



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 (HDL) 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, HDL 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 HDL 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 HDL.

Conclusions: Greater excess body weight exacerbated the effects of TG, but not TC or HDL, on CHD, suggesting that additional effort is required to reduce TG in the overweight and obese.

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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 (HDL) 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 $> 60 \text{ kg/m}^2$) 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, HDL 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) $12.0 \leq \text{BMI} < 18.5$, underweight; $18.5 \leq \text{BMI} < 23.0$, normal; $23.0 \leq \text{BMI} < 25.0$, high-normal; $25.0 \leq \text{BMI} < 30.0$, overweight; and $30.0 \leq \text{BMI} < 60.0 \text{ kg/m}^2$, obese. Within each category of BMI, hazard ratios (HRs) with 95% confidence intervals (CIs) for CHD were estimated by quarters of each lipid: $\text{TC} < 4.4$; $4.4 \leq \text{TC} < 5.0$, $5.0 \leq \text{TC} < 5.8$, $\text{TC} \geq 5.8 \text{ mmol/l}$; $\text{HDL} < 1.1$, $1.1 \leq \text{HDL} < 1.4$, $1.4 \leq \text{HDL} < 1.6$, $\text{HDL} \geq 1.6 \text{ mmol/l}$; $\text{TG} < 0.9$, $0.9 \leq \text{TG} < 1.2$, $1.2 \leq \text{TG} < 1.7$, $\text{TG} \geq 1.7 \text{ mmol/l}$. 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 $\text{TC} < 4.4 \text{ mmol/l}$, $\text{HDL} < 1.1 \text{ mmol/l}$ or $\text{TG} < 0.9 \text{ mmol/l}$ and $18.5 \leq \text{BMI} < 23.0 \text{ kg/m}^2$) 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 HDL, and 84,015 to those of TG (Table 1). Mean follow-up was 6.7, 7.2, and 8.3 years for TC, HDL 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 HDL 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 HDL 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 deviation) for continuous variables except median (interquartile interval) for triglycerides, and percentage for categorical variables.

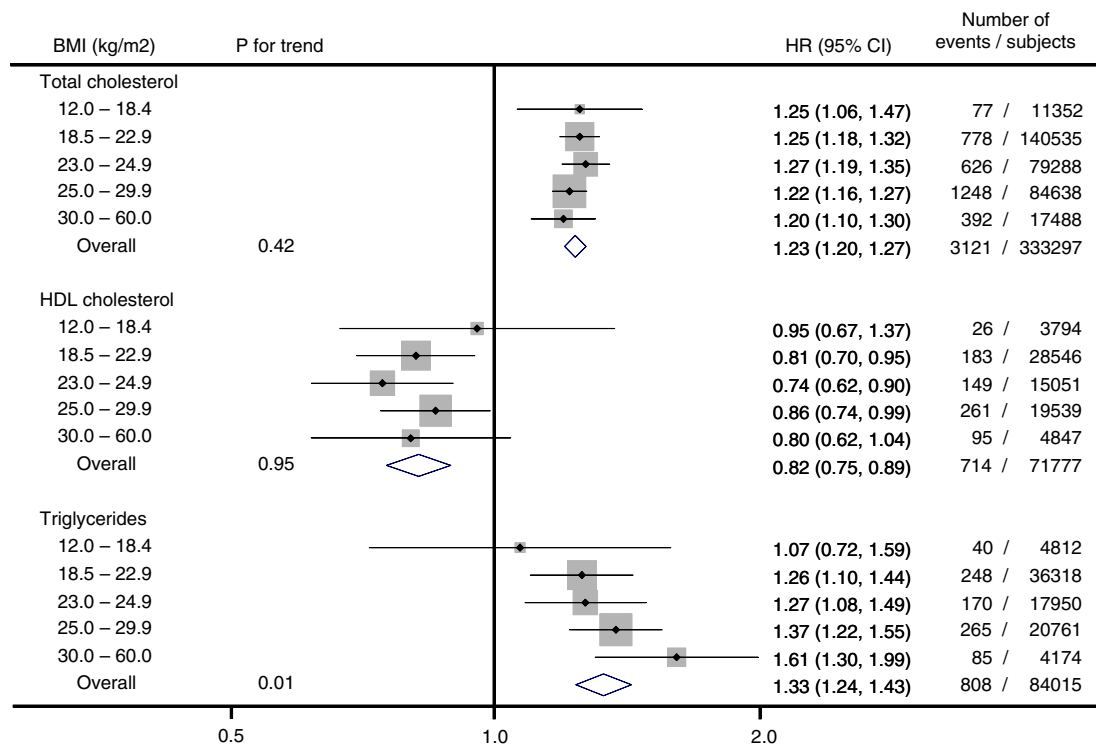


Fig. 1. Hazard ratios, stratified by study and sex and adjusted for age and smoking, for coronary heart disease associated with 1 standard deviation increase of lipids among body mass index categories. BMI, body mass index; HDL cholesterol, high density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval. Triglycerides were log-transformed. Bars show 95% CIs. The diamonds show overall results across all BMI categories. The vertical diagonal of the diamond indicates the estimate and the horizontal diagonal indicates the 95% CIs.

diabetes (Supplementary Figure 4) and additional adjustment for HDL and TG (Supplementary Figure 5). There were no significant differences between subgroups (all $p > 0.15$ for interaction). Compared with individuals with a normal weight and TC < 4.4 mmol/l, the risk of CHD increased independently with the elevation of BMI or TC levels, and was 3.2 times as high for obese individuals with TC ≥ 5.8 mmol/l (HR adjusted for age and smoking, 3.2; 95% CI, 2.5–4.0) (Supplementary Figure 6).

The effects of BMI on the association between high density lipoprotein cholesterol and coronary heart disease

There were similar patterns of decreasing risk of CHD with increasing HDL across all BMI categories in the age- and smoking-adjusted model, except for underweight individuals where there was no evidence of association, although the number at risk was small (Supplementary Figure 1). There was no evidence of difference in the effects of HDL across BMI categories ($p = 0.95$ for trend) (Fig. 1). The risk of CHD decreased by 16% (95% CI, 11%–25%) for a 1 standard deviation increase in HDL. These associations were unchanged after left-censoring by 2 years (Supplementary Figure 2), and after excluding participants with non-fasting blood samples (Supplementary Figure 3) but were slightly strengthened after additional adjustment for SBP and diabetes (Supplementary Figure 4), and further attenuated after further adjustment for other lipids (Supplementary Figure 5). There was no significant difference between subgroups (all $p > 0.15$ for interaction). Compared with individuals of normal weight in the lowest quarter of HDL, the risk of CHD decreased as HDL levels increased. These associations were less evident for underweight individuals with lower risk of CHD, irrespective of HDL levels (Supplementary Figure 6).

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

There were positive linear associations of TG with CHD, irrespective of BMI category in the age and smoking-adjusted model (Supplementary

Figure 2). Comparing the effects of TG across all BMI categories, there was a significant trend of increasing effects of TG with increasing BMI ($p = 0.01$ for trend) (Fig. 1). Sensitivity analyses showed the consistency of these associations after left-censoring by 2 years (Supplementary Figure 2), after excluding participants with non-fasting blood samples (Supplementary Figure 3) and after adjusting for age, smoking, systolic blood pressure and diabetes (supplementary figure 4). When further adjustment was made for TC and HDL, these associations were much attenuated, and not significant ($p = 0.07$) (Supplementary Figure 5). There were no significant differences between subgroups (all $p > 0.20$ for interaction). The risk of CHD for obese individuals with TG ≥ 1.7 mmol/l was triple that of those of normal weight with TG < 0.9 mmol/l (HR adjusted for age and smoking, 3.0; 95% CI, 2.0–4.5) (Supplementary Figure 6).

Supplementary Figures 7–9 show sensitivity analyses wherein we: combined the first and last two BMI groups; classified BMI into its equal fifths and omitted the smallest and largest 0.1% of values of each respective lipid—otherwise analysing as for Fig. 1. None of these changes had any important effect on the results.

Discussion

This is the first large-scale international study to investigate the effects of BMI on the association between lipid variables and the risk of CHD. We found that the risk of CHD was positively associated with increased TC and decreased HDL, independently of BMI. On the other hand, there was a significant increase in the effects of TG on CHD with increasing BMI, which was still evident after adjusting for HDL and TC.

Whilst BMI and lipids are often considered as separate cardiovascular risk factors, for example in the Framingham Risk Equation, BMI acts partially through lipids. Similarly, TC is partially determined by the diet, but is also synthesised de novo, and excess adiposity is known to play a role in this process. The underlying mechanism relating BMI, TG and CHD is complex. The common form of high TG and low HDL is characteristic of the metabolic syndrome with abdominal obesity and diabetes

and of background insulin resistance (Kannel and Vasan, 2009). TG and HDLC have a close inverse relationship as cholesterol is transferred from HDLC to TG-rich very low density lipoprotein (Feingold and Grunfeld, 2000). This profile is a marker for the underlying presence of highly atherogenic small dense low density lipoprotein cholesterol particles that penetrate the intima (Rajman et al., 1999) and are subject to oxidation (Tribble et al., 1992). In our analyses, the interaction of TG with BMI was attenuated but still positive after adjusting for HDLC and TC, a finding reflecting the atherogenic effects of the mixed dyslipidemia in obesity and the metabolic syndrome.

The present findings have public health implications in terms of specific education and health promotion measures to combat the obesity epidemic as well as the associated lipid disorders. Traditionally, targets for lipid lowering have ranged from TC/HDLC ratios (as in the Framingham Risk Equation) to LDLC (in multiple statin trials) to the more recent guidelines (established clinical disease or high calculated risk scores). Although severe hypertriglyceridemia should benefit from drug intervention (Berglund et al., 2012), lifestyle modification is still important for initial therapy and for patients with mild-to-moderate levels of TG. A CHD risk equation incorporating BMI and TG and their interaction would be useful to stratify individual risk and to determine a threshold for therapy.

The strength of our study is the large sample size that allows us to produce reliable estimates using several categories for lipid variables and BMI. A limitation is the lack of standard methods of data collection across the cohorts and a possible misclassification of events that could not always be verified using medical record or through autopsy data. In addition, information on the use of lipid lowering medications was not generally available. Our findings of statistical significance should be interpreted with the caveat that clinical and statistical significance are different issues.

To conclude, anthropometric and lipid variables are both strong predictors of CHD. BMI appears act independently of total and HDL cholesterol, yet high BMI exacerbates the effects of TG on CHD. This association was attenuated after adjusting for the other lipids but remained significant. Our study emphasizes the benefits of body weight control together with management of dyslipidemia to reduce the burden of CHD.

Conflict of interest statement

None declared.

Contributions of authors

YH carried out the data analysis and wrote the first draft in consultation with MW. MW conceived the analyses and revised the manuscript. All other authors contributed to data and interpretation of the manuscript and commented on draft manuscripts.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.pmedr.2015.12.012>.

References

- Bays, H.E., Toth, P.P., Kris-Etherton, P.M., Abate, N., Aronne, L.J., Brown, W.V., Gonzalez-Campoy, J.M., Jones, S.R., Kumar, R., La Forge, R., Samuel, V.T., 2013. Obesity, adiposity, and dyslipidemia: a consensus statement from the National Lipid Association. *J. Clin. Lipidol.* 7, 304–383.
- Berglund, L., Brunzell, J.D., Goldberg, A.C., Goldberg, I.J., Sacks, F., Murad, M.H., Stalenhoef, A.F., Endocrine society, 2012. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. *J. Clin. Endocrinol. Metab.* 97, 2969–2989.
- Feingold, K., Grunfeld, C., 2000. Obesity and Dyslipidemia [Updated 2015 Jun 12]. In: De Groot, L.J., Beck-Peccoz, P., Chrousos, G., et al. (Eds.), *Endotext* [Internet]. MDText.com, Inc., South Dartmouth (MA) (Available from: <http://www.ncbi.nlm.nih.gov/books/NBK305895/>).
- Kannel, W.B., Vasan, R.S., 2009 Jul. Triglycerides as vascular risk factors: new epidemiologic insights. *Curr. Opin. Cardiol.* 24 (4), 345–350.
- Klop, B., Elte, J.W., Cabezas, M.C., 2013. Dyslipidemia in obesity: mechanisms and potential targets. *Nutrients* 5, 1218–1240.
- Ni Mhurchu, C., Rodgers, A., Pan, W.H., Gu, D.F., Woodward, M., Asia Pacific Cohort Studies Collaboration, 2004. Body mass index and cardiovascular disease in the Asia-Pacific Region: an overview of 33 cohorts involving 310 000 participants. *Int. J. Epidemiol.* 33, 751–758.
- Parr, C.L., Batty, G.D., Lam, T.H., Barzi, F., Fang, X., Ho, S.C., et al., Asia-Pacific Cohort Studies Collaboration, 2010. Body-mass index and cancer mortality in the Asia-Pacific Cohort Studies Collaboration: pooled analyses of 424 519 participants. *Lancet Oncol.* 11, 741–752.
- Patel, A., Barzi, F., Jamrozik, K., Lam, T.H., Ueshima, H., Whitlock, G., Woodward, M., Asia Pacific Cohort Studies Collaboration, 2004. Serum triglycerides as a risk factor for cardiovascular diseases in the Asia-Pacific region. *Circulation* 110, 2678–2686.
- Rajman, I., Eacho, P.I., Chowienzyk, P.J., Ritter, J.M., 1999. LDL particle size: an important drug target? *Br. J. Clin. Pharmacol.* 48, 125–133.
- Tribble, D.L., Holl, L.G., Wood, P.D., Krauss, R.M., 1992. Variations in oxidative susceptibility among six low density lipoprotein subfractions of differing density and particle size. *Atherosclerosis* 93, 189–199.
- WHO/IASO/IOTF, 2000. The Asia-Pacific Perspective: Redefining Obesity and Its Treatment. Health Communications Australia, Melbourne, Australia.
- Woodward, M., 2015. *Epidemiology: Study Design and Data Analysis*. third ed. CRC Press, Boca Raton.
- Woodward, M., Barzi, F., Feigin, V., Gu, D., Huxley, R., Nakamura, K., Patel, A., Ho, S., Jamrozik, K., Asia Pacific Cohort Studies Collaboration, 2007. Associations between high-density lipoprotein cholesterol and both stroke and coronary heart disease in the Asia Pacific region. *Eur. Heart J.* 28, 2653–2660.
- World Health Organization, 2002. Quantifying selected major risks to health. The World Health Report 2002—Reducing Risks, Promoting Healthy Life. Chapter 4. World Health Organization, Geneva, pp. 47–97.
- World Health Organization, 2009. *Global Health Risks: Mortality and Burden of Disease Attributable to Selected Major Risks*. World Health Organization, Geneva.
- Zhang, X., Patel, A., Horibe, H., Wu, Z., Barzi, F., Rodgers, A., MacMahon, S., Woodward, M., Asia Pacific Cohort Studies Collaboration, 2003. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. *Int. J. Epidemiol.* 32, 563–572.