile.	1. MI 2. Stroke 3. Fatal CHD 4. Fatal CVD	Birth year, parity, birth weight, $BMI_{8y,}$ age at recruitment	1. Women: $p_{trend}=0.6$[b] Men: $p_{trend}=0.8$ 2. Women: $p_{trend}=0.6$ Men: $p_{trend}=0.6$ 3. Women: HR=2.26 (1.03-4.69)[c] Men: HR=1.93 (1.25-3.00) 4. Women: HR=2.38 (1.36-4.16) Men: HR=1.70 (1.19-2.43)

2017	Copen-hagen School Health Records [8]	Denmark	1930-87	151,955/ 3,529	155,722/ 5,370	Change per 0.5 BMI-SDS age 7-13 y	1. Early IS 2. Late IS	BMI-SDS at 7 years	1. Women: HR=1.10 (1.01-1.20)[d] Men: HR=1.08 (1.00-1.16) 2. Women: HR=1.06 (1.01-1.12) Men: HR=1.02 (0.97-1.06)

BMI: Body mass index; CHD: Coronary heart disease; CVD: Cardiovascular disease; HR: Hazard ratio with 95% confidence intervals; IS: Ischemic stroke; MI: Myocardial infarction; PI: Ponderal index; SDS: standard deviation score.

[a] This study is based on the same individuals as references [24] and [25] but reports sex specific results. d [b] P-value derived from chi-square test. [c] Estimates for the highest versus lowest tertile of BMI velocity. [d] Estimates among those with a BMI SDS at 7 years >0 is reported. Estimates for change in BMI SDS were similar among those with a BMI SDS at 7 years ≤0.

Table 2. Studies on growth from childhood to adulthood and adult cardiovascular disease

Year	Study (reference)	Country	Birth years	Women, N included/ N outcomes	Men, N included/ N outcomes	Growth pattern	Out-come	Adjustment	Main findings (adjusted models if available)
2012	Princeton Follow-up Study [31]	US	~1953-1971	770/19		Combinations of child overweight (5-20 y; CDC), and adult obesity (29-48 y).	CVD	None	$P_{chi\text{-}square}$=0.0005
2013	1946, 1958 and 1970 British Birth Cohorts [29]	UK	1946, 1958, 1970	5,842/ 105	5,605/	Combinations of child overweight (7-10 y; IOTF), overweight in adolescence (15-16) and adult obesity (34-43) (reference: never overweight).	CHD	Sex, year of birth, child age and height, birth weight, SEP at birth, SEP in adulthood, and adult smoking status	$OR_{Child\text{-}only}$=0.44 (0.20-1.89) $OR_{Adolescence\text{-}only}$=1.63 (0.37-7.19) $OR_{Adult\text{-}only}$=3.83 (1.98-7.42) $OR_{Child+Adolescence}$=3.43 (0.60-19.64) $OR_{Child+Adult}$=1.10 (0.14-8.48) $OR_{Adolescence+Adult}$=3.74 (1.35-10.35) $OR_{Child+Adolescence+Adult}$=6.62 (1.94-22.65)

2016	BMI Epide-miology Study [9]	Sweden	1945-61		37,672/ 710	Change in BMI-SDS age 8-20y	CVD-mortality	BMI-SDS at 8 years, birth year, country of birth.	HR=1.21 (1.13-1.30)
2017	Nurses' Health Study & Health Professio-nals Follow-up Study [30]	US	~1921-1946/ ~1911-1946	72,989/ 5,105	31,970/ 4,002	5-55-y-old body shape trajectories (reference: Lean-stable).	1. CVD (stroke, MI) 2. CHD 3. Stroke	Height, race, smoking, aspirin use, menopausal hormone therapy, physical activity, alcohol consumption, Alternate Healthy Eating Index score, and family history of diabetes.	1. Women: $HR_{lean\text{-}moderate\ increase}$=1.18 (1.08-1.29)[a] $HR_{lean\text{-}marked\ increase}$=1.38 (1.25-1.52) Men: $HR_{lean\text{-}moderate\ increase}$=1.16 (1.05-1.29) $HR_{lean\text{-}marked\ increase}$=1.28 (1.16-1.41) 2. Women: $HR_{lean\text{-}moderate\ increase}$=1.21 (1.06-1.38) $HR_{lean\text{-}marked\ increase}$=1.49 (1.30-1.71) Men: $HR_{lean\text{-}moderate\ increase}$=1.25 (1.10-1.41) $HR_{lean\text{-}marked\text{-}increase}$=1.40 (1.25-1.57) 3. Women: $HR_{lean\text{-}moderate\ increase}$=1.16 (1.03-1.31) $HR_{lean\text{-}marked\ increase}$=1.29 (1.13-1.47) Men: $HR_{lean\text{-}moderate\ increase}$=0.98 (0.82-1.18) $HR_{lean\text{-}marked\ increase}$=1.01 (0.86-1.19)

2017	BMI Epide-miology Study [7]	Sweden	1945-61		37,669/ 918 (IS: 672)	Change in BMI-SDS age 8-20y	1. Any stroke 2. IS	BMI-SDS at 8 years, birth year, country of birth.	1. HR=1.21 (1.14-1.28) 2. HR=1.19 (1.11-1.28)
2018	BMI Epide-miology Study [10]	Sweden	1945-61		37,670/ 342	Change in BMI age 8-20y (reference: first quartile).	Heart failure	BMI-SDS at 8 years, birth year, country of birth.	HR_{Q2}=1.21 (0.86-1.71) HR_{Q3}=1.51 (1.08-2.10) HR_{Q4}=2.26 (1.66-3.08)

CDC: Center for Disease Control and Prevention; HR: Hazard ratio; IOTF: International Obesity Task Force; IS: Ischemic stroke; OR: Odds ratio; SDS: standard deviation score; SEP: Socio economic position.

[a] Selected results reported for groups who increased in BMI from normal weight to overweight. See also Table S1.

Supplementary material

Appendix S1. Reference list

The reference list provides an overview of studies on childhood BMI changes and cardiovascular risk factors. Studies only investigating type 2 diabetes were not included.

Studies on childhood BMI changes and cardiovascular risk factor levels in the short term:

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Table S1. Additional results for studies on change in weight status group from childhood to adulthood and adult cardiovascular disease

Year	Study [reference]	Country	Birth years	Women	Men	Growth pattern	Outcome	Adjustment	Main findings (adjusted models if available)
2012	Princeton Follow-up Study [31]	US	~1953-1971	N=770 Cases=19		Combinations of child overweight (5-20 y; CDC), and adult obesity (29-48 y).	CVD	None	Incidence proportion$_{ormal\text{-}normal:=}$0.9% Incidence proportion$_{high\text{-}normal}$=2.5% Incidence proportion$_{normal\text{-}high}$=4.0% Incidence proportion$_{high\text{-}high}$=6.2%
2016	BMI Epide-miology Study [9]	Sweden	1945-61		N=37,672 Cases= 710	Combinations of child overweight (8 y, CDC), and adult overweight (20 y) (reference: NW-NW)	CVD-mortality after age 50 years	Birth year, country of birth.	$HR_{OW\text{-}NW}$=1.09 (0.68-1.74) $HR_{NM\text{-}OW}$=2.14 (1.56-2.96) $HR_{OW\text{-}OW}$=1.78 (1.13-2.78)
2017	Nurses' Health Study & Health Professionals Follow-up Study [30]	US	~1921-1946/ ~1911-1946	N=72,989 Cases= 5,105	N=31,970 Cases= 4,002	5-55-y-old body shape trajectories (reference: Lean-stable).	1. CVD 2. CHD 3. Stroke	Height, race, smoking, regular aspirin use, menopausal hormone therapy, physical activity, alcohol consumption, Alternate Healthy Eating Index score, and family	1. Women: $HR_{medium\text{-}stable}$=0.97 (0.89-1.06) $HR_{heavy\text{-}increase}$=1.55 (1.40-1.71) Men: $HR_{medium\text{-}stable}$=1.10 (0.98-1.23) $HR_{heavy\text{-}increase}$=1.35 (1.20-1.53) 2. Women: $HR_{medium\text{-}stable}$=0.99 (0.87-1.13) $HR_{heavy\text{-}increase}$=1.75 (1.52-2.02) Men: $HR_{medium\text{-}stable}$=1.17 (1.02-1.34) $HR_{heavy\text{-}increase}$=1.49 (1.29-1.72) 3. Women: $HR_{medium\text{-}stable}$=0.95 (0.84-1.07) $HR_{heavy\text{-}increase}$=1.33 (1.16-1.54) Men: $HR_{medium\text{-}stable}$=0.92 (0.75-1.12) $HR_{heavy\text{-}increase}$=1.00 (0.80-1.25)

								history of diabetes.	
2017	BMI Epidemio-logy Study [7]	Sweden	1945-61		N=37,669 Cases= 918 (IS: 672)	Combinations of child overweight (8 y, CDC), and adult overweight (20 y) (reference: NW-NW)	1. Stroke 2. IS	Birth year, country of birth.	1. HR_{OW-NW}=1.17 (0.83-1.63) HR_{NM-OW}=1.81 (1.41-2.33) HR_{OW-OW}=1.71 (1.22-2.38) 2. HR_{OW-NW}=1.17 (0.73-1.62) HR_{NM-OW}=1.48 (1.08-2.03) HR_{OW-OW}=1.78 (1.22-2.60)
2018	BMI Epidemio-logy Study [10]	Sweden	1945-61		N=37,670 Cases= 342	Combinations of child overweight (8 y, CDC), and adult overweight (20 y) (reference: NW-NW)	Heart failure	Birth year, country of birth.	HR_{OW-NW}=1.12 (0.63-2.00) HR_{NM-OW}=3.14 (2.25-4.38) HR_{OW-OW}=2.85 (1.83-4.45)

BMI: Body mass index; CDC: Center for Disease Control and Prevention; CHD: Coronary heart disease; CVD: Cardiovascular disease; HR: Hazard ratio with 95% confidence intervals; ICH: Intracerebral hemorrhage; IS: Ischemic stroke; NW: Normal weight; OW: Overweight;

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