Breast cancer risk and the interaction between adolescent body size and weight gain in later life: a case-control study

Ines Florath[1], Danja Sarink[2], Christobel Saunders[3], Jane Heyworth[4], Lin Fritschi[1]

[1]School of Public Health, Curtin University, Perth, Australia

[2]Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

[3]School of Surgery, University of Western Australia, Perth, Australia

[4]School of Population Health, University of Western Australia, Perth, Australia

Corresponding author:

Dr Ines Florath

School of Public Health

Curtin University

GPO Box U1987, Perth, Western Australia 6845

Tel.: +61 406642512

Email: ines.florath@curtin.edu.au

The Breast Cancer Environment and Employment Study was funded by a National Health and Medical Research Council Australia (NHMRC) project grant # 572530 and by a grant from the Cancer Council Western Australia (CCWA). L.F. is supported by fellowships from the NHMRC and CCWA.

Conflict of interest: none.

Abstract

Background: While the breast cancer risk associated with increasing adult BMI in postmenopausal women can be explained by increases in concentrations of endogenous estrogens the biologic mechanisms behind the inverse association between adolescent BMI and breast cancer risk are still a subject of controversial debate.

Methods: We investigated the association of breast cancer with body size and changes in body size across life time estimated by age-specific BMI Z scores and changes in BMI Z scores from teenage years to middle age in an age-matched population-based case-control study of 2994 Australian women. Logistic regression adjusted for the matching factor age and further potential confounders was used.

Results: Adolescent body leanness in postmenopausal women and excess adult weight gain in all study participants were associated with an increased breast cancer risk with an odds ratio [95% confidence interval] of 1.29 [1.08,1.54] and 1.31 [1.09,1.59], respectively. Interaction analyses restricted to postmenopausal women revealed an increased risk of breast cancer in those who were lean during adolescence and gained excess weight during adulthood (odds ratio [95% confidence interval]: 1.52 [1.19,1.95]) but not in women who were lean during adolescence and did not gain excess weight during adulthood (1.20 [0.97,1.48]) and not in women who were not lean during adolescence and but gained excess weight during adulthood (1.10 [0.95,1.27]) compared to postmenopausal women who were neither lean during adolescence nor gained excess weight.

Conclusion: In postmenopausal women adolescent leanness was only associated with increased breast cancer risk when excess weight was gained during adulthood.

(Words: 250)

Keywords: body mass index, weight gain, breast cancer, risk, childhood, adult

1. Introduction

Breast cancer is the most common cancer in women and second most common cancer overall worldwide, with nearly 1.7 million new cases diagnosed in 2012 [1]. Evidence for the role of obesity and adult weight gain in the carcinogenesis of breast cancer has been strengthened by many large cohort studies with over 50,000 or even 100,000 participants, where associations of BMI and especially adult weight gain with incident cases of breast cancer were observed [2-7]. Adult weight gain has been suggested to be a better metric than BMI, which is the most widely used metric of adiposity in adults, because weight gain captures the dynamic pattern of weight trajectory throughout adult life [5].

An inverse association of childhood and adolescent body size with breast cancer risk adjusted for other breast cancer risk factors has been reported previously based on data from the Nurses' Health Study [8-10] and the French E3N cohort study [11]. In these studies body size at a younger age was recalled using body shape figure rating scales. Case-control studies, such as the Women's Circle of Health Study, observed decreased postmenopausal breast cancer risk among white women who were heavier at menarche, after excluding hormone replacement therapy users [12]. The Carolina Breast Cancer Study observed decreased cancer risk with heavier childhood relative weight among premenopausal white women but not among black women and postmenopausal white women [13]. In these studies recalled body size at a younger age was assessed by comparative weight, where perceived weight in comparison to peers was reported. So far, there are only a few studies investigating the association of breast cancer risk with both childhood and adult weight. While all of these studies observed an inverse association of breast cancer risk with childhood or adolescent body size, contradictory results concerning the association with adult weight and weight gain were reported [10,12,13].

We investigated the association of breast cancer with both teenage and adult BMI Z scores and weight gain during lifetime calculated from recalled weight values as continuous variables. Therefore the same metric was used across lifetime and dose-response relationships were investigated using continuous variables. In comparison to previous studies, data on recalled weight values were collected in addition to recalled comparative weight assessment.

2. Methods

2.1. Study population

The Breast Cancer Environment and Employment Study (BCEES) is a population-based case–control study, which has been described in detail previously [14,15]. Briefly, eligible cases were women aged 18–80 years and diagnosed with breast cancer (ICD-10 C50) between 1 May 2009 and 31 January 2011 and reported to the Western Australian Cancer Registry before 31 July 2011. Among the 2089 eligible cases, 1,205 (58%) consented to participate. Age-matched controls were randomly selected from the electoral roll of Western Australia between May 2009 and July 2011. Voting is compulsory in Australia, and the electoral roll is considered an almost complete list of Australian citizens. Of the 4,358 eligible frequency age-matched controls 1,789 (41%) consented to participate. Compared with participants, those who did not consent to participate were older, while those who did not respond were younger [14].

The study was approved by the Human Research Ethics Committee of The University of Western Australia and the Western Australian Department of Health. Informed consent was obtained from all participants.

2.2. Exposure variables

Participants completed a questionnaire containing questions on their current height ("How tall are you?") and weight ("How much do you weigh now?"), their weight in their early teenage years ("How much did you weigh in your early teenage years (around the age of your first period)?"), and in their early thirties ("How much did you weigh when you were in your early 30s?", and their maximal weight ("What is the most you have ever weighed? (not including pregnancy")). Women were also asked about their comparative weight as a teenager ("When you were a teenager, what do you think you weighed compared with other girls of the same age and height?") and at age 30 years ("When you were in you early 30s, how did your weight compare with women the same age and height?"). Five responses were available, 'a lot less', 'a little less', 'about the same', 'a little more' and 'a lot more'.

We investigated five exposure variables characterizing body size and weight gain during life time: Z score of BMI in teenage years (Z_{teens}), Z score of BMI in early thirties years of age (Z_{30s}), Z score of maximal BMI during life time (Z_{max}), difference between Z scores of BMI in early thirties and in teenage years ($\Delta Z_{30s\text{-}teens}$), difference between Z scores of maximum BMI during life time and of BMI in early thirties ($\Delta Z_{max\text{-}30s}$). BMI at different ages was calculated as weight (kg) at different ages divided by squared height (m^2). To determine BMI in teenage years and in early thirties, we assumed that current height could be used as an estimate of height at those ages. We further assumed that the maximum BMI occurred after age 30.

Age-specific BMI Z scores were calculated based on the WHO reference using the LMS method, where a normal distribution after Box-Cox power transformation is assumed [16,17]. The median WHO reference for BMI in adulthood was taken as 22.5 kg/m^2 and in teenage years as 18.8 kg/m^2 at 13 years obtained from WHO growth reference [18].

2.3. Statistical analysis

To estimate odds ratios (OR) and 95% confidence intervals (CI) unconditional logistic regression with the matching factor age in 5-year groups included in all models was used [19] and the following variables were considered as potential confounders based on prior knowledge from scientific literature [2-15]: age at menarche (in years), body height, family history of breast cancer, number of children, age at first birth, breastfeeding, ever use of hormone contraception, education, country of birth, alcohol consumption and smoking status. Menopausal status and use of hormone replacement therapy were determined before cancer diagnosis for cases using the questions about age when the woman started to use hormone replacement therapy (HRT), age when menopause started and age at cancer diagnosis. Menopausal status and use of hormone replacement therapy for controls were assessed at current age minus one year since the study was conducted on average one year after the diagnosis of breast cancer.

For most of the variables the number of subjects with missing data was less than 5% of the total but for weight in teenage years and in early thirties the percentage was 31% and 12%, respectively (Table 1). To replace missing values, multiple imputation using the Markov chain Monte Carlo (MCMC) method creating five imputations was conducted. Missing BMI values in teenage years and early thirties, where comparative weight values were available, were replaced by a random sample (without replacement) of available BMI values stratified by comparative weight categories. Sensitivity analyses using the complete records for BMI values were conducted for comparison since different results have been reported previously for datasets using complete records and imputed data [20].

To investigate the dose-response association between the continuous confounding and exposure variables and the outcome (case/control status), and to check for the linearity

assumption of the logistic regression model, we used restricted cubic spline (RCS) regression [21]. Knots were set at 5th, 25th, 75th, 95th percentiles and reference values were set at the median [22]. Dose-response relationships were inspected and are shown in Figure 3 for exposure variables where the test for the non-linear association [21] was significant. Variables showing a non-linear association were included in the conditional logistic regression model in categorized form using quartiles as cutoffs. Because of the u-shaped association of the confounding variable 'age at first child' it was recoded together with the variable 'parity' into categories 'no parity', 'age at first child <22 years', 'age at first child >27 years' with 'age at first child between 22 and 27' as the reference. Interactions between the exposures of interest and effect modification by menopausal status and HRT-use were analyzed as recommended by Knol and VanderWeele [23,24].

Data were analysed using the SAS software package (Version 9.4 and Enterprise Guide 6.1, SAS Institute, Cary, NC). Covariates were described by median and interquartile range or by frequency. Two-sided p-values of 0.05 or 95% confidence intervals of odds ratio excluding 1 were considered significant.

3. Results

Based upon age at the time of the interview nearly 57% of the controls and of the cases were overweight or obese (Table 1). Around 68% of both cases and controls reported ever being overweight/obese. In teenage years and in early 30s approximately 20% of both cases and controls were overweight or obese (Table 1). Controls were more frequently older than cases but the median differed only by one year. Compared with controls, cases were more likely to have a family history of breast cancer, to have been born outside of Australia, to have delivered fewer

children and to have obtained a university degree, and were less likely to have taken hormone replacement therapy and to be postmenopausal (Table 1).

Table 1 Characteristics of 2994 Participants of the Breast Cancer Environment and Employment Study, Western Australia

Characteristics	**Missing N (%)**	**Median (Q1,Q3) or Number (%)[a]**	
		Controls	**Cases**
N		1789	1205
Current age (years)	0	59(51,66)	58(48,65)
Age at diagnosis (years)	0		57(48,65)
Age at menarche (years)	32(1)		
≤10		48(5)	56(5)
11		253(14)	176(15)
12		399(23)	311(26)
13		534(30)	334(28)
≥14		498(28)	316(26)
Current body size:			
Current body height (m)	29(1)	1.63(1.57,1.68)	1.63(1.59,1.68)
Current overweight/obese (BMI≥25)	71(2)	988(57)	670(57)
Current BMI (kg/m^2)		25.7(22.9,29.5)	25.8(22.8,29.8)
Z-score (Mean(SD))		0.83(0.77)	0.84(0.81)
Ever overweight/obese (BMI≥25)	192(6)	1153(68)	756(68)
Maximum BMI (kg/m^2)		27.2(24.2,31.6)	27.4(24.2,31.6)
Z-score (Mean(SD))		1.02(0.69)	1.04(0.72)
Body size at age in early 30s:			
Weight in comparison with others (%)	41(1)		
A lot less		83(5)	84(7)
Less		481(27)	327(28)
About the same		827(47)	555(47)
A little more		308(17)	172(14)
A lot more		71(4)	45(4)
Overweight/obese (BMI≥25) (%)	358(12)	324(20)	204(20)
BMI in early 30s (kg/m^2)		22.0(20.2,24.5)	21.8(20.1,24.2)
Z-score (Mean(SD))		0.16(SD=0.84)	0.13(SD=0.86)
BMI in early 30s (kg/m^2)[b]	0	22.0(20.2,24.5)	21.9(20.2,24.2)
Z-score (Mean(SD))[b]		0.18(SD=0.82)	0.17(SD=0.85)

Body size in teenage years:			
Weight in comparison with others	22(1)		
A lot less		134(7)	94(8)
Less		346(20)	256(21)
About the same		922(52)	608(51)
A little more		304(17)	201(17)
A lot more		69(4)	38(3)
Overweight/obese (BMI≥21.8, %)[c]	930(31)	358(20)	240(20)
BMI in teenage years (kg/m^2)		19.5(17.8,21.5)	19.2(17.5,21.3)
Z-score (Mean(SD))		0.10(0.96)	0.02(0.92)
BMI in teenage years (kg/m^2)[b]	16	19.7(17.9,21.5)	19.5(17.6,21.5)
Z-score (Mean(SD))[b]		0.13(0.90)	0.07(0.93)
Δ Z-score between Maximum and early 30s[b]	0		
(Mean(SD)) (adult weight gain)		0.84(0.62)	0.87(0.70)
Δ Z-score between early 30s and teenage	16		
years[b] (Mean(SD))		0.05(0.90)	0.10(0.99)
Smoking status	10(0.3)		
Never smoker		1022(57)	658(55)
Former/current smoker		761(43)	543(45)
Alcohol use (g/week)	53(2)	81(18,294)	83(12,300)
Education	0		
Finished year 9, 10 or 11		646(36)	436(36)
Year 12 or equivalent		403(22)	248(21)
Trade/Apprenticeship/Diploma		436(24)	259(22)
University education		304(17)	262(22)
Other country of birth	0	598(33)	437(36)
SES of residential area (quintiles from ABS)	5		
Lowest (most disadvantaged)		51(3)	32(3)
2nd		286(16)	180(15)
3rd		444(25)	272(23)
4th		384(22)	247(21)
Highest (least disadvantaged)		622(35)	471(39)
Family history of breast cancer	8(0.3)	504(28)	472(39)
Parity	0		
0		188(10)	158(13)
1		138(8)	115(10)
≥2		1463(82)	932(77)
Age at birth of first child (years)	3(0.1)	24(21,28)	24(21,28)
No parity		188 (10)	158 (13)
Age at birth <22		423 (24)	300 (25)
Age at birth 22-27		758 (42)	457 (37)

Age at birth >27		420 (24)	290 (24)
Total months breastfeeding	55(2)	11(4,22)	11(3,21)
Ever used hormone contraceptives	321(11)	1017(64)	681(63)
Age at menopause	127(6)	48(42,52)	49(43,52)
Post-menopausal status 1 year ago/before diagnosis	46(2)	1374(78)	843(73)
Age starting HRT use	82(3)	48(44,52)	49(45,52)
HRT use 1 year ago/before diagnosis	35(1)	678(38)	408(34)

[a] for Z-scores means and standard deviation (SD) are reported as indicated

[b] missing data replaced by random samples of BMI stratified by non-overlapping subgroups of comparative weight

[c] at age 13 years from WHO growth reference [18]

Q1-first quartile

Q3-third quartile

3.1. Replacement of missing BMI values using a random sample of BMI derived from reported weight values stratified by comparative weight categories

Of the weight values recalled from teenage years and early thirties, 31% and 12%, respectively, were missing. In contrast, the comparative weight was recalled much better with only 0.7% and 1.4% missing, respectively in teenage years and early thirties (Table 1). We compared the comparative weight for women who reported their weight values versus those who did not report them in their early thirties (Figure 1A) and in their teenage years (Figure 1B). For both ages, women who did not report their weight values tended to be heavier than their peers assessed by comparative weight ($p<0.001$, for both ages). This suggests that recalled weight values were not missing at random.

In Figure 2 the distributions of BMI overall and for each comparative weight category for women who reported both weight values and comparative weight, are depicted. Figure 2a shows that the BMI calculated from the reported weight values parallels the reported comparative weight. The density plots for BMI of comparative weight categories ‘a lot less’ and ‘less’ were shifted to the left and the density plots for BMI of comparative weight categories ‘a little more’ and ‘a lot more’ were shifted to the right from the distribution for the category ‘about the same’. The same picture was seen for the BMI distributions based on the weight recalled from teenage years although the density plots were less clearly separated (Figure 2b).

Based on our findings that the weight values were not missing at random and our observation of an agreement between comparative weight categories and BMI values in women reporting both metrics we replaced missing BMI values by random samples of BMI obtained from women reporting both metrics for each comparative weight category. Using all BMI values, calculated and replaced by random sampling, Z score of BMI at all ages were calculated. At all ages the BMI Z scores were larger than zero, which means that the study population at all ages was more overweight or obese than the WHO reference. The Z scores of BMI in teenage years and in early thirties increased after replacement of missing values reflecting that women who did not report their weight values had higher comparative weight.

3.2. *Association of BMI and weight gain with breast cancer risk*

We observed a significant non-linear u-shaped association of breast cancer risk with weight gain after an age of 30 years ($\Delta Z_{max\text{-}30s}$) with a p-value for non-linear association of 0.006 (Figure 3A). In the ~~conditional~~ logistic regression model a categorical variable using the 1st and 3rd quartile with 0.43 and 1.2, respectively, were used as cutoffs (Table 2). For all other exposure

variables the test for the non-linear association by Desquilbet et al. [21] was not significant and they were included into the logistic regression models as continuous variables.

Z_{teens}, Z_{30s}, Z_{max}, and $\Delta Z_{30s\text{-}teens}$, were not associated with breast cancer risk (Table 2). Excess adult weight gain after an age of 30 years ($\Delta Z_{max\text{-}30s}$>1.2) was associated with increased breast cancer risk in the age-adjusted and multivariable-adjusted analyses, as well as in the sensitivity analysis including only the observations with complete records of weight values (Table 2). Compared to the reference category (0.43≤Z score≤1.2).breast cancer risk was increased in participants with a maximal weight gain during life time of more than 2.3 kg/m^2 (Z score >1.2).

Table 2 Odds Ratios (OR) and 95% Confidence Intervals (CI) For the Association of Breast Cancer with Z-Scores and Changes in Z-Scores For BMI at Different Ages During Life Time.

Variable of interest	**Odds ratio (95% CI) based on**	
	All records	**Complete records[a]**
Z_{teens}		(N=2052)
Age-adjusted	0.93 (0.86,1.01)	0.92 (0.84,1.01)
Multivariable-adjusted[b]	0.94 (0.86,1.02)	0.93 (0.84,1.03)
Z_{30s}		(N=2636)
Age-adjusted	0.96 (0.88,1.05)	0.94 (0.86,1.03)
Multivariable-adjusted[b]	0.96 (0.88,1.06)	0.94 (0.85,1.04)
Z_{max}		n.a.
Age-adjusted	1.06 (0.95,1.18)	
Multivariable-adjusted[b]	1.05 (0.93,1.17)	
$\Delta Z_{30s\text{-}teens}$		(N=1959)
Age-adjusted	1.04 (0.96,1.13)	1.05 (0.94,1.17)
Multivariable-adjusted[b]	1.03 (0.95,1.12)	1.04 (0.93,1.17)
$\Delta Z_{max\text{-}30s}$ (adult weight gain)		(N=2636)
Age-adjusted		
<0.43	1.09 (0.91,1.31)	1.06 (0.87,1.29)
0.43-1.2	1	1

>1.2	**1.33 (1.10,1.60)**	**1.31 (1.08,1.60)**
Multivariable-adjusted[b]		
<0.43	1.09 (0.90,1.31)	1.06 (0.87,1.30)
0.43-1.2	1	1
>1.2	**1.31 (1.09,1.59)**	**1.31 (1.07,1.60)**

[a]with weight values at the respective age

[b]adjusted for age at menarche, body height, family history of breast cancer, no parity and age at first birth, breastfeeding, use of hormone replacement therapy, use of hormone contraception, education, country of birth, alcohol consumption, smoking and postmenopausal status

n.a. – not replaced by random samples, comparative weight was not asked

When the analysis was restricted to postmenopausal women we found a trend for a significant non-linear association of adolescent body size (Z_{teens}) with breast cancer risk with a p-value for non-linear association of 0.08 (Figure 3B). Women with a BMI Z score smaller than the median of 0.16 in their teenage years (lean adolescents) had an increased breast cancer risk, while women with a teenage BMI Z score larger than the median had a decreased risk (Figure 3B). This association was confirmed in adjusted logistic regression analyses and in sensitivity analysis using only complete records of weight values and with comparative weight (Table 3). The odds ratio was increased by nearly 1.3 times in postmenopausal women who had a lower weight in their teenage years than the median of the study population. This association was not observed in premenopausal women (Table 3). In postmenopausal women the association of excess adult weight gain ($\Delta Z_{max\text{-}30s}$ >1.2) with breast cancer was significant in the adjusted regression models and the sensitivity analyses restricted to complete records of weight values (Table 3). The exposure variables Z_{30s}, Z_{max}, or $\Delta Z_{30s\text{-}teens}$, were not significantly associated with breast cancer risk (Table 3) in the stratified analysis.

Table 3 Adjusted[a] Odds Ratios (OR) and 95% Confidence Intervals (CI) For the Association of Breast Cancer with Z-Scores and Changes in Z-Scores for BMI at Different Ages During Life Time Stratified by Menopausal Status.

	Premenopausal	**Postmenopausal**	
	N=729	**N=2265**	**Complete records**
Z_{teens} (adolescent leanness)			(N=1560)
BMI Z score <0.16	1.0 (0.73,1.36)	**1.29 (1.08,1.54)**	**1.28 (1.03,1.58)**
≥0.16	1	1	1
Comparative weight in teenage years[b]			
Less	0.95 (0.62,1.46)	**1.34 (1.02,1.75)**	
About the same	0.96 (0.65,1.66)	1.14 (0.90,1.45)	
More	1	1	
Z_{30s}			
continuous	0.89 (0.72,1.09)	0.99 (0.89,1.10)	
Z_{max}			
continuous	0.96 (0.77,1.20)	1.09 (0.95,1.25)	
$\Delta Z_{30s\text{-}teens}$			
continuous	0.99 (0.82,1.19)	1.07 (0.98,1.18)	
$\Delta Z_{max\text{-}30s}$ (adult weight gain)			(N=1956)
Δ Z score <0.43	0.95 (0.66,1.35)	1.17 (0.93,1.47)	1.11 (0.87,1.42)
Δ Z score ≥0.43 and ≤1.2	1	1	1
Δ Z score >1.2	1.34 (0.81,2.22)	**1.33 (1.08,1.64)**	**1.32 (1.06,1.65)**

[a]adjusted for matching variable age, age at menarche, body height, family history of breast cancer, no parity and age at first birth, breastfeeding, use of hormone replacement therapy, use of hormone contraception, education, country of birth, alcohol consumption, smoking and postmenopausal status

[b]N=728 and N=2244 for comparative weight, respectively for pre- and postmenopausal women

We investigated the interaction between the two risk factors, adolescent leanness (Z_{teens}<0.16) and excess adult weight gain ($\Delta Z_{max\text{-}30s}$ >1.2) (Table 4). In postmenopausal women being lean during adolescence and gaining excess weight after an age of 30 (Z_{teens}<0.16 and $\Delta Z_{max\text{-}30s}$ >1.2) was associated with an increased breast cancer risk while the risk was not significantly increased in women with adolescent leanness but who did not gain excess adult weight (Z_{teens}<0.16 and $\Delta Z_{max\text{-}30s}$<1.2) and in women who were not lean during adolescence but gained excess adult weight (Z_{teens}>0.16 and $\Delta Z_{max\text{-}30s}$ >1.2) compared to postmenopausal women who were neither lean during adolescence nor gained excess weight. (Table 4). The interaction was positive on the multiplicative scale with a measure of 1.15 (multiplicative interaction is positive if >1 and negative if <1) as well as on the additive scale with a measure 0.22 (additive interaction positive if >0 and negative if <0) [24].

Table 4 Analysis of Interaction between Adolescent Leanness (Z_{teens} <0.16) and Excess Adult Weight Gain ($\Delta Z_{max\text{-}30s}$>1.2) in Postmenopausal Women

	Non-lean adolescents (Z_{teens}≥0.16) OR (CI)	**Lean adolescents (Z_{teens} <0.16) OR (CI)**	OR for Z_{teens}<0.16 within strata $\Delta Z_{max\text{-}30s}$
Non-excess adult weight gain ($\Delta Z_{max\text{-}30s}$≤1.2)	1	1.20 (0.97,1.48)	1.20 (0.97,1.49)
Excess adult weight gain ($\Delta Z_{max\text{-}30s}$>1.2)	1.10 (0.95,1.27)	**1.52 (1.19,1.95)**	1.32 (0.94,1.84)
OR for $\Delta Z_{max\text{-}30s}$>1.2 within strata Z_{teens}	1.19 (0.88,1.61)	1.25 (0.96,1.63)	

[a]adjusted for matching variable age, age at menarche, body height, family history of breast cancer, no parity and age at first birth, breastfeeding, use of hormone contraception, education, country of birth, alcohol consumption, smoking

(CI-confidence interval, OR-odds ratio)

4. Discussion

In our case-control study of nearly 3000 women we confirmed the association of breast cancer with excess adult weight gain and with adolescent leanness in postmenopausal women. Interaction analysis restricted to postmenopausal women revealed that adolescent leanness was only associated with increased breast cancer risk when accompanied with excess weight gain during adulthood. In postmenopausal women who were lean during adolescence but did not gain excess weight in adult life we did not observe any increased breast cancer risk. The sample size was smaller for premenopausal women and no statistically significant associations were observed.

In addition, we showed here an approach that overcomes the handicap that comparative weights are easier to recall than weight values. By having data on both comparative weight and weight values, missing BMI values can be replaced by random samples of calculated BMI values for each comparative weight category derived from samples where both metrics were available. This approach is more appropriate than other imputation methods that assume data are missing at random, an assumption which was not valid in the described situation. As a result the derived continuous metric BMI Z score (used throughout life course) offers the opportunity to investigate dose-response relationships and to observe reasonable cutoffs.

The association of adult weight gain with breast cancer has been supported recently by large cohort studies with up to 4663 incident cases [3-5,7]. Increased risk of breast cancer was reported for women with adult weight gain by more than 5% [4], more than 11% [5] and by more than 15-20 kg [3]. We observed an increased breast cancer risk in women who gained more than 2.3 kg/m^2, which corresponds to weight changes by more than 15% and by more than 8.7 kg (on average by 28 kg).

An inverse association between childhood and adolescent body fatness and breast cancer risk has been observed previously in large cohort studies, in the Nurses' Health Study [8,10,25] and in the French E3N cohort [11] although the biological mechanisms are still unclear. Some investigators proposed that the inverse association with childhood and adolescent BMI may be mediated by more rapid adolescent growth [26,27] which could increase levels of growth hormones and epithelial proliferation in the breast. Childhood and adolescent body size have been found to be inversely associated with adult insulin-like growth factor 1 levels [28,29]. The association between adolescent body fatness and breast cancer risk might be partially mediated by adult mammographic density [10,31,32], but is probably not modified by adolescent physical activity [9].

The results reported by two case-control studies were inconsistent. In the Women's Circle of Health Study an inverse association with postmenopausal breast cancer was found among Caucasian non-HRT users reporting to be heavier than their peers at menarche but no association with adult weight gain was found [12]. In the Carolina Breast Cancer Study decreased cancer risk was associated with heavier childhood relative weight among premenopausal and among non HRT-using Caucasians, adult weight gain was associated with increased breast cancer risk in postmenopausal White non HRT-users [13]. In the present study increased risk of postmenopausal breast cancer was associated with excess adult weight gain and decreased risk was associated with heavier adolescent body size than their peers (or increased risk with lean adolescent body size) in postmenopausal women, were consistent with the findings in the large previous cohort studies investigating either the association with adolescent or adult body size [3-5,7-9,11]. In contrast to previous studies, we investigated and observed an association of breast cancer with both risk factors, excess adult weight gain and adolescent leanness, in postmenopausal women and were able to investigate the interaction between both factors.

The strengths of our study include the determination of postmenopausal status and HRT-use before cancer diagnosis, and investigation of ever maximal weight gain after an age of 30 years instead of using weight reported at the time of interview to reduce the influence of weight changes during cancer treatment. In a population-based cohort of 1,436 women diagnosed with first primary breast cancer was observed that 26% lost and 14% gained more than 5% of their pre-diagnosis weight after breast cancer diagnosis [30]. Furthermore the same body size metrics throughout the life course (BMI Z scores) were investigated while previous case-control studies used categorized comparative weight in youth and adult BMI [12,13].

Several of the limitations of this work should be noted. The BMI values were based on recalled, self-reported weight and height values, which are subject to recall and response bias. The few studies that used measured height and weight during adolescence or adulthood reported also an inverse association with adolescent body size [31-34] or an association with adult weight gain as well [4,7]. Since the participants were not asked at which age their weight was maximal we assumed that the maximal weight occurred after an age of 30 years, which seemed to be the case for most of the participants since the averaged BMI Z score increased from 0.18 (20% overweight) in early thirties to 0.83 (57% overweight) at the time of study recruitment.

Furthermore, we assumed the same body height from adolescence till a median age of 57 years, obtained from the question “How tall are you?”, which was asked to obtain the current height of participants. Since people do not usually measure their height as regularly as their weight it is unclear when the reported height was measured. A discrepancy in height of around 7cm for teenagers estimated from WHO growth charts [35] and around 4-5cm in older age since in women the typically height loss is 5cm from age 30 to 70 [36], might occur. Additionally, there will be some individual variability in height grow since some women attain their maximum height around age at menarche while others keep growing. However, using comparative weight

categories in teenage years, which was answered by 99% of the participants the association of breast cancer with leaner body composition was observed as well (Table 2).

There might be some selection bias due the study being conduct around one year after diagnosis resulting in exclusion of cases with highly aggressive breast cancer and due to the low response rate. Although such selection processes might limit the representativeness of our results for the general population they would not necessarily limit internal validity of the study.

In conclusion, both weight-related risk factors, adolescent body leanness and excess adult weight gain, were associated with breast cancer risk in our case-control study. To our knowledge, this is the first study investigating the interaction between these two risk factors, revealing that the adolescent leanness was only associated with increased breast cancer risk when accompanied with excess weight gain during adulthood in postmenopausal women. This seems to indicate that rapid weight gain rather than adolescent leanness is associated with increased breast cancer risk. Future studies collecting detailed weight data from childhood to older age are necessary to examine the association of breast cancer with critical time periods or the velocity of weight gain across life time.

Acknowledgement

This work was supported by a National Health and Medical Research Council Australia (NHMRC) project grant # 572530 and by a grant from the Cancer Council Western Australia (CCWA).

References

1. World Cancer Research Fund International, http://www.wcrf.org. Accessed March 10, 2016
2. Lahmann PH, Hoffmann K, Allen N, et al. Body size and breast cancer risk: findings from the European Prospective Investigation into Cancer And Nutrition (EPIC). Int J Cancer. 2004;111:762-71.
3. Lahmann PH, Schulz M, Hoffmann K, et al. Long-term weight change and breast cancer risk: the European prospective investigation into cancer and nutrition (EPIC). Br J Cancer. 2005;93:582-9.
4. Neuhouser ML, Aragaki AK, Prentice RL, et al. Overweight, Obesity, and Postmenopausal Invasive Breast Cancer Risk: A Secondary Analysis of the Women's Health Initiative Randomized Clinical Trials. JAMA Oncol. 2015;1:611-21.
5. Keum N, Greenwood DC, Lee DH, et al. Adult weight gain and adiposity-related cancers: a dose-response meta-analysis of prospective observational studies. J Natl Cancer Inst. 2015;107.
6. White AJ, Nichols HB, Bradshaw PT, Sandler DP. Overall and central adiposity and breast cancer risk in the Sister Study. Cancer. 2015;121:3700-8.
7. Emaus MJ, van Gils CH, Bakker MF, et al. Weight change in middle adulthood and breast cancer risk in the EPIC-PANACEA study. Int J Cancer. 2014;135:2887-99.
8. Baer HJ, Tworoger SS, Hankinson SE, Willett WC. Body fatness at young ages and risk of breast cancer throughout life. Am J Epidemiol. 2010;171:1183-94.
9. Oh H, Boeke CE, Tamimi RM, et al. The interaction between early-life body size and physical activity on risk of breast cancer. Int J Cancer. 2015;137:571-81.
10. Harris HR, Tamimi RM, Willett WC, Hankinson SE, Michels KB. Body size across the life course, mammographic density, and risk of breast cancer. Am J Epidemiol. 2011;174:909-18.

11. Fagherazzi G, Guillas G, Boutron-Ruault MC, Clavel-Chapelon F, Mesrine S. Body shape throughout life and the risk for breast cancer at adulthood in the French E3N cohort. Eur J Cancer Prev. 2013;22:29-37.
12. Bandera EV, Chandran U, Zirpoli G, et al. Body size in early life and breast cancer risk in African American and European American women. Cancer Causes Control. 2013;24:2231-43.
13. Robinson WR, Tse CK, Olshan AF, Troester MA. Body size across the life course and risk of premenopausal and postmenopausal breast cancer in Black women, the Carolina Breast Cancer Study, 1993-2001. Cancer Causes Control. 2014;25:1101-17.
14. Fritschi L, Erren TC, Glass DC, et al. The association between different night shiftwork factors and breast cancer: a case-control study. Br J Cancer. 2013;109:2472-80.
15. Girschik J, Heyworth J, Fritschi L. Self-reported sleep duration, sleep quality, and breast cancer risk in a population-based case-control study. Am J Epidemiol. 2013;177:316-27.
16. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000;320:1240–1245.
17. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull WorldHealth Organ 2007;85:660–667.
18. World Health Organization. Growth reference. BMI-for-age 5-19 years. http://www.who.int/growthref/who2007_bmi_for_age/en/. Accessed November 25, 2015
19. Pearce N. Analysis of matched case-control studies. BMJ 2016;352:i969
20. Sauerbrei W1, Abrahamowicz M, Altman DG, le Cessie S, Carpenter J; STRATOS initiative. STRengthening analytical thinking for observational studies: the STRATOS initiative. Stat Med. 2014;33:5413-32.

21. Desquilbet L, Mariotti F. Dose–response analyses using restricted cubic spline functions in public health research. Stat Med 2010;29:1037–1057
22. Harrell F. Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis (Springer Series in Statistics) 2010. Springer
23. Knol MJ and VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. Int J Epidemiology 2012;41:514–520.
24. VanderWeele TJ and Knol MJ. A Tutorial on Interaction. Epidemiol. Methods 2014;3:33–72.
25. Baer HJ, Colditz GA, Rosner B, et al. Body fatness during childhood and adolescence and incidence of breast cancer in premenopausal women: a prospective cohort study. Breast Cancer Res. 2005;7:R314-25.
26. Berkey CS, Frazier AL, Gardner JD, et al. Adolescence and breast carcinoma risk. Cancer. 1999;85:2400–2409.
27. De Stavola BL, dos Santos Silva I, McCormack V, Hardy RJ, Kuh DJ, Wadsworth ME. Childhood growth and breast cancer. Am J Epidemiol. 2004; 159:671–82.
28. Schernhammer ES, Tworoger SS, Eliassen AH, et al. Body shape throughout life and correlations with IGFs and GH. Endocr Relat Cancer. 2007;14:721–732.
29. Poole EM, Tworoger SS, Hankinson SE, Schernhammer ES, Pollak MN, Baer HJ. Body size in early life and adult levels of insulin-like growth factor 1 and insulin-like growth factor binding protein 3. Am J Epidemiol. 2011;174:642–51.
30. Bradshaw PT, Ibrahim JG, Stevens J, et al. Postdiagnosis change in bodyweight and survival after breast cancer diagnosis. Epidemiology. 2012;23:320-7.

31. Andersen ZJ, Baker JL, Bihrmann K, Vejborg I, Sørensen TIA, Lynge E. Birth weight, childhood body mass index, and height in relation to mammographic density and breast cancer: a register-based cohort study. Breast Cancer Research 2014,16:R4.
32. Hopper JL, Nguyen TL, Stone J, et al. Childhood body mass index and adult mammographic density measures that predict breast cancer risk. Breast Cancer Res Treat. 2016;156(1):163-70.
33. Ahlgren M, Melbye M, Wohlfahrt J, Sørensen TIA. Growth patterns and the risk of breast cancer in women. N Engl J Med 2004; 351:1619-1626.
34. Keinan-Boker L, Levine H, Derazne E, Molina-Hazan V, Kark JD. Measured adolescent body mass index and adult breast cancer in a cohort of 951,480 women. Breast Cancer Res Treat. 2016;158:157-67.
35. World Health Organization. Growth reference. Height-for-age 5-19 years. http://www.who.int/growthref/who2007_height_for_age/en/.
36. Sorkin JD, Muller DC, Andres R. Longitudinal change in height of men and women: implications for interpretation of the body mass index: the Baltimore Longitudinal Study of Aging. Am J Epidemiol. 1999;150:969-77.

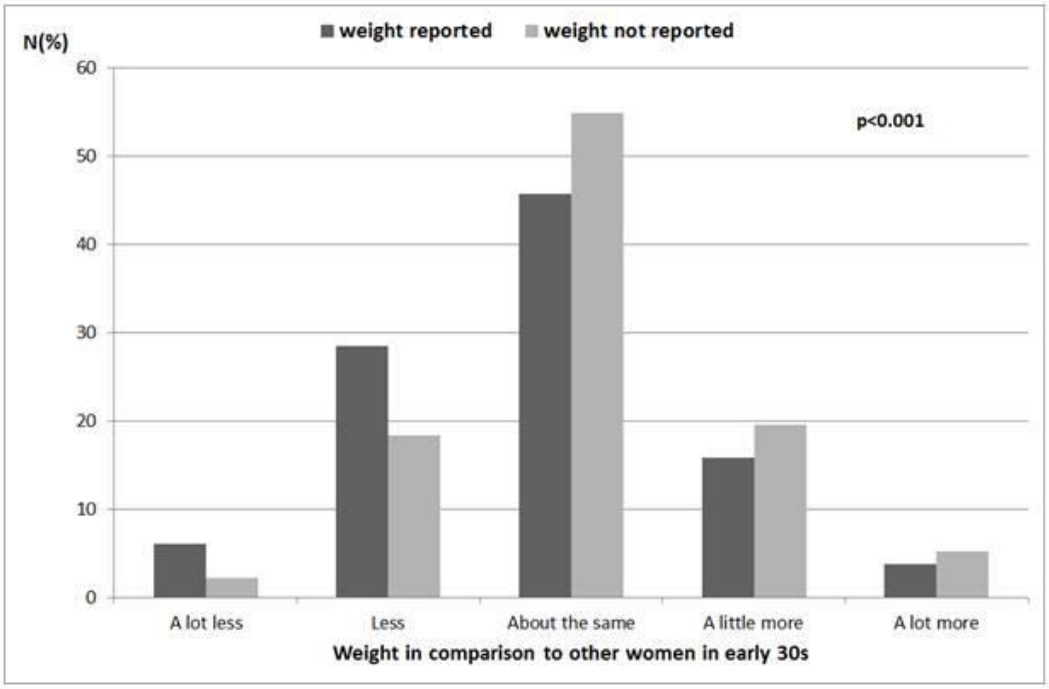
Figure legends

Figure 1 Comparison of the distribution of comparative weight categories by women who reported and who did not report their weight values. Comparative weight recalled from early thirties (A). Comparative weight recalled from teenage years (B).

Figure 2 Density probability plots estimating the distribution of BMI for each comparative weight category. BMI calculated based on recalled weight values from early thirties (A). BMI calculated based on recalled weight values from teenage years (B).

Figure 3 Dose–response relationships estimated by restricted cubic spline regression. Dose–response relationship between breast cancer risk and difference between Z scores of maximal BMI at any time during life and at the age of early thirties ($\Delta Z_{max\text{-}30s}$) where the reference value is a median of 0.77 (A). Dose–response relationship between breast cancer risk and Z score of BMI in teenage years (Z_{teens}) where the reference value is a median of 0.16 (B). Dashed lines represent 95% confidence intervals. Thin solid line represents Odds Ratio (OR) =1.

A


N(%)
weight reported
weight not reported
60
50
40
30
20
10
0
p<0.001
A lot less
Less
About the same
A little more
A lot more
Weight in comparison to other women in early 30s

B

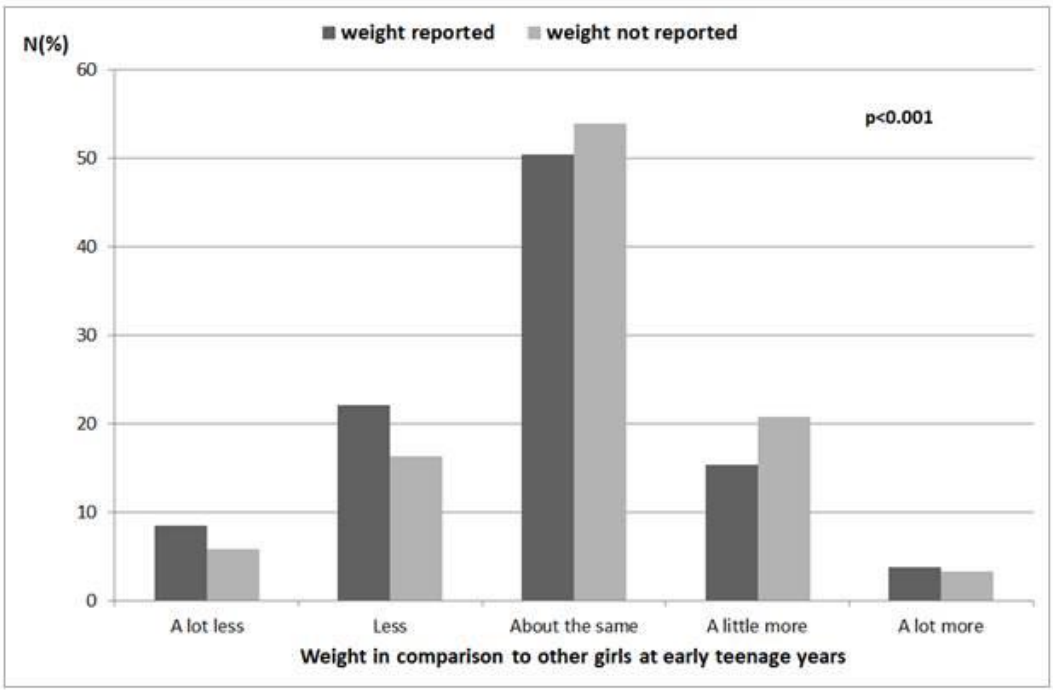
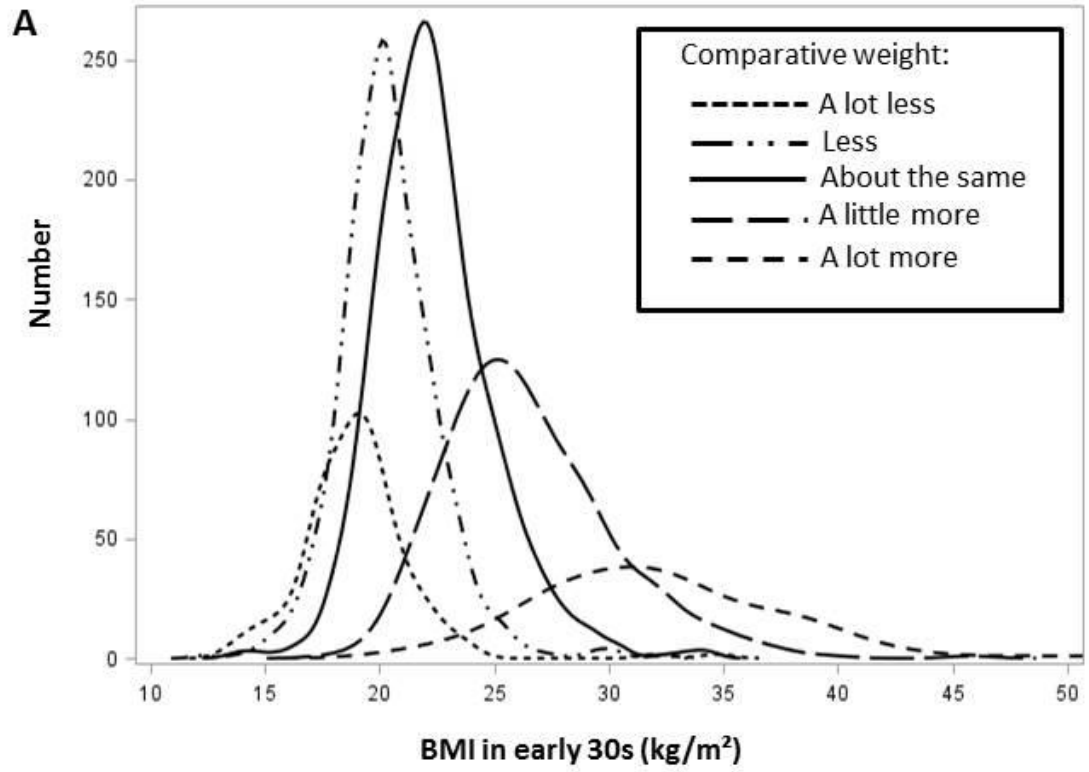

N(%)
weight reported
weight not reported
60
50
40
30
20
10
0
p<0.001
A lot less
Less
About the same
A little more
A lot more
Weight in comparison to other girls at early teenage years

Figure 1


A
Number
250
200
150
100
50
0
10
15
20
25
30
35
40
45
50
BMI in early 30s (kg/m²)
Comparative weight:
A lot less
Less
About the same
A little more
A lot more

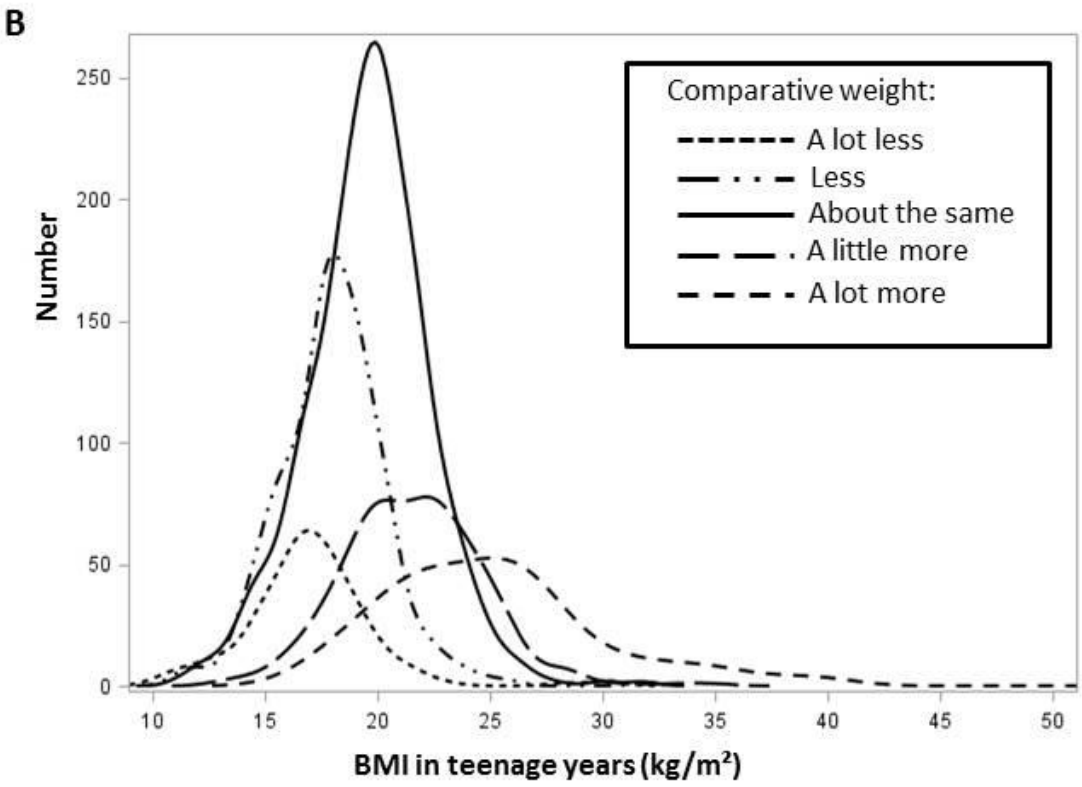

B
Number
250
200
150
100
50
0
10
15
20
25
30
35
40
45
50
BMI in teenage years (kg/m²)
Comparative weight:
A lot less
Less
About the same
A little more
A lot more

Figure 2

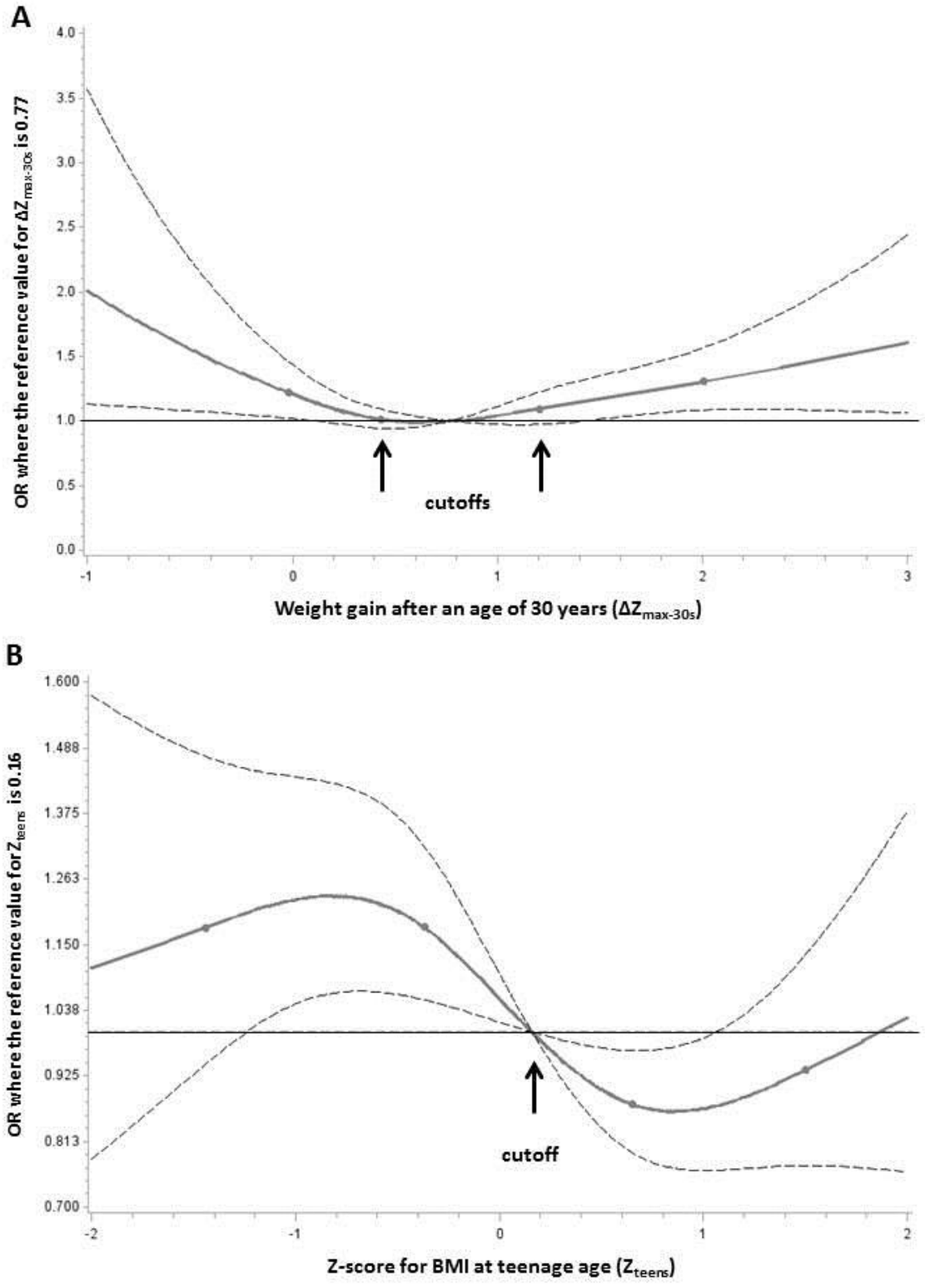

A
OR where the reference value for $\Delta Z_{max-30s}$ is 0.77
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
cutoffs
-1
0
1
2
3
Weight gain after an age of 30 years ($\Delta Z_{max-30s}$)
B
OR where the reference value for Z_{teens} is 0.16
1.600
1.488
1.375
1.263
1.150
1.038
0.925
0.813
0.700
cutoff
-2
-1
0
1
2
Z-score for BMI at teenage age (Z_{teens})

Figure 3