Influence of Calendar Period on the Association Between BMI and Coronary Heart Disease: A Meta-Analysis of 31 Cohorts

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Objective: The association between obesity and coronary heart disease (CHD) may have changed over time, for example due to improved pharmacological treatment of CHD risk factors. This meta-analysis of 31 prospective cohort studies explores the influence of calendar period on CHD risk associated with body mass index (BMI).

Design and Methods: The relative risks (RRs) of CHD for a five-BMI-unit increment and BMI categories were pooled by means of random effects models. Meta-regression analysis was used to examine the influence of calendar period (>1985 v ≤ 1985) in univariate and multivariate analyses (including mean population age as a covariate).

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Results: The age, sex, and smoking adjusted RR (95% confidence intervals) of CHD for a five-BMI-unit increment was 1.28(1.22:1.34). For underweight, overweight and obesity, the RRs (compared to normal weight) were 1.11(0.91:1.36), 1.31(1.22:1.41), and 1.78(1.55:2.04), respectively. The univariate analysis indicated 31% (95%CI: −56:0) lower RR of CHD associated with a five-BMI-unit increment and a 51% (95%CI: −78: −14)) lower RR associated with obesity in studies starting after 1985 ($n = 15$ and 10, respectively) compared to studies starting in or before 1985 ($n = 16$ and 10). However, in the multivariate analysis, only mean population age was independently associated with the RRs for a five-BMI-unit increment and obesity (−29(95%CI: −55: −5)) and −31(95%CI: −66:3), respectively) per 10-year increment in mean age.

Conclusion: This study provides no consistent evidence for a difference in the association between BMI and CHD by calendar period. The mean population age seems to be the most important factor that modifies the association between the risk of CHD and BMI, in which the RR decreases with increasing age.

Introduction

The prevalence of both overweight and obesity has increased worldwide over the past decades, especially after the 1980s in Europe and the USA (1-3). This is a major concern because obesity is associated with increased mortality, disability, decreased quality of life, high health care costs, and morbidity including coronary heart disease (CHD) (1,4).

Despite the rise in the prevalence of obesity, CHD mortality rates have declined since the 1960s-1970s in Western Europe, Australia and the USA (5,6). This decline can be explained by major improvements in coronary treatments and CHD management since the mid 1980s and by changes in risk factors—even in overweight and obese persons—such as a decrease in the prevalence of smoking, and in blood pressure and cholesterol levels (7-10). Additional in this period, the lifestyle approach was advocated within health-care procedures to combat CHD (11,12). Because of all these developments, we expected that the risk of incidence and mortality of CHD associated with being overweight or obese has decreased over time.

The impact of time on CHD risk associated with obesity in adults has not been examined in a large meta-analysis before. Knowledge of time-dependent shifts in CHD risk associated with obesity not only provides indirect "evidence" for improved health care procedures in the obese, but is also important for forecasting future deaths from chronic diseases, as presented in leading publications (13,14). This in turn is fundamental for underpinning the needs for policies on obesity and CVD management.

The present meta-analysis, including 31 prospective cohort studies from various countries, comprising 389,212 persons, examined the influence of calendar period (the year in which the study started) on the association between BMI and CHD, adjusted for age, sex and smoking. The analysis took additional study characteristics (i.e., mean age of the population and length of follow-up) into account that have been proposed to influence the association between body weight and CHD (15,16). To test for the impact of changes in risk factors over time (induced by treatment developments), we additionally examined the influence of calendar period on the association between BMI and CHD in a subset of 21 cohort studies with additional adjustments for physical activity, blood pressure and cholesterol. We expected that the influence of calendar period would be attenuated by adjusting for CHD risk factors.

Methods

Data sources, study selection and data extraction were previously described in detail (17). Briefly, studies were identified by a PubMed/Medline search until 2007 by using the following search strategy: obesity, body mass index, BMI, or overweight in either the title or in the Medical Subject Heading (MeSH) and either coronary heart disease in the title or coronary disease in MeSH, plus either prospective or cohort. Also, we examined reference lists of identified articles, and got suggestions through colleagues. Eligible studies were prospective cohort studies conducted in healthy, mainly Caucasian populations. Seventy cohort studies were identified and 62 investigators were contacted of whom 31 agreed to participate. The 31 cohort studies had data available on BMI, age, sex and smoking and CHD incidence or mortality. Eighteen studies used mortality from CHD and 13 studies used incidence of CHD (both fatal and non-fatal events) as their endpoint. Twenty-one studies had extra data available on physical activity, blood pressure and cholesterol. The investigators from the participating cohort studies were requested to calculate hazard ratios (further on called relative risks (RR)) of CHD for BMI and their 95% confidence intervals (CIs) with systematic adjustments for age, sex and smoking, and if available also for physical activity, blood pressure, and cholesterol levels.

Data synthesis

In this study, we examined the influence of calendar period on the pooled RR for BMI as a continuous variable (i.e., risk per five units increase in BMI; $N = 31$) as well as for BMI-categories (i.e., categories underweight (<18.5 kg m^{-2}; $N = 17$), overweight (25.0-29.9 kg m^{-2}; $N = 20$) and obesity (≥ 30.0 kg m^{-2}; $N = 20$), as compared to the reference category (18.5-24.9 kg m^{-2})). For the 10 studies which only provided RRs for BMI categories, the RRs were transformed to their continuous form for each set of adjustments by applying the method of Greenland and Longnecker (18), using the numbers of cases as observed rather than their fitted values (19). The adjusted RRs for BMI were plotted to visualize variation in results between studies.

Calendar period was calculated by using the baseline year of each cohort study. Recruitment and data collection at baseline took in most cohort studies more than 1 year. Therefore, baseline year was defined as the mean of the first year and last year in which baseline

measurements were conducted. The studies were then divided into two strata to examine whether the pooled RRs differed by calendar period (≤1985 and >1985). The 1985 cut-point chosen, corresponded with the period when major changes occurred regarding the management of CHD and the increase in advocating lifestyle approaches within health-care procedures (7-12). Furthermore, the influence of other important study characteristics on the association between BMI and CHD, i.e. age of the population (defined as the mean age of the population at baseline) and length of follow-up (defined as the mean length in years the population was followed to their endpoint) were examined.

Statistical analysis

Descriptive statistics were used to describe the main characteristics of the cohort studies, i.e., baseline year, mean age of the population and length of follow-up.

The age, sex, and smoking adjusted log RRs for BMI as a continuous and categorical variable were pooled by means of a random effects model (20), using the MIXED procedure in SAS (version 9.1). The pooled RR and the 95% confidence interval (95%CI) was estimated by exponentiating the results from this model. Heterogeneity of RRs between cohort studies was tested using chi-squared tests.

To determine sensitivity of the results, meta-analyses with 30 studies (continuous BMI) and with 16 and 19 studies (BMI categories) were performed, leaving repeatedly each individual study out of the pooled risk. Further, to check for potential bias due to misclassification of BMI based on self-reported weight and height, analyses were repeated after excluding cohorts with self-reported BMI. This meant exclusion of four studies in the analysis for continuous BMI, overweight, and obesity and three studies for underweight. Publication bias was investigated using a funnel plot.

To examine the influence of calendar period (>1985 vs. ≤1985), age of the population and length of follow-up (expressed per 10 year increment), a meta-regression analysis (including the random effects model) was used. In this meta-regression analysis, the age, sex, and smoking adjusted log RR of the studies was regressed onto the study characteristics. This was done by using a univariate (i.e., calendar period, age and length of follow-up in separate models) and a multivariate analysis (i.e., calendar period and age of the population adjusted for each other). Calendar period and length of follow-up were not simultaneously entered into the model to prevent multicollinearity since baseline year and length of follow-up were highly correlated (Pearson's $r = -0.86$; $P < 0.001$). Similar models were used for the categories underweight, overweight and obesity.

These analyses were then repeated in a subset of cohort studies (continuous BMI: $N = 21$, underweight: $N = 12$, overweight and obesity: $N = 14$) with log RRs additionally adjusted for physical activity, blood pressure and cholesterol.

The influence of study characteristics is reported as a percentage change of the RR of CHD associated with BMI by the study characteristic term. To give insight in how the percentage change was calculated, we present the following hypothetical example:

Suppose the regression coefficients for the log(RR) are 0.3 for the intercept and -0.1 for the calendar period effect. In that case, the RR of studies starting before and in 1985 is $e^{0.3} = 1.35$ and the RR for studies starting after 1985 is $e^{(0.3 + -0.1)} = 1.22$. This gives a percentage change of $((1.22 - 1) - ((1.35 - 1))/(1.35 - 1) \times 100\% = -37\%$. To indicate whether the influence of a study characteristic was statistically significant, the accompanying 95% confidence intervals are presented.

Results

Characteristics of cohorts

Table 1 presents the characteristics of the study populations, comprising a total of 389,212 persons. During follow-up in total 20 652 CHD events were observed. Some studies provided RRs for a longer length of follow-up than in the original articles. The cohorts used for analysis regarding BMI categories are marked in Table 1.

Table 2 presents the descriptive statistics of baseline year, age of the population and length of follow-up. For the earlier studies (≤1985), age of the population was lower in comparison with the later studies (>1985). The length of follow-up was longer for the earlier studies.

Relative risks of CHD associated with BMI

For the 31 studies, the age, sex, and smoking adjusted RR of CHD was increased for a five-BMI-unit increment, overweight and obesity (Table 3). Underweight was not associated with the risk of CHD (RR 1.11 (0.91:1.36). After adjustment for physical activity, blood pressure and cholesterol, the RRs for a five-BMI-unit increment, overweight and obesity were lower but still significant as reported previously (17).

There was substantial heterogeneity between study results of the 31 cohorts ($P < 0.001$; Figure 1) and between the study results for each BMI category ($P < 0.05$; not shown). The sensitivity analysis indicated no strong influence by individual studies as the change in RR of CHD associated with BMI ranged maximally from -0.08 to 0.06 when single studies were excluded. Exclusion of studies that used self-reported BMI resulted in somewhat lower RRs in the remaining cohorts concerning increasing BMI, underweight, overweight and obesity (respectively, 1.26 (1.20:1.32); 1.09 (0.84:1.42); 1.26 (1.18:1.35); 1.66 (1.45:1.91)).

The funnel plot suggested that studies with higher estimates of relative risk were not overrepresented, suggesting that there was no publication bias using the 31 cohorts (Appendix 1).

Influence of calendar period and other factors on the relative risk of CHD for BMI

The relationships between study characteristics and the RR of CHD associated with BMI as a continuous and categorical variable are graphically displayed in Appendix 2.

Table 3 presents the percentage changes in the RR of CHD associated with BMI by calendar period, age of the population and length of follow-up for the univariate and multivariate meta-regression analyses. Because underweight was not associated with CHD, the influences of the study characteristics were not examined for this

TABLE 1 Characteristics of studies included in the pooled analysis

Study	% male	Age range	Baseline year(s)	Median or mean follow-up(y)	% Current smokers	No. available for analysis	No. cases	Description of endpoint
Australian national heart foundation risk factor prevalence study (21)[a,b]	49	20-70	1989-1990	8.3	24	9,099	76	death from CHD: ICD-9 codes 410-414
Busselton health study (22)	49	40-75	1966-1981	10	34	3,891	187	death from CHD: ICD-9 codes 410-414
Caerphilly cohort Study (23,24)[c]	100	47-67	1984-1988	12	44	2,160-2,357	398	fatal and non-fatal events: death from CHD; clinical non-fatal (definite acute) MI; electrocardiographic MI
Dubbo study of Australian elderly (25)[c]	44	60-94	1988	13	15	2,805	968	fatal and non-fatal events: hospitalisation or death ICD-9-CM codes 410-414
ECCIS study (26)	100	40-59	1989-1992	5	38	4,850	73	fatal and non-fatal events: definite MI; sudden coronary death; cases judged of coronary origin although manifested only as heart failure, arrhythmia and blocks
Finnish Mobile Clinic Health Examination Survey (27)[a,b]	53	30-69	1967-1972	22	34	30,765	3,319	death from CHD: ICD-8 codes 410-414
Finnish Twin Cohort Study (28,29)[d,b]	50	24-60	1981	19.7	30	15,127	155	death from CHD: ICD-8 410-414, ICD9 410-414, ICD10 I21-25
Fletcher Challenge (30)[a,b]	72	20-89	1992	4.8	24	10,201	110	death from CHD
Gubbio Population Study (31)	45	35-74	1983-1985	6	35	2,963	126	fatal and non-fatal events: definite MI; sudden coronary death; cases judged of coronary origin although manifested only as heart failure, arrhythmia and blocks
Iowa Women's Health Study (32)[a,b,d]	0	55-69	1986	15.8	15	32,011/30,741	1,121	death from CHD
Italian Rural Areas (33)[c]	100	40-59	1960	35	61	1,622	214	death from CHD: definite fatal MI; other forms of fatal ischemia; sudden death from CHD
Kuopio Ischaemic Heart Disease Risk Factor Study (34)[b] (KIHD)	100	42-61	1984-1989	10.6	31	1,597	155	fatal and non-fatal events: definite and probable acute MI; prolonged chest pain episodes
Malmö Preventive Project (35)[b] (MPP)	100	27-61	1974-1984	17.7	49	22,025	1,727	fatal and non-fatal events: acute MI (ICD code 410); death from chronic CHD (ICD codes 412 and 414)
Manresa Catalonia study (36)	100	30-59	1968	18.5	67	1,059	135	fatal and non-fatal events: fatal MI; other death, sudden or non-sudden, presumed due to CHD (ICDA 410-413, 795, 427.0, 427.2 and 427.9); non-fatal MI
Melbourne Collaborative Cohort Study (37)[a,b]	41	27-75	1990-1994	5.6	11	41,119	323	death from CHD
Multifactor Primary Prevention Study (38)[a,b] (MPPS) Göteborg	100	47-55	1970-1973	22.0	50	7,371	1,688	fatal and non-fatal events: death from CHD (ICD-8/9 codes 410-414); non-fatal MI
NHANES I Epidemiologic Follow-up Study (39)[a,b] (NHEFS)	44	25-74	1971-1975	20	45	5,139/5,078	543	death from CHD: ICD-9 codes 410-414.9
Nijmegen Cohort Study (40)[a,b]	48	20-52	1977-1978	18	58	5,898	268	fatal and non-fatal events: MI; angina pectoris

TABLE 1 (Continued)

Study	% male	Age range	Baseline year(s)	Median or mean follow-up(y)	% Current smokers	No. available for analysis	No. cases	Description of endpoint
Norwegian Counties Study (41)[a,b]	51	35-49	1974-1978	26	45	43,896	1,564	death from CHD: ICD-8/9 codes 410-414, ICD-10 codes I21-25; sudden deaths (ICD-8 codes: 782.4, 795; ICD-9 codes: 798.1-798.2; ICD-10 codes: R96)
Nurses' Health Study (42)[a,b,d]	0	34-59	1980	20	28	76,615	1,996	fatal and non-fatal events: death from CHD; nonfatal MI; sudden death within 1 h of onset of symptoms in women with no other plausible cause other than CHD
Perth Cohort (43,44)[a,b]	52	20-90	1979-1994	14.4	25	9,727	187	death from CHD
PRIME study(45)[c]	100	50-59	1991-1993	5	28	9,757	317	fatal and non-fatal events: MI; death from CHD; angina pectoris
Rome Railroad Cohort(46)[c]	100	40-59	1962	25	66	726	88	death from CHD: definite fatal MI; sudden death from CHD; cases judged of CHD origin although manifested only as heart failure, arrhythmia and blocks
Scottish Heart Health Study (47)[a,b]	51	40-59	1984-1987	7.6	39	10,262	171	fatal and non-fatal events: MI; coronary artery surgery; death from CHD
SENECA (48)[a,b]	48	70-77	1988-1989	10	18	1,196	55	death from CHD: ICD 410-414
Swedish Annual Level-of-Living Survey (49)[a,b,d] (SALLS)	51	35-74	1988-1989	11.7	27	5,196	373	fatal and non-fatal events: ICD-9 410-414, ICD10 I20-I25
US Railroad cohort (46)[c]	100	40-59	1957-1959	25	60	2,415	481	death from CHD: definite fatal MI; sudden death from CHD; cases judged of CHD origin although manifested only as heart failure, arrhythmia and blocks
Ventimiglia di Sicilia Heart Study (50) (VHS)	43	20-69	1989	8	17	835	8	death from CHD: defined MI; sudden death
Western Australian Abdominal Aortic Aneurysm Study (51,52)[a,b]	100	65-84	1996	1.2	11	12,194	240	death from CHD
Whitehall Study (53,54)[a,b]	100	40-64	1967-1969	33	41	17,475	3,503	death from CHD: ICD-8 codes 410-414
Zutphen Elderly Study (55)[a,b]	100	64-84	1985	10.3	33	575	83	death from CHD: ICD-9 codes 410-414

Abbreviations: CHD, Coronary Heart Disease: ICD, International Classification of Disease (-8, -9, -10 indicate the revision number; CM Clinical Modification); MI, myocardial infarction; NHANES, National Health and Nutrition Examination Survey; PRIME, Prospective Epidemiological Study of Myocardial Infarction.

[a]Cohort used for analysis regarding underweight.
[b]Cohort used for analysis regarding overweight and obesity.
[c]No results available for both the categories moderate overweight (body mass index, 25.0-29.9 [calculated as weight in kilograms divided by height in meters squared]) and obesity (body mass index, ≥30.0).
[d]Body mass index based on self-report of the participants.

TABLE 2 Mean (range) study characteristics

Studies in the body mass index analyses	Baseline year	Age of population (yr)	Length of follow-up (yr)
All studies ($N = 31$)[a]	1981 (1958-1996)	51.5 (35.0-73.0)	15.0 (1.2-35.0)
Studies ≤1985 ($N = 16$)	1973 (1958-1985)*	48.1 (35.0-71.1)*	20.8 (6.0-35.0)*
Studies >1985 ($N = 15$)	1989 (1986-1996)	55.1 (43.4-73.0)	8.9 (1.2-15.8)
Studies in the overweight and obesity analyses			
Total ($N = 20$)[a]	1983 (1969-1996)	51.0 (35.0-73.0)	15.2 (1.2-33.0)
Studies ≤1985 ($N = 10$)	1976 (1969-1985)*	47.1 (35.0-71.1)	21.3 (15-33.0)*
Studies >1985 ($N = 10$)	1989 (1986-1996)	54.8 (43.4-73.0)	9.0 (1.2-15.8)

*Significant difference between calendar period strata: $P < 0.05$.
[a]The mean study characteristics did not change substantially in the subset of studies used in the model with additional adjustments for physical activity, blood pressure and cholesterol, although the range was slightly reduced with ~4 years in baseline year and follow-up period.

category. Table 4 presents the RRs of CHD associated with continuous and categorical BMI stratified by calendar period.

Relative risks adjusted for age, sex, and smoking. The difference in the RR of CHD for a five-BMI-unit increment and obesity between calendar periods, that was observed in the univariate analysis (−31% (95%CI: −56:0) and −51% (95%CI: −78: −14), respectively) (Tables 3 and 4), was no longer observed in the multivariate analysis (Table 3). However, in the multivariate analysis, age of the population still (near) significantly lowered the RR by 29% (95%CI: −55: −5) and 31% (95%CI: −66:3) respectively for each 10-year

increase in age of the population (Table 3). No interaction effect between calendar period and mean age was found.

Length of follow-up (only examined in the univariate analysis) had a significant influence on the RR associated with a five-BMI-unit increment (+25% (95%CI: 0:52)) and with obesity (+53% (95%CI: 9-109)) (Table 3).

We repeated these analyses in a subset of studies ($N = 13$; $N = 6$ ≤1985; $N = 7$ >1985) with a length of follow-up between 10 and 19.9 years to reduce correlation between baseline year and length of follow-up (Pearson's $r = −0.48$, $P = 0.10$) and overlap in time

TABLE 3 Relative risks (RR) of coronary heart disease per five body mass index-unit increment, overweight and obesity and the percentage change by covariates: calendar period, age of the population and length of follow-up

BMI measure of interest	Model ($n_{studies}$)	Meta-regression analysis[a]	Pooled RR[b] (95% CI)	Calendar period (>1985 v ≤1985)	Age of population (per 10 yr increment)	Length of follow-up (per 10 yr increment)
				Percentage change (95% CI) in relative risks (%)[c]		
Continuous 5-BMI-unit increment	1 ($n = 31$)[d]	Univariate analysis	1.28 (1.22:1.34)	−31 (−56:0)	−32 (−52: −13)	25 (0:52)
		Multivariate analysis	-	−9 (−41:36)	−29 (−55: −5)	-
	2 ($n = 21$)	Univariate analysis	1.16 (1.11:1.21)	−36 (−78:15)	−44 (−90: −4)	6 (−29:52)
		Multivariate analysis	-	−10 (−61:84)	−40 (−105:6)	-
Overweight	1 ($n = 20$)[d]	Univariate analysis	1.31 (1.22:1.41)	−27 (−70:34)	−48 (−87: −12)	22 (−19:78)
		Multivariate analysis	-	20 (−44:145)	−55 (−128: −11)	-
	2 ($n = 14$)	Univariate analysis	1.17 (1.11:1.23)	6 (−82:148)	−24 (−148:51)	−12 (−50:49)
		Multivariate analysis	-	21 (−87:260)	−30 (−220:52)	-
Obesity	1 ($n = 20$)[d]	Univariate analysis	1.78 (1.55:2.04)	−51 (−78: −14)	−43 (−72: −13)	53 (9-109)
		Multivariate analysis	-	−32 (−68:26)	−31 (−66:3)	-
	2 ($n = 14$)	Univariate analysis	1.49 (1.32:1.67)	−51 (−96:10)	−42 (−135:28)	29 (−21:104)
		Multivariate analysis	-	−45 (−97:40)	−25 (−107:39)	-

Model 1: the RRs are adjusted for age, sex and smoking at baseline.
Model 2: Model 1 with additional adjustment physical activity, blood pressure and cholesterol at baseline.
[a]Univariate analysis: calendar period, age and follow-up period in separate models; Multivariate analysis: calendar period and age adjusted for each other.
[b]The pooled RR (intercept) changed slightly in the meta-regression analysis, but not substantially with regard to the magnitude of the RR.
[c]Indicates the percentage change in RR of BMI or BMI category on CHD associated with the specified change in each study characteristic
[d]The results of percentage change in the age, sex and smoking adjusted RR by each study characteristic in the univariate and multivariate were in the same order when examining this in the subset of studies used in model 2.
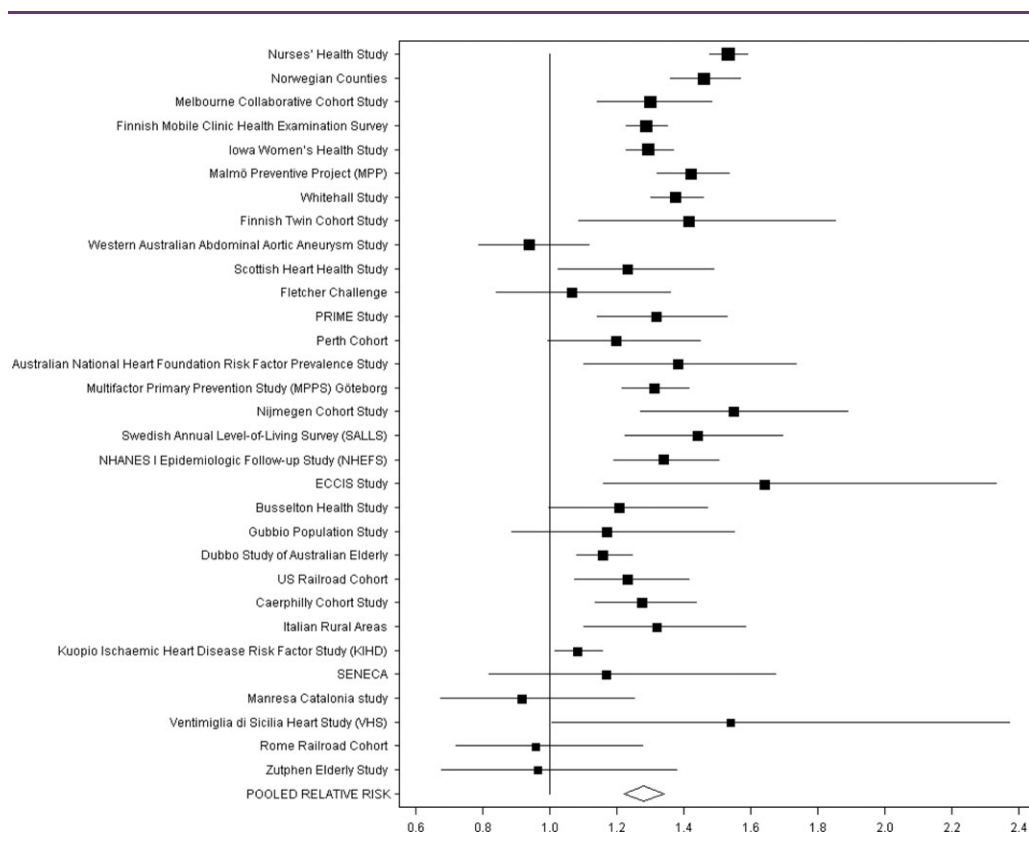
FIGURE 1 Relative risks of coronary heart disease per increment of 5 kg m^{-2}, adjusted for age, sex and smoking. Horizontal lines indicate 95% confidence intervals.

period. In this subset, the results for calendar period and age of the population were similar (data not shown).

Also, to take both baseline year and length of follow-up into account together with age of the population, we repeated the analyses with the variables age of the population and half of the follow-up length added up to baseline year. Then, calendar period had not an influence on the association between BMI and CHD in the univariate or

multivariate analysis, while the influence of age of the population remained the same (data not shown).

Relative risks additionally adjusted for physical activity, blood pressure and cholesterol. When the RRs were additionally adjusted for physical activity, blood pressure and cholesterol, the univariate analysis indicated no longer a significant influence of

TABLE 4 Relative risks (RR) of CHD per five BMI-unit increment, overweight and obesity stratified by calendar period (>1985 v ≤1985)

BMI measure of interest	Model ($n_{studies}$)	Pooled RR (95% CI)[a]	
		Calendar period ≤1985	Calendar period >1985
Continuous 5-BMI-unit	1 (n = 31)	1.33 (1.27:1.41)	1.23 (1.16:1.31)
increment	2 (n = 21)	1.19 (1.13:1.24)	1.12 (1.04:1.20)
Overweight	1 (n = 20)	1.35 (1.23:1.48)	1.25 (1.11:1.42)
	2 (n = 14)	1.17 (1.10:1.24)	1.18 (1.03:1.35)
Obesity	1 (n = 20)	2.05 (1.75:2.40)	1.51 (1.26:1.81)
	2 (n = 14)	1.57 (1.39:1.78)	1.28 (1.04:1.58)

Model 1: the RRs are adjusted for age, sex and smoking at baseline.
Model 2: Model 1 with additional adjustment physical activity, blood pressure and cholesterol at baseline.
[a]Calculated from the univariate meta-regression analysis including calendar period, see explanation in text and Table 3 for the percentage difference between calendar periods.

calendar period on the associations between a five-BMI-unit increment and CHD and obesity and CHD, but the percentage changes remained in the same order of magnitude (−36% (95%CI: −78:15) and −51% (95%CI: −96:10), respectively) (Tables 3 and 4). Age of the population remained significant for the association between a five-BMI-unit increment and CHD (−44% (95%CI: −90: −4), but not for overweight and obesity (Table 3).

The multivariate analysis indicated that age of the population did not significantly influence the association between overweight or obesity and CHD, but a trend was still visible for the association between a five-BMI-unit increment and CHD (−40% (95%CI: −105:6)) (Table 3).

Length of follow-up had no longer a significant influence on the association between a five-BMI-unit increment and CHD and obesity and CHD (Table 3).

Because we used two endpoints, we examined whether there was a difference between incidence and mortality regarding the RR of BMI (categories). We found no differences and also the influence of calendar period, follow-up period or mean age on the RR did not differ by the endpoint used in the analyses (data not shown).

Discussion

In this meta-analysis of 31 cohorts worldwide including 389 212 mainly Caucasian persons and 20 652 CHD events, we explored the hypothesis whether the RR of CHD associated with BMI is lower in later studies compared to earlier studies. Further, we took other important study characteristics, i.e., age of the population and length of follow-up into account. By taking these study characteristics into account and carrying out extra analyses with RRs adjusted for CHD risk factors, we found no longer a difference in the RR of CHD associated with BMI between calendar periods. The most important and consistent cohort characteristic influencing the association between BMI and CHD was age of the population.

Strengths and limitations

The strength of our analysis lies in the large number of cohorts including populations from various countries and the systematic adjustments for relevant cohort variables (i.e., length of follow-up and age of the population). No indication of publication bias was found, as was discussed also in a previous publication (17).

Another strength of our meta-analysis is that we were able to account for CHD risk factors (i.e., physical activity, blood pressure, and cholesterol) which could influence the change in the association between BMI and CHD over time.

Several limitations should be addressed. First, we did not use studies with a baseline year in the 21st century. This limited our time span to examine the influence of calendar period and to give insight on recent developments of the association between BMI and CHD. Second, length of follow-up was found to be a strong confounder, but was also strongly correlated with baseline year and associated with the RR of CHD for BMI (categories). However, in a previous analysis of data from the NHANES study, adjustment for length of follow-up did not affect the outcome of the trend of decreasing RRs of

all cause mortality for obesity over time (13). Third, for some studies the RRs for categories of BMI were transformed to RRs for BMI as a continuous variable, which may have introduced some inaccuracy. Finally, we did not adjust for important confounders such as dietary variables or weight (loss) history because these were not available in most studies although those have been shown to be related to BMI and CHD (56,57). Nevertheless, in the Nurses' Health Study (the largest included study) adjustment for diet had virtually no impact on the association between BMI and risk of CHD (42).

Findings in the context of the literature

We found increased RRs of CHD for a five-BMI-unit increment, overweight and obesity of 1.28, 1.31, and 1.78, respectively. The accompanying RRs with the additional adjustments were 1.16, 1.17, and 1.49, respectively. This corresponds well with relative risks found in other studies (58-61).

With regard to time-dependent changes in the association between obesity and health risks, a previous meta-analysis found in overweight and obese elderly an RR of total mortality of 0.47 (0.40:0.55) and 0.66 (0.51:0.71), using five cohorts starting in or after 1990 (62). In 13 and 15 cohorts starting before 1990, they found respectively an RR of 1.00 (0.96:1.04) and 1.02 (0.98:1.07) (62). In the National Health and Nutrition Examination Surveys (NHANES I, II and III), a similar trend of decreasing RR of total mortality in obese US adults (≥25 years) was found (13). Our results also indicated an association between calendar period and the RR of CHD for (increasing) BMI and obesity, but not when study characteristic mean age of the population was taken into account. In addition, we expected that the influence of calendar period would be attenuated by the additional adjustments for physical activity, blood pressure and cholesterol, because of the hypothesis that the blood pressure and cholesterol profile in persons were unfavorable at baseline in studies starting before 1985 compared to studies starting after 1985 due to improvements of treatment of CHD risk factors and lifestyle. However, after the additional adjustments in the univariate analysis, the magnitude of the percentage changes on the RRs for a five-BMI-unit increment and obesity remained in the same order as for the age, sex and smoking adjusted RRs.

In summary, we did not find a clear difference between calendar periods in the association between BMI and CHD. This suggests that earlier studies may not be ruled out for use in predictive models forecasting future deaths of chronic diseases. However, as discussed before, length of follow-up and age of the population might have confounded our results, since these factors were different between calendar periods. Therefore, we cannot conclude beyond doubt that there is no difference between calendar periods. To examine changes by calendar period more thoroughly, a meta-analysis should be performed with similar study characteristics to exclude this kind of confounding. Also, systematic adjustments including information on medication use should be considered to test our hypothesis.

Nevertheless, our study yields sufficient evidence to draw the conclusion that age of the population is an important factor modifying the association between BMI and CHD. Throughout all analyses we found a significant influence of age of the population on the association between BMI and CHD, except in the univariate and multivariate analyses with CHD and overweight and obesity adjusted for the additional CHD risk factors. These exceptions can easily be

explained by the low number of included studies with an old population ($N = 1$), which in turn made it less accurate to regress the log RR on age for the higher age ranges. All together, our results stress the importance of taking age of a population into account in predictive models forecasting future deaths attributable to overweight and obesity.

The decrease in RR of CHD for a five-BMI-unit increment with each 10 year increment of age was comparable to previous studies who found a decreasing trend in the RR of CHD associated with BMI with increasing age (58,63). An explanation for the reduction in RR at higher BMI levels with increasing age is complicated. In the elderly, the value of BMI as an indicator of body fatness is reduced because of the higher total fat mass (because of an age-dependent loss of lean body mass), fat redistribution and age-related decline in height (64). Unintentional age-related weight loss which might be caused by (un)diagnosed illnesses can confound the association between BMI and risk of disease/mortality in the elderly (64). Also, the ones susceptible for the consequences of obesity might have died earlier in life, while the remaining obese elderly persons survived (64). Furthermore, several studies reported that the lowest mortality from all-causes or CVD in elderly persons lies within the overweight category, which indicates that a BMI of 18.5-24.9 kg m^{-2} is not appropriate for the elderly (65-67) and therefore another anthropometric measure such as waist circumference, waist-hip ratio, body fat or lean body mass might be more useful (68,69).

Conclusion

We found no consistent evidence for a difference in the association between BMI and the risk of CHD by calendar period, but we cannot conclude beyond doubt that no difference exists. Further research, that excludes the possible influence of follow-up length, is needed to clarify this. A clear finding of our study is, however, that age of the population was consistently associated with the RR of CHD for BMI. In older populations the RR of CHD associated with BMI is lower than in younger populations. Therefore, for models used to predict mortality and prevalence of CHD in general populations, for example as used by the WHO, data from earlier studies may not be ruled out completely, but applying an age specific approach can be highly recommended.

Acknowledgments

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Appendix 1: Funnel plot for age, sex, and smoking-adjusted (log) relative risks vs precision
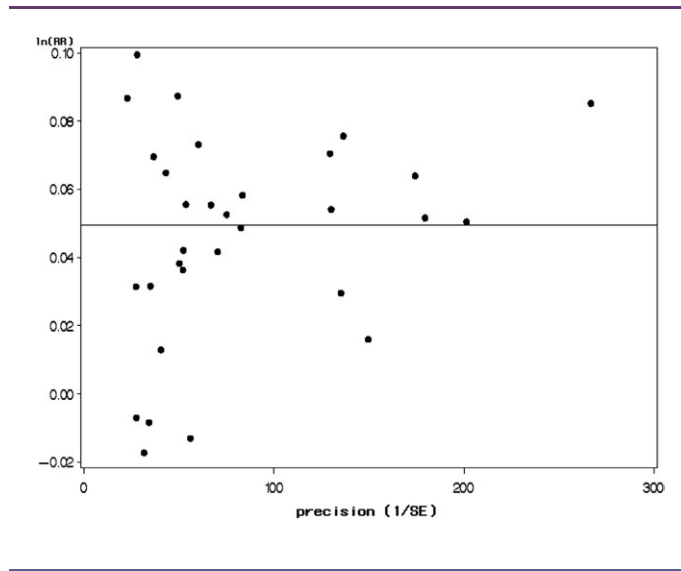
Appendix 2: Relative risks of coronary heart disease (CHD) associated with body mass index (BMI) graphically displayed against study characteristics.
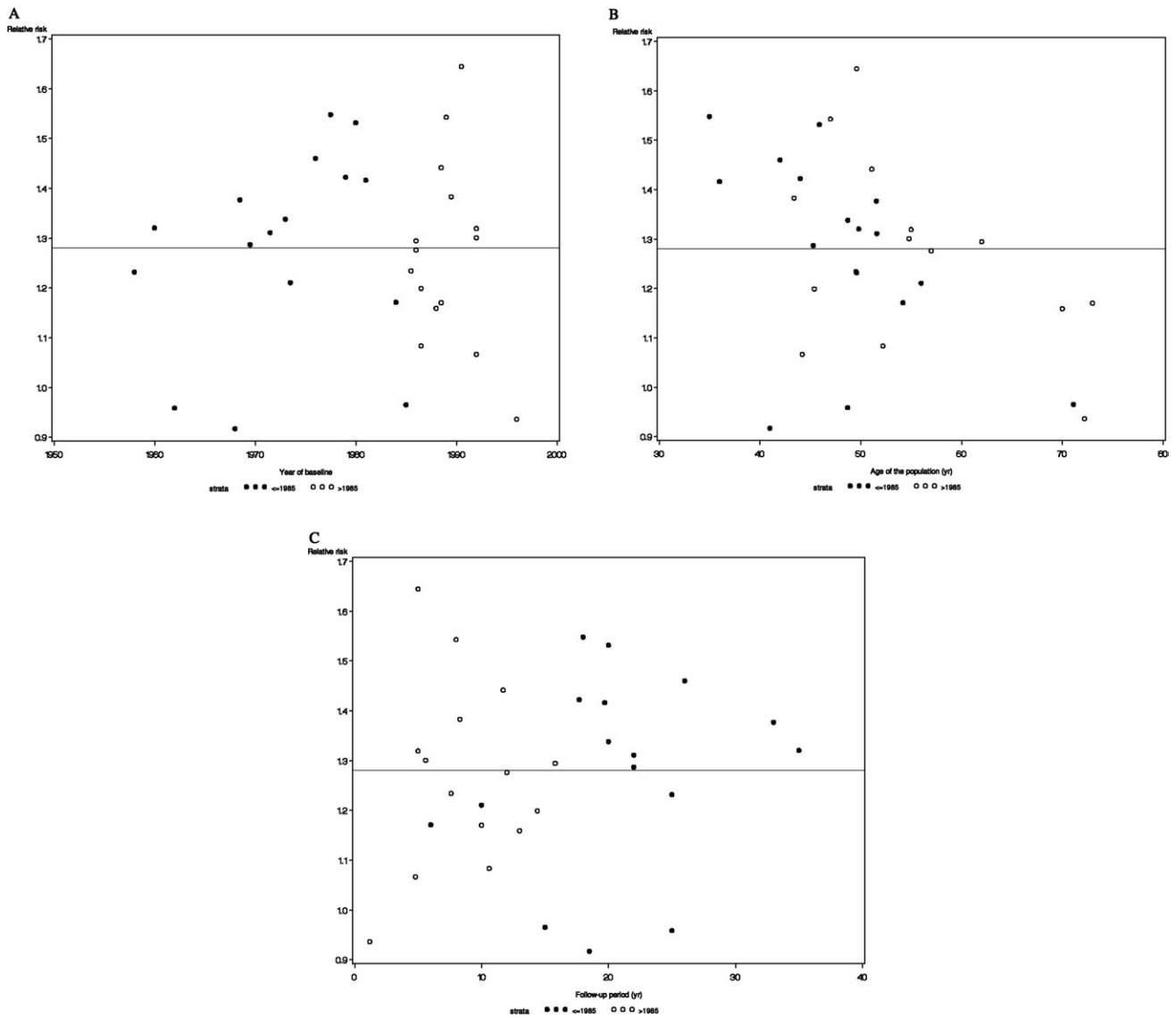

FIGURE 1 Relative risks of CHD for a five-unit-BMI increment adjusted for age, sex and smoking (*N* = 31) plotted against year of baseline (**A**), age of the population (**B**), and follow-up period (**C**) stratified by calendar period (≤1985 vs >1985).
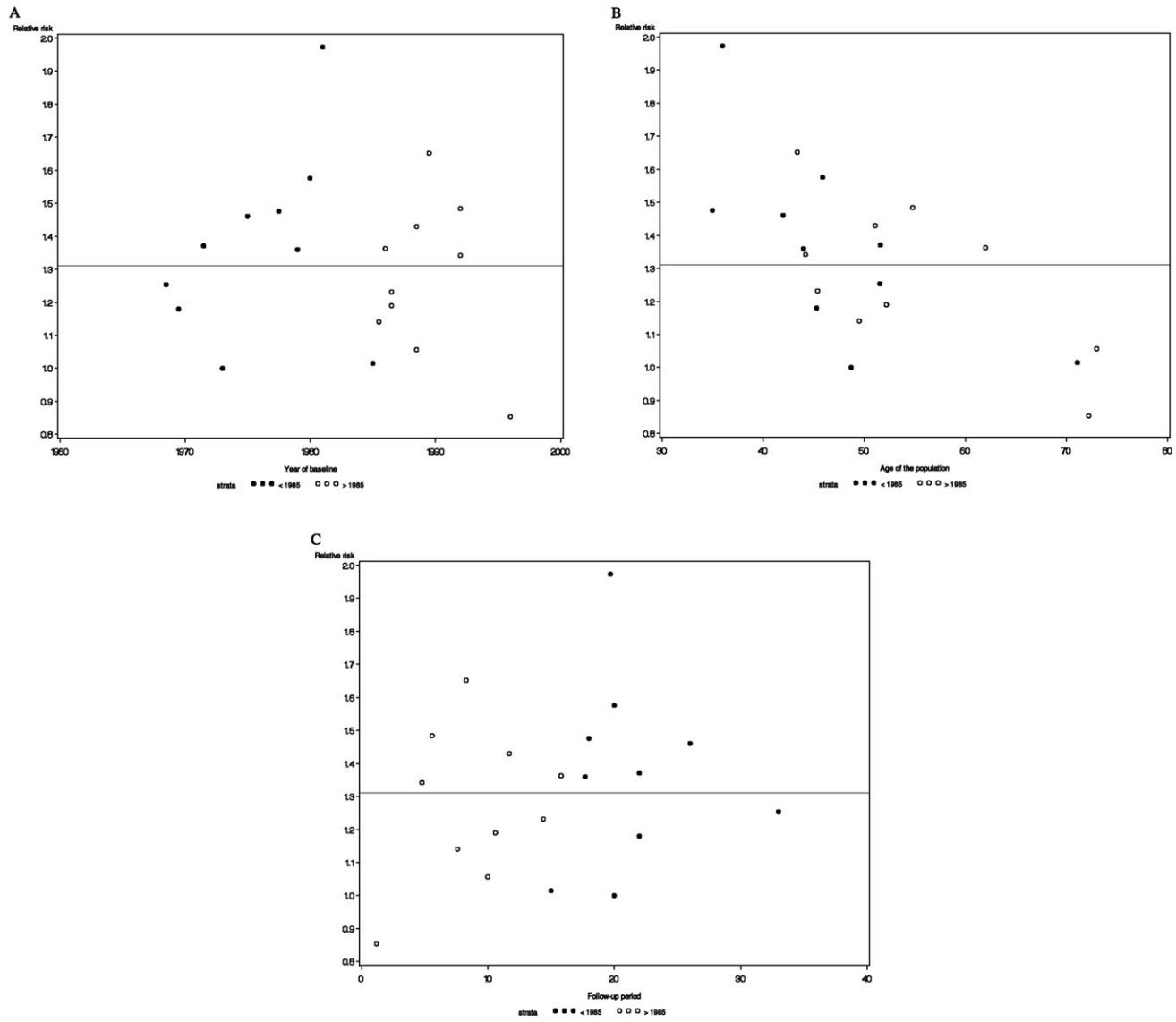
FIGURE 2 Relative risks of CHD for overweight adjusted for age, sex and smoking (*N* = 20) plotted against year of baseline (A), age of the population (B), and follow-up period (C) stratified by calendar period (≤1985 vs >1985).
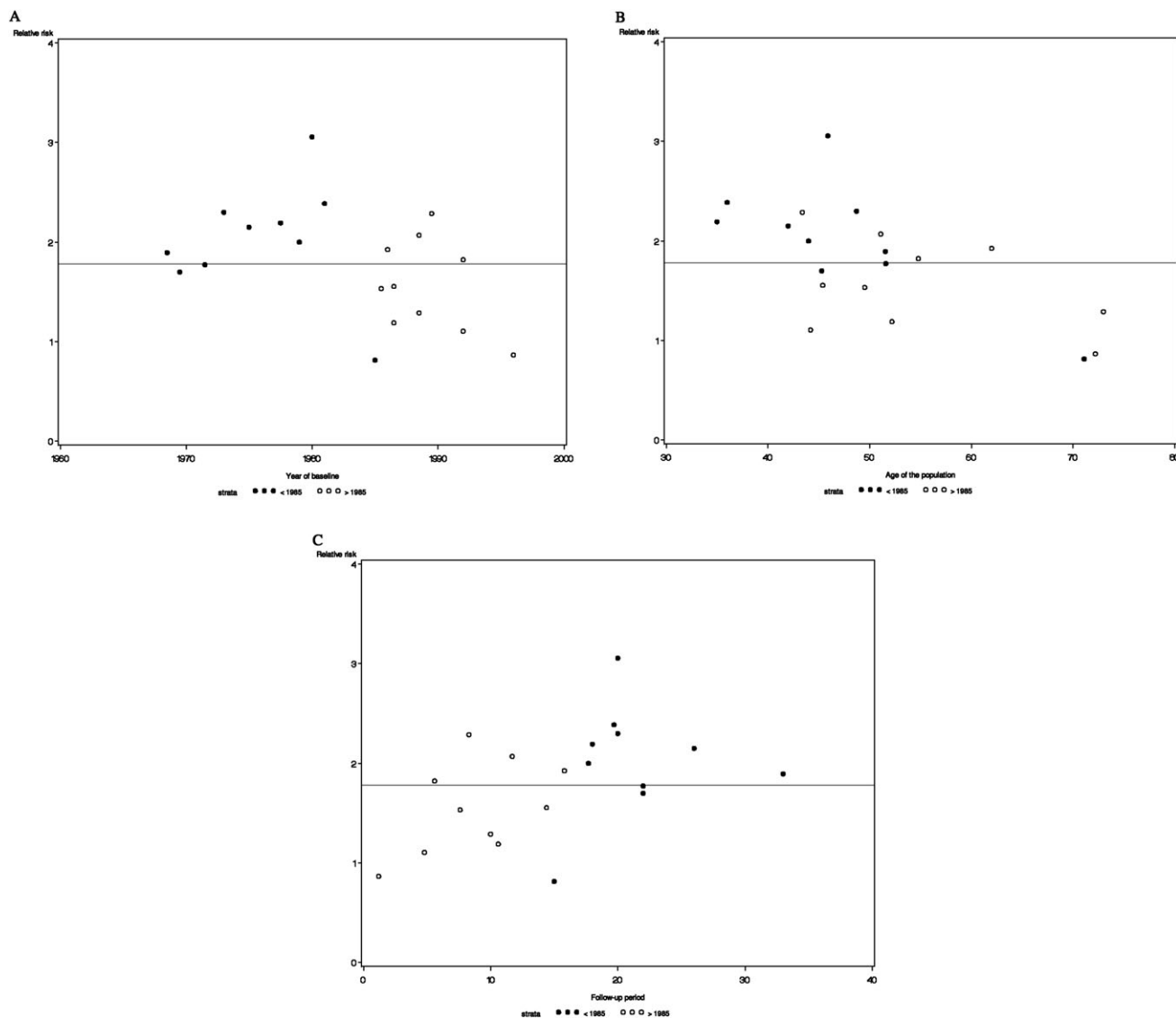
FIGURE 3 Relative risks of CHD for obesity adjusted for age, sex and smoking ($N = 20$) by year of baseline (**A**), age of the population (**B**), and follow-up period (**C**) stratified by calendar period ($\leq$1985 vs >1985).
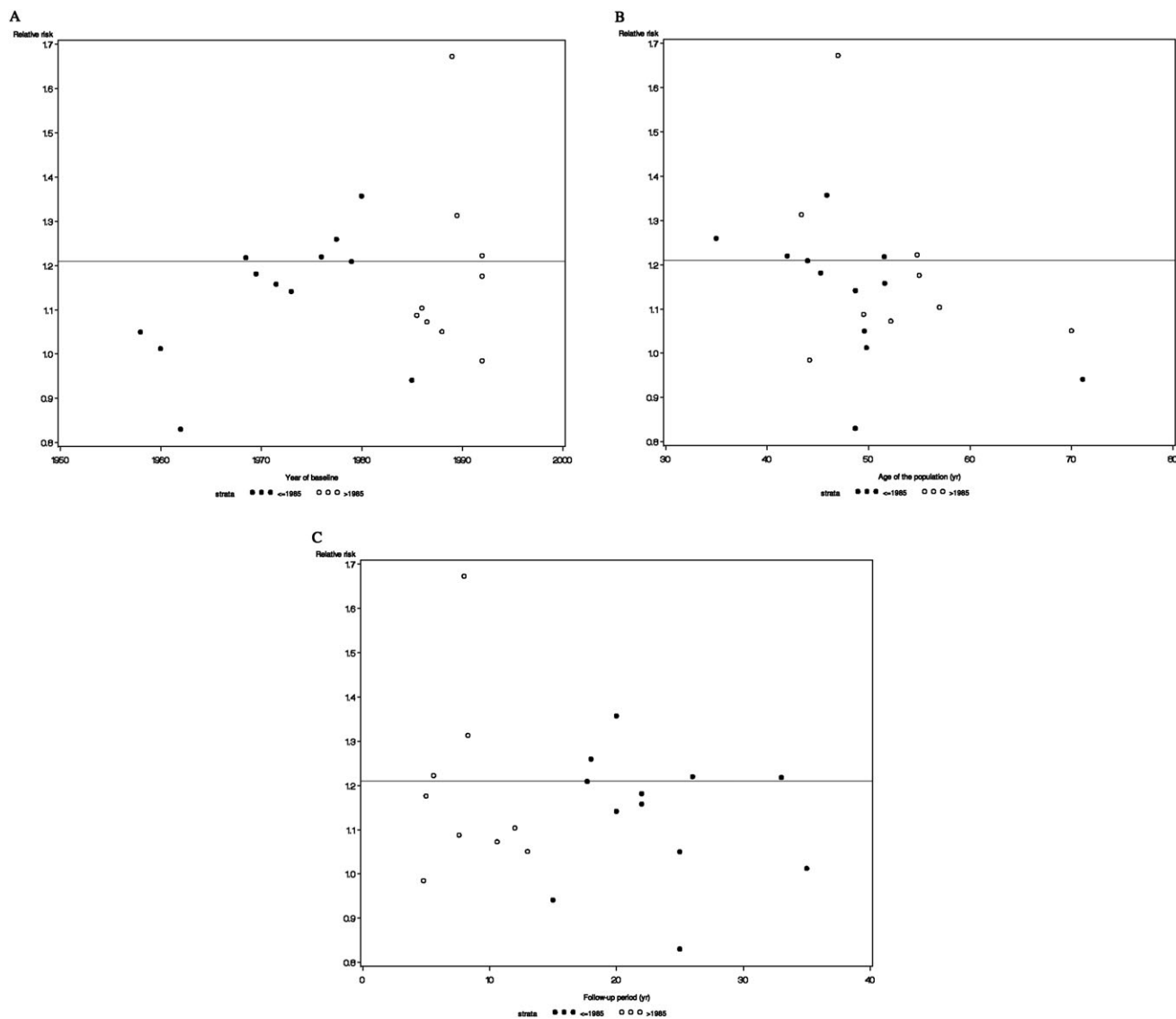
FIGURE 4 Relative risks of CHD for a five-unit-BMI increment adjusted for age, sex, smoking, *physical activity, blood pressure,* and *cholesterol* (*N* = 21) plotted against year of baseline (**A**), age of the population (**B**), and follow-up period (**C**) stratified by calendar period (≤1985 vs >1985)
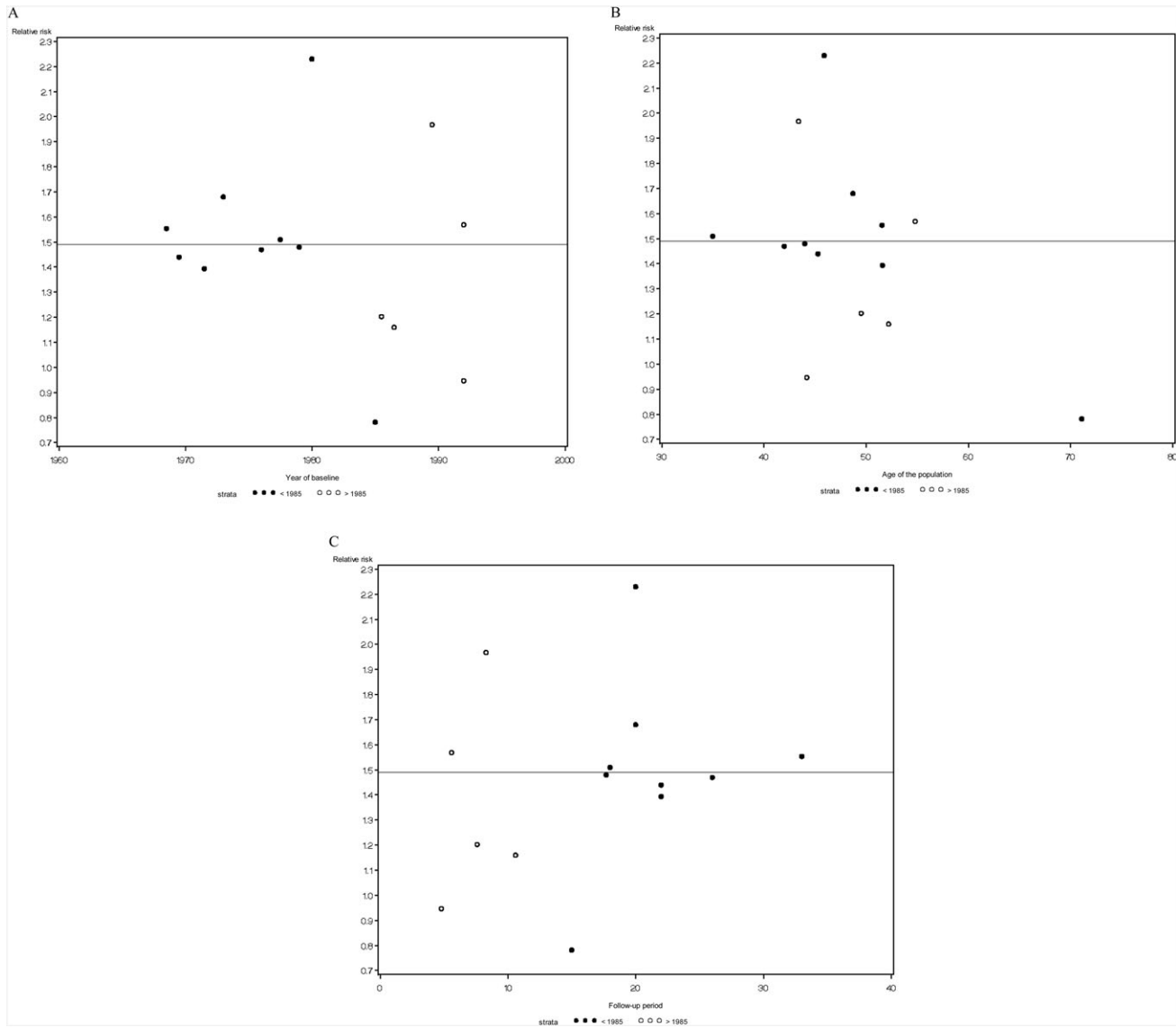
FIGURE 5 Relative risks of CHD for overweight adjusted for age, sex, smoking, *physical activity, blood pressure* and *cholesterol* ($N = 14$) plotted against year of baseline (**A**), age of the population (**B**) and follow-up period (**C**) stratified by calendar period ($\leq$1985 vs >1985).
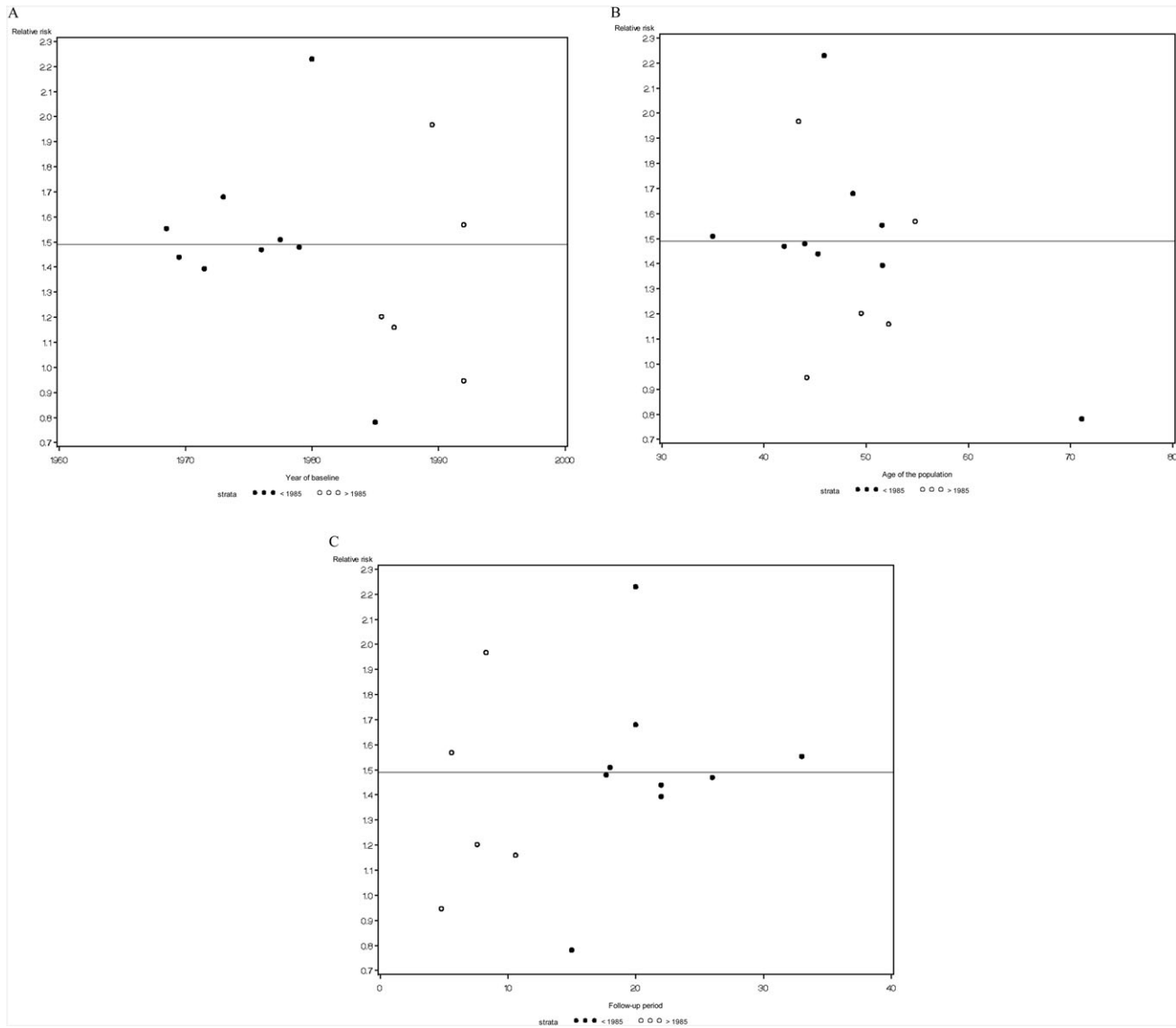
FIGURE 6 Relative risks of CHD for obesity adjusted for age, sex, smoking, *physical activity, blood pressure and cholesterol* (N = 14) plotted against year of baseline (**A**), age of the population (**B**) and follow-up period (**C**) stratified by calendar period (≤1985 vs >1985).