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The impact of body mass index on the associations of lipids with the risk of coronary heart disease in the Asia Pacific region

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ABSTRACT

Objective: To assess whether body mass index (BMI) modifies the associations of lipids with coronary heart disease (CHD).
Methods: In the Asia Pacific Cohort Studies Collaboration, total cholesterol (TC), high density lipoprotein cholesterol (HDLC) and triglycerides (TG) were measured for 333,297, 71,777 and 84,015 participants, respectively. All participants had measured BMI, categorized into underweight, normal, high-normal, overweight and obese, using standard definitions. For each BMI subgroup the effects of lipids on CHD were estimated per 1 standard deviation (SD) increase using Cox proportional hazard models, stratified by study and sex, adjusted for age and smoking. They were compared across the BMI groups, testing for interactions.
Results: In the analyses for TC, HDLC and TG, there were 3121, 714 and 808 CHD events during a mean follow-up of 6.7 years. The risk of CHD increased monotonically with increasing TC and decreasing HDLC in all BMI subgroups without evidence of heterogeneity (p for interaction >0.4). In contrast, the hazard ratio for CHD for a one SD increase in log-transformed TG increased from 1.07 (95%CI 0.72–1.59) in underweight, 1.26 (1.10–1.44) in normal weight, 1.27 (1.08–1.49) in high-normal weight, 1.37 (1.22–1.55) in overweight, to 1.61(1.30–1.99) in obesity ($p = 0.01$ for interaction trend). These associations were attenuated ($p = 0.07$ for interaction) but remained significant in the overweight and obese after further adjustment for TC and HDLC.
Conclusions: Greater excess body weight exacerbated the effects of TG, but not TC or HDLC, on CHD, suggesting that additional effort is required to reduce TG in the overweight and obese.

Introduction

Overweight and obesity are consistently shown to be associated with high morbidity and mortality for coronary heart disease (CHD) (Ni Mhurchu et al., 2004), with 23% of the global burden of CHD attributable to overweight/obesity (World Health Organization, 2009). Dyslipidemia is also an established risk factor for CHD (Zhang et al., 2003; Woodward et al., 2007; Patel et al., 2004), with more than half of global cases attributed to it (World Health Organization, 2002). Overweight/obesity is likely to co-occur with dyslipidemia,(Bays et al., 2013) through their common linkage with unfavorable lifestyles and through accumulated visceral fat that promotes insulin resistance and subsequent hyperinsulinemia, the key factor for lipid disorders in obesity (Klop et al., 2013). Additionally, one might hypothesize that obesity could intensify the association of dyslipidemia with subsequent risk of CHD but current evidence on such effect modification is lacking.

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We examined the joint effects of BMI and lipid variables on CHD using data from the Asia Pacific Cohort Studies Collaboration (APCSC).

Methods

APCSC is an overview, using individual participant data, of prospective cohort studies from the Asia-Pacific region. APCSC's design and methods have been previously described in detail (Ni Mhurchu et al., 2004; Zhang et al., 2003; Woodward et al., 2007; Patel et al., 2004). All studies had 5000+ person-years of follow-up. Studies were excluded if enrolment was dependent on having a particular condition or a risk factor. The present report included participants aged ≥20 years with information on BMI, smoking status and either total cholesterol (TC), high-density lipoprotein cholesterol (HDLC) or triglycerides (TG) at study entry, measured in 34, 25 and 26 studies, respectively, among the 44 studies included in the APCSC.

BMI was calculated as weight (kg) divided by squared height (m^2). Participants at extremes of the BMI spectrum (<12 or >60 kg/m^2) were excluded (Parr et al., 2010). Smoking status was defined as current or not. Lipid measurements were determined from serum samples, among which <10% were non-fasting. Since the studies were initiated between 1966 and 1994, the assays for TC, HDLC and TG varied (Zhang et al., 2003; Woodward et al., 2007; Patel et al., 2004). SBP was generally measured at rest in the seated position using a standard mercury sphygmomanometer. Diabetes was taken as present either from a self-reported history, elevated fasting glucose greater than 6.1 mmol/l for serum samples, and greater than 7 mmol/l for plasma samples, or elevated non-fasting glucose greater than 10 mmol/l for serum samples, and greater than 11.1 mmol/l for plasma samples.

All studies reported deaths by underlying cause; a subset also reported nonfatal CHD events. Most studies used database linkages to identify deaths, whereas others also included scheduled follow-up visits or examined hospital records, particularly to identify nonfatal events, defined as those that did not result in death within 28 days. The outcome considered in this analysis was fatal or nonfatal CHD (Ninth Revision of International Classification of Disease: 410–414).

Statistical methods

Cox proportional hazard models, stratified by sex and cohort, were used to estimate the joint effects of lipid variables and BMI on CHD risk. Age and smoking status were adjusted for in all analyses. BMI was categorized into 5 groups based on the World Health Organization criteria for Asia-Pacific populations: (WHO/IASO/IOTF, 2000) 12.0 ≤ BMI < 18.5, underweight; 18.5 ≤ BMI < 23.0, normal; 23.0 ≤ BMI < 25.0, high-normal; 25.0 ≤ BMI < 30.0, overweight; and 30.0 ≤ BMI < 60.0 kg/m^2, obese. Within each category of BMI, hazard ratios (HRs) with 95% confidence intervals (CIs) for CHD were estimated by quarters of each lipid: TC < 4.4; 4.4 ≤ TC < 5.0, 5.0 ≤ TC < 5.8, TC ≥ 5.8 mmol/l; HDLC < 1.1, 1.1 ≤ HDLC < 1.4, 1.4 ≤ HDLC < 1.6, HDLC ≥ 1.6 mmol/l; TG < 0.9, 0.9 ≤ TG < 1.2, 1.2 ≤ TG < 1.7, TG ≥ 1.7 mmol/l. The joint effects of lipid variables with BMI were examined by comparing the HRs for CHD across the 20 groups (4 × 5 categories) taking the group with the lowest 25% of values for the index lipid variable and with normal weight (i.e. either TC < 4.4 mmol/l, HDLC < 1.1 mmol/l or TG < 0.9 mmol/l and 18.5 ≤ BMI < 23.0 kg/m^2) as the reference group. HRs were also estimated per standard deviation increment for each lipid variable within each category of BMI and were compared across these categories by testing the trend for interaction of the continuous lipid variable with BMI categories (Woodward, 2015). Sensitivity analyses were done after left-censoring by 2 years to reduce the chance of reverse causality; after excluding participants with non-fasting blood samples; and after adjusting for systolic blood pressure (SBP) and diabetic status, as well as age and smoking status. Further adjustment was also made for the other two lipids in addition to other confounders. Heterogeneity of the linear interactions between lipids and BMI were tested between subgroups defined by age groups (≤65 years/>65 years, sex (male/female), smoking status (current/not) and region (Asia/Australia and New Zealand) by adding three-way interaction terms to Cox models with all two-way interactions. Statistical analyses were performed using SAS Release 9.30 (SAS Institute Inc, Cary, NC).

Results

Overall, 333,297 individuals contributed to the analyses of TC, 71,777 to those of HDLC, and 84,015 to those of TG (Table 1). Mean follow-up was 6.7, 7.2, and 8.3 years for TC, HDLC and TG, respectively. Mean age was 47–49 years, about half of participants were female, and 70% were Asian. Mean BMI at baseline varied, between studies, from 21.5 to 26.9 kg/m^2, mean TC from 4.1 to 5.9 mmol/l, mean HDLC from 0.9 to 1.6 mmol/l and median TG from 0.7 to 1.5 mmol/l (Supplementary table 1). On average, BMI and TC were higher in those cohorts sourced from Australia or New Zealand compared with those from Asia, whereas average levels of HDLC and TG were similar between Australasia and Asia.

The effects of BMI on the association between total cholesterol and coronary heart disease

The age and smoking-adjusted HR for CHD was higher in the highest quarter of TC compared with the lowest quarter among all BMI categories (Supplementary Figure 1). There was no difference in the effects of TC between BMI categories ($p = 0.42$ for trend); overall, for every 1 standard deviation increase in TC there was a 23% (95% CI, 20%–27%) increase in the risk of CHD (Fig. 1). Similar associations were obtained in the sensitivity analyses after left-censoring by 2 years (Supplementary Figure 2), after excluding participants with non-fasting blood samples (Supplementary Figure 3) and after further adjustment for SBP and

Table 1
Baseline characteristics of Asian and Australasian (Australia and New Zealand) regions.

Risk factors	Asia	Australasia	Overall
Analysis set for total cholesterol			
No. of participants	249,206	84,091	333,297
Age, year	45.9 (9.1)	50.5 (13.0)	47.0 (10.4)
Female, %	37.7	51.6	41.2
Smoker, %	37.8	18.4	32.9
Body mass index, kg/m^2	22.9 (2.8)	26.3 (4.3)	23.7 (3.6)
Total cholesterol, mmol/l	4.9 (1.0)	5.6 (1.1)	5.1 (1.0)
Systolic blood pressure, mmHg	123.2 (17.0)	134.1 (20.6)	126.0 (18.6)
Diabetes mellitus, %	6.9	4.0	6.2
Follow-up period, years	5.6 (3.6)	10.0 (6.1)	6.7 (4.8)
Analysis set for HDL cholesterol			
No. of participants	48016	23761	71777
Age, year	50.3 (12.1)	47.6 (14.7)	49.4 (13.1)
Female, %	44.2	50.3	46.2
Smoker, %	33.7	23.6	30.3
Body mass index, kg/m^2	22.9 (3.4)	25.7 (4.3)	23.8 (3.9)
HDL cholesterol, mmol/l	1.4 (0.4)	1.4 (0.4)	1.4 (0.4)
Systolic blood pressure, mmHg	126.2 (21.0)	129.8 (20.2)	127.4 (20.8)
Diabetes mellitus, %	6.3	2.9	5.2
Follow-up period, year	6.2 (3.5)	9.4 (4.9)	7.2 (4.3)
Analysis set for triglycerides			
No. of participants	65832	18183	84015
Age, year	49.6 (12.2)	46.2 (15.6)	48.9 (13.1)
Female, %	47.3	50.4	48.0
Smoker, %	32.6	23.7	30.7
Body mass index, kg/m^2	22.9 (3.3)	25.4 (4.2)	23.4 (3.7)
Triglycerides, mmol/l	1.2 (0.8–1.7)	1.2 (0.8–1.7)	1.2 (0.8–1.7)
Systolic blood pressure, mmHg	126.0 (21.0)	128.9 (20.2)	126.6 (20.9)
Diabetes mellitus, %	5.6	2.9	5.0
Follow-up period, year	7.9 (4.6)	9.8 (5.5)	8.3 (4.9)

HDL cholesterol, high density lipoprotein cholesterol.
Values are mean (standard deciation) for continuous variables except median (interquartile interval) for triglycerides, and percentage for categorical variables.