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Original Article

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Sex Difference in the Association between Lipid Profile and Incident Cardiovascular Disease among Young Adults

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Aim: Using a nationwide epidemiological database, we sought to examine whether there was a sex difference in the association between lipid profiles and subsequent cardiovascular disease (CVD) in young adults.

Methods: Medical records of 1,909,362 young adults (20–49 years old) without a prior history of CVD and not taking lipid-lowering medications were extracted. We conducted multivariable Cox regression analyses to identify the association between the number of abnormal lipid profiles and incident CVD.

Results: After a mean follow-up of 3.4 ± 2.6 years, myocardial infarction (MI), angina pectoris (AP), stroke, and heart failure (HF) developed in 2,575 (0.1%), 26,006 (1.4%), 10,748 (0.6%), and 24,875 (1.3%) subjects, respectively. The incidence of MI, AP, and HF increased with the number of abnormal lipid profiles in both men and women, whereas the incidence of stroke increased with the number of abnormal lipid profiles only in men but not in women. Multivariable adjusted hazard ratios (HRs) for MI per 1-point higher abnormal lipid profile were 1.57 (95% confidence interval [CI] 1.49–1.65) in men and 1.25 (95% CI 1.07–1.47) in women. HRs for AP, stroke, and HF per 1-point higher abnormal lipid profile were 1.14 (95% CI 1.12–1.16), 1.06 (95% CI 1.02–1.09), and 1.10 (95% CI 1.08–1.12) in men and 1.18 (95% CI 1.13–1.23), 1.09 (95% CI 1.03–1.16), and 1.10 (95% CI 1.05–1.14) in women.

Conclusion: Our analysis demonstrated an association between the number of abnormal lipid profiles and incident CVD in both men and women. The association between the number of abnormal lipid profiles and incident MI was pronounced in men.

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Key words: Sex difference, Young adults, Lipid profile, Cardiovascular disease, Preventive cardiology, Epidemiology

Introduction

Dyslipidemia plays a central role in the pathogenesis of cardiovascular disease (CVD)[1-4], which is a major cause of mortality and morbidity worldwide[5-7]. Particularly, the incidence of CVD in young adults is reported to be stagnating or even increasing[8-11], and therefore, the importance of risk

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stratification and prevention of CVD in young adults is currently being recognized. Regarding CVD in young adults, we previously reported that dyslipidemia was associated with a greater risk of subsequent CVD events in young adults aged <50 years[12]. Further, dyslipidemia is one of the most frequently observed risk factors in more than 1 million young patients with myocardial infarction (MI) in the United States. Dyslipidemia was seen in more than half of the study population in both men and women[13]. Thus, dyslipidemia could have an important role in the development of CVD among young people irrespective of sex. Sex differences and CVD in women are also important issues in the field of cardiovascular medicine, particularly preventive cardiology. Nevertheless, little is known about sex differences in the association between lipid profiles and incident CVD among young adults. In this study, we analyzed the association between lipid profiles and incident CVD stratified by sex and further examined whether there was a sex difference in the association between lipid profiles and subsequent CVD in young adults, using a nationwide epidemiological database.

Methods

Study Subjects and Design

The JMDC Claims Database is available for anyone who purchases it from JMDC Inc. (https://www.jmdc.co.jp/en/index).

This retrospective observational study analyzed data from the JMDC Claims Database (JMDC Inc., Tokyo, Japan) between January 2005 and April 2020[14-17]. The JMDC contracts with more than 60 insurers and includes data for health insurance claims on insured individuals who are mostly employees of relatively large Japanese companies. The JMDC Claims Database includes health checkup data on prior medical history, status of medications, laboratory data, and clinical follow-up data from claims records. The incidence of CVD events including MI (I210, I211, I212, I213, I214, I219), angina pectoris (AP) (I200, I201, I208, I209), stroke (ICD-10: I630, I631, I632, I633, I634, I635, I636, I638, I639, I600, I601, I602, I603, I604, I605, I606, I607, I608, I609, I610, I611, I613, I614, I615, I616, I619, I629, G459), and heart failure (HF) (I500, I501, I509, I110) from each individual's claim records was evaluated using the International Classification of Disease, 10th Revision (ICD-10), diagnosis codes[18].

We extracted data for 4,306,951 subjects with available data on lipid profiles, including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides. We excluded subjects aged <20 years (n=43,732) and ≥ 50 years (n=1,411,212); taking lipid-lowering medications (n=52,307); with missing data on lipid-lowering medications (n=258,704); with prior history of CVD (n=49,358); and with missing data on body mass index (n=1,015), waist circumference (n=256,084), blood pressure (n=987), fasting plasma glucose (n=316,882), medications (n=51), and cigarette smoking (n=7,257). Finally, we analyzed 1,909,362 participants. A flowchart is shown in **Fig. 1**.

Ethics

This study was approved by the Ethical Committee of The University of Tokyo (2018-10862) and conducted in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived because all data in the JMDC Claims Database were anonymized. All data were compliant with the International Conference on Harmonization guidelines[19].

Definitions

Abnormal lipid profiles were defined as levels of LDL-C ≥ 140 mg/dL, HDL-C <40 mg/dL, or triglycerides ≥ 150 mg/dL. Obesity was defined as a body mass index of ≥ 25 kg/m^2. High waist circumference was defined as waist circumference of ≥ 85 cm for men and ≥ 90 cm for women[20]. Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg or a diastolic blood pressure of ≥ 90 mmHg or the use of blood pressure-lowering medications. Diabetes mellitus was defined as a fasting glucose level of ≥ 126 mg/dL or the use of glucose-lowering medications.

Statistical Analysis

Descriptive statistics are reported as median (interquartile range) and number (percentage). Categorical and continuous variables were compared using the chi-square test and unpaired t-test, respectively, for both men and women. We conducted Cox regression analysis to identify the association of the number of abnormal lipid profiles with incident CVD in men and women. Model 1 is unadjusted. Model 2 includes adjustment for age. Model 3 includes adjustment for age, obesity, high waist circumference, hypertension, diabetes mellitus, and cigarette smoking. The P values for interactions between men and women were calculated in a multivariable model. We also analyzed the association between abnormal lipid profiles and incident CVD. There were missing data, as shown in **Fig. 1**. Hence, we used multiple imputation to replace those missing data with other plausible values by creating multiple

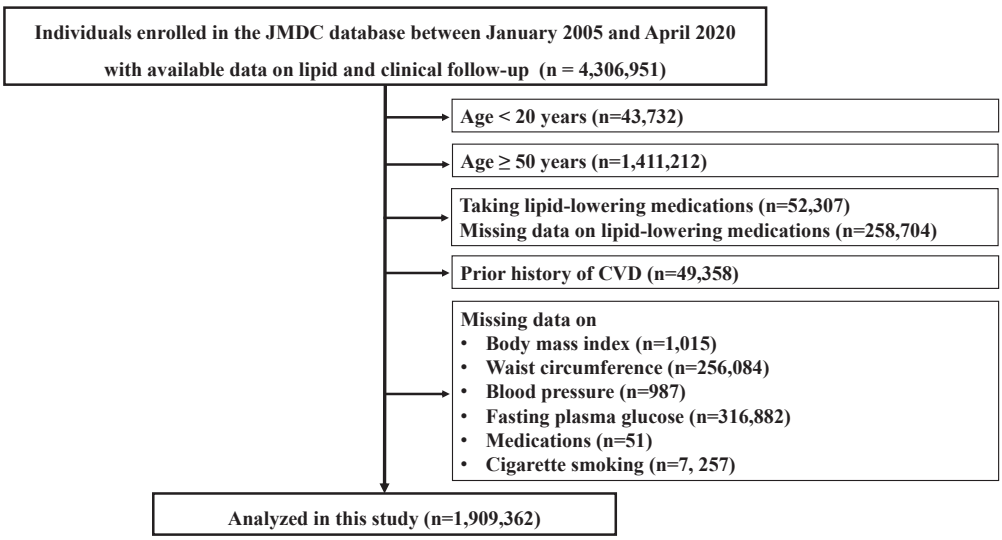

Fig. 1. Flowchart

We extracted data for 4,306,951 subjects with available data on serum lipid profiles including low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. We excluded subjects aged <20 years (n=43,732) and ≥ 50 years (n=1,411,212), taking lipid-lowering medications (n=52,307), with missing data on lipid-lowering medications (n=258,704), with prior history of cardiovascular disease (n=49,358), and with missing data on body mass index (n=1,015), waist circumference (n=256,084), blood pressure (n=987), fasting plasma glucose (n=316,882), medications (n=51), and cigarette smoking (n=7,257). Finally, we analyzed 1,909,362 participants in this study.

filling-in patterns to avert bias caused by missing data[21]. This is also recognized as an alternative approach to analyzing incomplete data[22]. Here, we replaced each missing data with a set of substituted plausible values by creating 20 filled-in complete data sets using multiple imputation by the chained equation method[23]. Covariates included in the multivariable Cox regression analysis were used in the multiple imputation process. Hazard ratios (HRs) and standard errors were calculated using Rubin's rules. Statistical significance was set at $p<0.05$. We examined the relationship between the number of abnormal lipid profiles and incident CVD in men and women including people aged 20–45 years. All statistical analyses were performed using SPSS software (version 25, SPSS Inc., Chicago, IL, USA) and STATA (version 16, StataCorp LLC, College Station, TX, USA).

Results

Baseline Characteristics

The clinical characteristics of the study population are summarized in **Table 1**. Among 1,909,362 participants analyzed in this study, 1,062,902 (55.7%) were men. The number of abnormal lipid profiles, including levels of LDL-C ≥ 140 mg/dL, HDL-C <40 mg/dL, and triglycerides ≥ 150 mg/dL, was higher in men than in women. The proportion of participants with the levels of LDL-C ≥ 140 mg/dL (27.5% vs. 14.4%), HDL-C <40 mg/dL (6.9% vs. 0.9%), and triglycerides ≥ 150 mg/dL (21.8% vs. 4.5%) was higher in men than in women. Obesity, high waist circumference, hypertension, diabetes mellitus, and cigarette smoking were all more common in men than in women.

The mean follow-up period was 3.4±2.6 years. MI, AP, stroke, and HF occurred in 2,030 (0.2%), 17,074 (1.6%), 6,761 (0.6%), and 15,798 (1.5%) men and 545 (0.1%), 8,932 (1.1%), 3,987 (0.5%), and 9,077 (1.1%) women, respectively.

The Frequency of Events, Corresponding Incidence Rates, and Hazard Ratios for Cardiovascular Disease Events

The incidence of MI, AP, and HF increased with the number of abnormal lipid profiles in both men and women, whereas the incidence of stroke increased with the number of abnormal lipid profiles only in men but not in women. Multivariable Cox regression analyses showed that the number of abnormal lipid profiles was dose-dependently associated with the incidence of MI, AP, stroke, and HF in men. The number of abnormal lipid profiles was dose-dependently associated with the incidence of MI, AP, and HF in women **(Table 2)**. Multivariable adjusted HRs for MI per 1-point higher abnormal lipid profile were 1.57 (95% confidence interval [CI] 1.49–1.65)

Table 1. Clinical Characteristics

	Men (n=1,062,902)	Women(n=846,460)	P value
Number of Abnormal Lipid Profile			<0.001
0, *n* (%)	617,975 (58.1)	699,078 (82.6)	
1, *n* (%)	307,289 (28.9)	128,294 (15.2)	
2, *n* (%)	123,193 (11.6)	18,035 (2.1)	
3, *n* (%)	14,445 (1.4)	1,053 (0.1)	
Low-Density Lipoprotein Cholesterol ≥ 140 mg/dL, *n* (%)	291,913 (27.5)	121,520 (14.4)	<0.001
High-Density Lipoprotein Cholesterol <40 mg/dL, *n* (%)	73,760 (6.9)	7,804 (0.9)	<0.001
Triglycerides ≥ 150 mg/dL, *n* (%)	231,337 (21.8)	38,199 (4.5)	<0.001
Low-Density Lipoprotein Cholesterol, mg/dL	120 (100-142)	107 (90-127)	<0.001
High-Density Lipoprotein Cholesterol, mg/dL	56 (47-65)	69 (60-80)	<0.001
Triglycerides, mg/dL	93 (64-140)	60 (46-83)	<0.001
Age, years	40 (35-45)	41 (36-45)	<0.001
Body Mass Index, kg/m^2	23.1 (21.1-25.5)	20.7 (19.1-23.0)	<0.001
Obesity, *n* (%)	311,137 (29.3)	120,633 (14.3)	<0.001
Waist Circumference, cm	82 (76-88)	75 (70-81)	<0.001
High Waist Circumference, *n* (%)	397,827 (37.4)	69,497 (8.2)	<0.001
Hypertension, *n* (%)	137,090 (12.9)	47,407 (5.6)	<0.001
Systolic Blood Pressure, mmHg	119 (110-128)	109 (100-119)	<0.001
Diastolic Blood Pressure, mmHg	74 (66-81)	67 (60-74)	<0.001
Diabetes Mellitus, *n* (%)	27,550 (2.6)	7,442 (0.9)	<0.001
Fasting Plasma Glucose, mg/dL	91 (86-98)	88 (83-93)	<0.001
Cigarette Smoking, *n* (%)	397,860 (37.4)	101,523 (12.0)	<0.001

Data are expressed as median (interquartile range) or number (percentage). P values were calculated using the unpaired t-test for continuous variables and chi-square tests for categorical variables.

in men and 1.25 (95% CI 1.07–1.47) in women. Multivariable adjusted HRs for AP per 1-point higher abnormal lipid profile were 1.14 (95% CI 1.12–1.16) in men and 1.18 (95% CI 1.13–1.23) in women. Multivariable adjusted HRs for stroke per 1-point higher abnormal lipid profile were 1.06 (95% CI 1.02–1.09) in men and 1.09 (95% CI 1.03–1.16) in women. Multivariable adjusted HRs for HF per 1-point higher abnormal lipid profile were 1.10 (95% CI 1.08–1.12) in men and 1.10 (95% CI 1.05–1.14) in women. The P values for interaction between men and women for MI, AP, stroke, and HF were 0.008, 0.145, 0.348, and 0.917, respectively.

Association between High LDL-C, Low HDL-C, High Triglycerides, and Incident Cardiovascular Disease

Multivariable Cox regression analyses demonstrated that the levels of LDL-C ≥ 140 mg/dL, HDL-C <40 mg/dL, and triglycerides ≥ 150 mg/dL were all associated with the development of MI, AP, and HF and the levels of LDL-C ≥ 140 mg/dL and HDL-C <40 mg/dL were associated with incident stroke in men. In women, LDL-C level ≥ 140 mg/dL alone was associated with incident MI or stroke, and the levels of LDL-C ≥ 140 mg/dL and triglycerides ≥ 150 mg/dL were associated with incident AP. The levels of HDL-C <40 mg/dL and triglycerides ≥ 150 mg/dL were associated with incident HF **(Table 3)**.

The Frequency of Events, Corresponding Incidence Rates, and Hazard Ratios for Cardiovascular Disease Events after Multiple Imputation for Missing Data

After multiple imputation for missing data, we analyzed 2,491,638 participants (1,426,120 men and 1,065,518 women). MI, AP, stroke, and HF occurred in 2,492 (0.2%), 21,138 (1.5%), 8,318 (0.6%), and 19,433 (1.4%) men and 645 (0.1%), 10,449 (1.0%), 4,654 (0.4%), and 10,761 (1.0%) women, respectively. The association between the number of abnormal lipid profiles and incident CVD stratified by sex did not change after multiple imputation for missing data **(Table 4)**.

The Frequency of Events, Corresponding Incidence Rates, and Hazard Ratios for Cardiovascular Disease Events among People aged 20–45 Years

We analyzed 845,937 men and 664,835 women aged 20–45 years. Similar to our main analysis, the

Table 2. The Frequency of Events, Corresponding Incidence Rates, and Hazard Ratios for Cardiovascular Disease Events

	Men Number of Abnormal Lipid Profiles					Women Number of Abnormal Lipid Profiles				
	0	1	2	3	*P* for trend	0	1	2	3	*P* for trend
Number	617,975	307,289	123,193	14,445		699,078	128,294	18,035	1,053	
Myocardial Infarction										
No. of Events	675	704	521	130	-----	398	119	25	3	-----
Incidence	3.2 (2.9-3.4)	6.3 (5.9-6.8)	11.5 (10.6-12.5)	24.8 (20.9-29.5)	-----	1.8 (1.7-2.0)	3.0 (2.5-3.6)	4.5 (3.0-6.6)	9.0 (3.1-26.5)	-----
Model 1	1 [Reference]	1.99 (1.79-2.21)	3.62 (3.22-4.05)	7.84 (6.50-9.46)	<0.001	1 [Reference]	1.62 (1.32-1.99)	2.45 (1.64-3.67)	4.93 (1.58-15.34)	<0.001
Model 2	1 [Reference]	1.78 (1.60-1.98)	3.19 (2.85-3.58)	7.07 (5.86-8.53)	<0.001	1 [Reference]	1.46 (1.19-1.80)	2.19 (1.46-3.29)	4.41 (1.42-13.73)	<0.001
Model 3	1 [Reference]	1.51 (1.36-1.68)	2.27 (2.01-2.56)	4.48 (3.69-5.45)	<0.001	1 [Reference]	1.28 (1.04-1.59)	1.44 (0.94-2.21)	2.46 (0.78-7.78)	0.005
Angina Pectoris										
No. of Events	8,039	5,642	2,987	406	-----	6,782	1,797	327	26	-----
Incidence	38.1 (37.3-38.9)	51.3 (49.9-52.6)	67.0 (64.7-69.5)	78.8 (71.5-86.8)	-----	31.4 (30.7-32.2)	45.3 (43.3-47.5)	59.5 (53.4-66.3)	79.8 (54.5-117.0)	-----
Model 1	1 [Reference]	1.34 (1.30-1.39)	1.76 (1.68-1.83)	2.07 (1.87-2.29)	<0.001	1 [Reference]	1.45 (1.37-1.52)	1.90 (1.70-2.12)	2.55 (1.74-3.75)	<0.001
Model 2	1 [Reference]	1.23 (1.19-1.28)	1.59 (1.52-1.66)	1.90 (1.72-2.10)	<0.001	1 [Reference]	1.30 (1.24-1.37)	1.70 (1.52-1.90)	2.28 (1.55-3.35)	<0.001
Model 3	1 [Reference]	1.11 (1.07-1.15)	1.30 (1.25-1.36)	1.52 (1.37-1.68)	<0.001	1 [Reference]	1.20 (1.14-1.27)	1.33 (1.18-1.49)	1.65 (1.12-2.43)	<0.001
Stroke										
No. of Events	3,281	2,270	1,058	152	-----	3,006	844	131	6	-----
Incidence	15.4 (14.9-16.0)	20.4 (19.6-21.3)	23.4 (22.1-24.9)	29.1 (24.8-34.1)	-----	13.9 (13.4-14.4)	21.2 (19.8-22.6)	23.6 (19.9-28.0)	18.0 (8.3-39.3)	-----
Model 1	1 [Reference]	1.32 (1.25-1.39)	1.51 (1.41-1.62)	1.88 (1.60-2.21)	<0.001	1 [Reference]	1.53 (1.42-1.65)	1.70 (1.43-2.03)	1.30 (0.58-2.89)	<0.001
Model 2	1 [Reference]	1.18 (1.12-1.24)	1.33 (1.24-1.42)	1.69 (1.44-1.99)	<0.001	1 [Reference]	1.30 (1.20-1.40)	1.43 (1.20-1.70)	1.09 (0.49-2.42)	<0.001
Model 3	1 [Reference]	1.06 (1.00-1.12)	1.08 (1.00-1.16)	1.34 (1.14-1.59)	0.001	1 [Reference]	1.17 (1.08-1.27)	1.06 (0.88-1.27)	0.73 (0.33-1.63)	0.006
Heart Failure										
No. of Events	7,396	5,285	2,756	361	-----	6,930	1,771	346	30	-----
Incidence	35.0 (34.2-35.8)	47.9 (46.6-49.2)	61.6 (59.4-64.0)	69.7 (62.9-77.3)	-----	32.1 (31.3-32.8)	44.6 (42.6-46.8)	62.9 (56.6-69.8)	91.9 (64.4-131.2)	-----
Model 1	1 [Reference]	1.36 (1.32-1.41)	1.76 (1.68-1.83)	2.00 (1.80-2.22)	<0.001	1 [Reference]	1.39 (1.32-1.47)	1.96 (1.76-2.19)	2.87 (2.01-4.11)	<0.001
Model 2	1 [Reference]	1.26 (1.21-1.30)	1.59 (1.53-1.67)	1.84 (1.66-2.05)	<0.001	1 [Reference]	1.25 (1.19-1.32)	1.75 (1.57-1.95)	2.56 (1.79-3.67)	<0.001
Model 3	1 [Reference]	1.08 (1.05-1.12)	1.20 (1.15-1.26)	1.35 (1.22-1.51)	<0.001	1 [Reference]	1.09 (1.03-1.15)	1.18 (1.06-1.32)	1.54 (1.07-2.21)	<0.001

The incidence rate was per 10000 person-years. Unadjusted and adjusted odds ratios (95% confidence intervals) associated with the number of abnormal lipid profiles are shown. Model 1 is unadjusted. Model 2 includes adjustment for age. Model 3 includes adjustment for age, obesity, high waist circumference, hypertension, diabetes mellitus, and cigarette smoking.

Table 3. Association between High LDL-C, Low HDL-C, High Triglycerides and incident Cardiovascular Disease

	Men			Women		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Myocardial Infarction						
LDL-C ≥ 140 mg/dL	2.12 (1.94-2.32)	1.97 (1.80-2.15)	1.85 (1.69-2.02)	1.64 (1.34-2.01)	1.48 (1.20-1.82)	1.34 (1.09-1.66)
HDL-C < 40 mg/dL	1.91 (1.68-2.17)	1.96 (1.73-2.22)	1.64 (1.44-1.86)	1.38 (0.70-2.72)	1.40 (0.71-2.76)	1.14 (0.57-2.25)
Triglycerides ≥ 150 mg/dL	1.81 (1.64-1.99)	1.69 (1.54-1.86)	1.32 (1.19-1.45)	1.61 (1.17-2.23)	1.54 (1.12-2.13)	1.12 (0.80-1.57)
Angina Pectoris						
LDL-C ≥ 140 mg/dL	1.31 (1.27-1.35)	1.23 (1.19-1.27)	1.17 (1.13-1.20)	1.41 (1.34-1.49)	1.27 (1.20-1.34)	1.19 (1.13-1.26)
HDL-C < 40 mg/dL	1.16 (1.10-1.22)	1.18 (1.11-1.24)	1.10 (1.04-1.16)	1.28 (1.07-1.53)	1.30 (1.08-1.56)	1.17 (0.98-1.41)
Triglycerides ≥ 150 mg/dL	1.39 (1.34-1.44)	1.31 (1.27-1.36)	1.13 (1.09-1.17)	1.44 (1.32-1.57)	1.37 (1.26-1.50)	1.15 (1.06-1.26)
Stroke						
LDL-C ≥ 140 mg/dL	1.21 (1.15-1.27)	1.11 (1.05-1.17)	1.07 (1.01-1.12)	1.43 (1.32-1.55)	1.21 (1.12-1.31)	1.12 (1.03-1.21)
HDL-C < 40 mg/dL	1.15 (1.06-1.26)	1.18 (1.08-1.29)	1.11 (1.02-1.21)	0.96 (0.71-1.30)	0.98 (0.72-1.34)	0.87 (0.64-1.18)
Triglycerides ≥ 150 mg/dL	1.32 (1.25-1.39)	1.21 (1.15-1.28)	1.02 (0.97-1.08)	1.46 (1.29-1.66)	1.36 (1.20-1.54)	1.09 (0.95-1.24)
Heart Failure						
LDL-C ≥ 140 mg/dL	1.23 (1.19-1.27)	1.16 (1.12-1.20)	1.08 (1.04-1.12)	1.30 (1.23-1.37)	1.17 (1.11-1.23)	1.05 (0.99-1.11)
HDL-C < 40 mg/dL	1.26 (1.20-1.33)	1.28 (1.21-1.35)	1.17 (1.11-1.24)	1.40 (1.18-1.66)	1.42 (1.20-1.68)	1.21 (1.02-1.43)
Triglycerides ≥ 150 mg/dL	1.42 (1.37-1.47)	1.33 (1.29-1.38)	1.08 (1.04-1.12)	1.61 (1.48-1.74)	1.53 (1.41-1.66)	1.17 (1.07-1.27)

Unadjusted and adjusted odds ratios (95% confidence intervals) associated with each abnormal lipid profile are shown. Model 1 is unadjusted. Model 2 includes adjustment for age. Model 3 includes adjustment for age, obesity, high waist circumference, hypertension, diabetes mellitus, and cigarette smoking.

incidence of MI, AP, and HF increased with the number of abnormal lipid profiles in both men and women, whereas the incidence of stroke increased with the number of abnormal lipid profiles only in men but not in women. Multivariable Cox regression analyses showed that the number of abnormal lipid profiles was dose-dependently associated with the incidence of MI, AP, stroke, and HF in men but with the incidence of MI, AP, and HF in women **(Supplementary Table 1)**. Multivariable adjusted HRs for MI per 1-point higher abnormal lipid profile were 1.53 (95% CI 1.43–1.64) in men and 1.26 (95% CI 1.00–1.55) in women. Multivariable adjusted HRs for AP per 1-point higher abnormal lipid profile were 1.12 (95% CI 1.09–1.15) in men and 1.21 (95% CI 1.15–1.28) in women. Multivariable adjusted HRs for stroke per 1-point higher abnormal lipid profile were 1.07 (95% CI 1.02–1.11) in men and 1.12 (95% CI 1.03–1.22) in women. Multivariable adjusted HRs for HF per 1-point higher abnormal lipid profile were 1.09 (95% CI 1.06–1.11) in men and 1.11 (95% CI 1.05–1.17) in women.

Discussion

Our analysis of a nationwide population-based database including approximately 2 million young adults without a history of CVD demonstrated that the number of abnormal lipid profiles was dose-dependently associated with the incidence of MI, AP, stroke, and HF in men and that of MI, AP, and HF in women. The association between the number of abnormal lipid profiles and incident MI was seemingly more pronounced in men than in women.

Dyslipidemia is widely known as one of the most important risk factors for CVD. Recent epidemiological statistics show that CVD in young adults is an urgent healthcare issue, and public health measures for CVD prevention are required. Although the association between dyslipidemia and CVD is solid, there are insufficient data for young adults. Recently, we demonstrated a close relationship between lipid profile and subsequent CVD in young adults aged < 50 years, suggesting the importance of maintaining an optimal lipid profile for the primary prevention of CVD even in young people[12].

The lipid profile is generally better in women before menopause than in men[24]. Accordingly, the number of abnormal lipid profiles was greater in men than in women, and the prevalence of high LDL-C, low HDL-C, and high triglyceride levels was higher in men than in women. In women, cholesterol levels rise after menopause and exceed those of men[25]. In this study, we focused on young people and included

Table 4. The Frequency of Events, Corresponding Incidence Rates, and Hazard Ratios for Cardiovascular Disease Events after Multiple Imputation for Missing Data

	Men					Women				
	Number of Abnormal Lipid Profiles					Number of Abnormal Lipid Profiles				
	0	1	2	3	*P* for trend	0	1	2	3	*P* for trend
Number	849,545	399,280	158,918	18,377		883,502	157,095	23,630	1,291	
Myocardial Infarction										
No. of Events	824	883	634	151	-----	474	136	32	3	-----
Incidence	2.8 (2.6-3.0)	6.1 (5.7-6.5)	10.8 (10.0-11.7)	22.5 (19.2-26.4)	-----	1.8 (1.6-1.9)	2.8 (2.4-3.3)	4.4 (3.1-6.3)	7.4 (2.5-21.7)	-----
Model 1	1 [Reference]	2.16 (1.96-2.37)	3.83 (3.45-4.24)	7.98 (6.71-9.50)	<0.001	1 [Reference]	1.59 (1.32-1.93)	2.50 (1.75-3.58)	4.17 (1.34-12.96)	<0.001
Model 2	1 [Reference]	1.85 (1.68-2.03)	3.18 (2.86-3.53)	6.75 (5.67-8.03)	<0.001	1 [Reference]	1.43 (1.18-1.73)	2.25 (1.57-3.22)	3.70 (1.19-11.52)	<0.001
Model 3	1 [Reference]	1.57 (1.43-1.73)	2.28 (2.04-2.55)	4.33 (3.61-5.19)	<0.001	1 [Reference]	1.25 (1.02-1.52)	1.48 (1.01-2.17)	2.02 (0.64-6.36)	0.004
Angina Pectoris										
No. of Events	9,993	6,942	3,710	493	-----	7,943	2,090	386	30	-----
Incidence	34.4 (33.7-35.1)	48.5 (47.4-49.7)	64.3 (62.2-66.4)	74.5 (68.2-81.4)	-----	29.9 (29.2-30.6)	43.8 (41.9-45.7)	54.2 (49.0-59.8)	75.4 (52.8-107.7)	-----
Model 1	1 [Reference]	1.41 (1.36-1.45)	1.86 (1.79-1.93)	2.17 (1.98-2.37)	<0.001	1 [Reference]	1.47 (1.40-1.54)	1.82 (1.64-2.01)	2.53 (1.77-3.62)	<0.001
Model 2	1 [Reference]	1.24 (1.20-1.28)	1.60 (1.54-1.66)	1.89 (1.72-2.06)	<0.001	1 [Reference]	1.29 (1.23-1.36)	1.61 (1.45-1.78)	2.21 (1.54-3.16)	<0.001
Model 3	1 [Reference]	1.12 (1.08-1.15)	1.31 (1.26-1.37)	1.50 (1.37-1.65)	<0.001	1 [Reference]	1.19 (1.13-1.25)	1.26 (1.13-1.40)	1.60 (1.11-2.29)	<0.001
Stroke										
No. of Events	4,027	2,783	1,331	177	-----	3,517	961	170	6	-----
Incidence	13.8 (13.4-14.2)	19.3 (18.6-20.0)	22.8 (21.6-24.0)	26.4 (22.8-30.6)	-----	13.2 (12.8-13.7)	20.0 (18.8-21.3)	23.6 (20.3-27.5)	14.8 (6.8-32.2)	-----
Model 1	1 [Reference]	1.39 (1.33-1.46)	1.64 (1.54-1.75)	1.91 (1.64-2.22)	<0.001	1 [Reference]	1.52 (1.41-1.63)	1.79 (1.54-2.09)	1.12 (0.50-2.49)	<0.001
Model 2	1 [Reference]	1.18 (1.13-1.24)	1.35 (1.27-1.44)	1.60 (1.38-1.86)	<0.001	1 [Reference]	1.27 (1.18-1.36)	1.51 (1.29-1.76)	0.92 (0.41-2.05)	<0.001
Model 3	1 [Reference]	1.05 (1.00-1.11)	1.08 (1.02-1.16)	1.25 (1.07-1.46)	0.001	1 [Reference]	1.14 (1.06-1.23)	1.12 (0.95-1.31)	0.62 (0.28-1.38)	0.005
Heart Failure										
No. of Events	9,124	6,432	3,428	449	-----	8,219	2,078	428	36	-----
Incidence	31.4 (30.7-32.0)	44.8 (43.7-45.9)	59.2 (57.2-61.2)	67.6 (61.6-74.1)	-----	30.9 (30.2-31.6)	43.5 (41.6-45.4)	60.0 (54.6-66.0)	90.5 (65.4-125.3)	-----
Model 1	1 [Reference]	1.43 (1.38-1.47)	1.88 (1.81-1.96)	2.16 (1.96-2.37)	<0.001	1 [Reference]	1.41 (1.34-1.48)	1.94 (1.76-2.14)	2.93 (2.11-4.06)	<0.001
Model 2	1 [Reference]	1.26 (1.22-1.30)	1.62 (1.55-1.68)	1.87 (1.71-2.06)	<0.001	1 [Reference]	1.25 (1.19-1.31)	1.73 (1.57-1.90)	2.57 (1.85-3.56)	<0.001
Model 3	1 [Reference]	1.08 (1.04-1.11)	1.21 (1.16-1.26)	1.36 (1.24-1.50)	<0.001	1 [Reference]	1.09 (1.03-1.14)	1.18 (1.07-1.31)	1.56 (1.12-2.17)	<0.001

The incidence rate was per 10000 person-years. Unadjusted and adjusted odds ratios (95% confidence intervals) associated with the number of abnormal lipid profiles are shown. Model 1 is unadjusted. Model 2 includes adjustment for age. Model 3 includes adjustment for age, obesity, high waist circumference, hypertension, diabetes mellitus, and cigarette smoking.

adults aged <50 years. Given that the menopausal age of Japanese women is approximately 50 years on average and the effects of menopause usually take years to manifest[26], the influence of menopause was not so large in this study. Furthermore, considering the possibility of early menopause, we conducted a sensitivity analysis including people aged 20–45 years, and our main results did not change in this sensitivity analysis.

There are sex differences in cardiometabolic risk factors and the associated subsequent CVD. For example, prolonged smoking and diabetes mellitus are significantly more hazardous for women than for men. Huxley *et al.* conducted a meta-analysis including data from 74 prospective cohort studies with nearly 2.4 million men and women and 44,000 coronary events and showed that women who smoke had a 25% greater relative risk of CVD than men, independent of differences in baseline characteristics[27]. They also showed that the relative risk of CVD was 44% greater in women with diabetes mellitus than in similarly affected men in a pooled analysis of over 850,000 individuals and 28,000 coronary events[28]. By contrast, the association between systolic blood pressure and risk of stroke was reported to be similar between men and women, using data from prospective cohort studies on more than 1.2 million individuals and over 50,000 cardiovascular events[29].

Little is known about sex differences in the relationship between dyslipidemia and incident CVD. Lewington *et al.* analyzed approximately 900,000 individuals and observed over 33,000 deaths due to coronary artery disease. They demonstrated that a lower total cholesterol level reduced the risk of mortality from CVD in both men and women, and there were no apparent sex differences[30]. Angelantonio *et al.* analyzed 302,430 people without a history of vascular disease from 68 long-term prospective studies and showed no evidence of a sex difference in the association of HDL-C and triglycerides with the risk of CVD[31]. Eslami *et al.* investigated 2,235 men aged 30–54 years and 3,703 women aged 30–64 years without a previous history of CVD and reported that high total cholesterol and low HDL-C levels, respectively, conferred a higher impact for premature CVD in men than in women[32]. Therefore, whether the association between dyslipidemia and incident CVD would be modified by sex in young population remains unclear.

In this study, the multivariable adjusted model showed that the number of abnormal lipid profiles was associated with incident CVD in both men and women. The *P* value for interaction was statistically significant for MI, whereas the *P* values for interaction were not statistically significant for AP, stroke, and HF, suggesting that the influence of the number of abnormal lipid profiles on MI was modified by sex, and the association between abnormal lipid profiles and incident MI would be more pronounced in men. It is also important that dyslipidemia was significantly associated with an increased incidence of CVD in young women. The incidence of CVD in women is generally lower than that in men. However, once it occurs, the prognosis of several CVDs such as acute MI in women is known to be worse than that in men[33, 34]. Therefore, risk stratification and preventive efforts for CVD are important in women. Considering that the risk of CVD steeply increases after menopause with a worsening lipid profile, the optimal management of lipid profiles for CVD prevention would be essential in young women.

Although in the management of dyslipidemia in our clinical practice, we are prone to focusing on high LDL-C levels more than on low HDL-C and high triglyceride levels, our study showed that low HDL-C and high triglyceride levels were also associated with incident CVD, suggesting the importance of comprehensive lipid profile management to prevent CVD among both young men and women. However, comprehensive lipid profile management was not easy. Particularly, the optimization of HDL-C is an unresolved issue in this field. Although we generally recommend patients with low HDL-C levels lifestyle modification including body weight reduction (if they were overweight or obese) and maintaining physical activity, it is difficult to normalize HDL-C levels. From this point of view, we need to clarify whether a pharmacological or non-pharmacological approach would prevent the development of CVD among young men and women. Particularly, given that we studied young people in this study, we need to consider that the mainstay of treatment for premenopausal women with dyslipidemia should be lifestyle modification rather than a pharmacological approach from the perspectives of both preventive medicine and medical economics. Further investigations are required to establish the optimal management strategy for young people with dyslipidemia.

This study has several limitations. The JMDC Claims Database is an administrative insurance database in Japan, and therefore, we need to consider the limitation of using administrative data for the CVD diagnosis (particularly, overestimation of CVD events). Some physicians might register the specific disease name only for reimbursement (e.g., biomarker measurement or imaging tests). For example, if physicians measure the serum brain natriuretic peptide

level for patients who might have HF, most physicians in Japan registered "suspect of heart failure." Therefore, we excluded participants registered having disease codes with "suspect" and analyzed only those with a fixed diagnosis for CVD. Additionally, the incidence of CVD in the JMDC Claims Database is comparable to that in other epidemiological data in Japan[35, 36]. Although data on the accuracy (e.g., sensitivity or specificity) of the diagnoses in the administrative database in Japan are limited, a previous study investigated the validity of the diagnoses of the administrative database in Japan, and the specificity of recorded diagnoses was high. For example, the specificity of MI and HF diagnosis was 99.7% and 97.5%, respectively[37]. Taking these into consideration, the possibility of misclassification (particularly, overestimation of the incidence of CVD) would not influence our results so largely. However, we should acknowledge that recorded diagnoses of administrative databases including the JMDC Claims Database are generally considered less well validated, and therefore, there remains uncertainty regarding the accuracy of diagnosis for CVD events. Although we performed multivariable Cox regression analyses, unmeasured confounders and residual bias (e.g., dietary component and socioeconomic status) could have influenced the results. Considering the age range of the study participants and the mean follow-up period, a large proportion of CVD events documented in this study were premature CVDs, and therefore, genetics might play a significant role. We should acknowledge that this would be a residual bias in this study. Since the data from the JMDC Claims Database were mainly obtained from a working-age population, selection bias (healthy worker bias) should be acknowledged. Further studies are required to generalize our results to other populations. Menopausal age was not available in the JMDC Claims Database. We also need to consider the significant changes in lipid profiles that could occur during menopausal transition when interpreting results. Further, the substantial proportion of women in this study could have primary ovarian insufficiency and early menopause, which could have influenced the results.

Conclusion

Our analysis of a nationwide population-based database showed that the incidence of CVD increased with the number of abnormal lipid profiles in both young men and women. Particularly, the relationship of the abnormal lipid profiles with the risk for subsequent MI was pronounced in men. Optimization of lipid profiles is important in both young men and women for the primary CVD prevention.

Author Contribution

Conception and design: HK, HM, HY, and IK. Analysis of data: TK, HI, SM, KM, HK, NM, TJ, and HY. Interpretation of data: HK, KF, HM. KN. HY, and IK. Drafting of the manuscript: HK, NT, and HM. Critical revision for important intellectual content: NT, HM, HY, and IK. Final approval of the submitted manuscript: SN, HY, and IK. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this paper.

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Disclosures

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References

1) Goff DC, Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Sr., Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC, Jr., Sorlie P, Stone NJ, Wilson PWF. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol, 2014; 63: 2935-2959
2) D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General

cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation, 2008; 117: 743-753
3) Kannel WB, Castelli WP, Gordon T, McNamara PM. Serum cholesterol, lipoproteins, and the risk of coronary heart disease. The Framingham study. Ann Intern Med, 1971; 74: 1-12
4) Nordestgaard BG. Triglyceride-Rich Lipoproteins and Atherosclerotic Cardiovascular Disease: New Insights From Epidemiology, Genetics, and Biology. Circ Res, 2016; 118: 547-563
5) Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Shay CM, Spartano NL, Stokes A, Tirschwell DL, VanWagner LB, Tsao CW, American Heart Association Council on E, Prevention Statistics C, Stroke Statistics S. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. Circulation, 2020; 141: e139-e596
6) Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, Ahmed M, Aksut B, Alam T, Alam K, Alla F, Alvis-Guzman N, Amrock S, Ansari H, Arnlov J, Asayesh H, Atey TM, Avila-Burgos L, Awasthi A, Banerjee A, Barac A, Barnighausen T, Barregard L, Bedi N, Belay Ketema E, Bennett D, Berhe G, Bhutta Z, Bitew S, Carapetis J, Carrero JJ, Malta DC, Castaneda-Orjuela CA, Castillo-Rivas J, Catala-Lopez F, Choi JY, Christensen H, Cirillo M, Cooper L, Jr., Criqui M, Cundiff D, Damasceno A, Dandona L, Dandona R, Davletov K, Dharmaratne S, Dorairaj P, Dubey M, Ehrenkranz R, El Sayed Zaki M, Faraon EJA, Esteghamati A, Farid T, Farvid M, Feigin V, Ding EL, Fowkes G, Gebrehiwot T, Gillum R, Gold A, Gona P, Gupta R, Habtewold TD, Hafezi-Nejad N, Hailu T, Hailu GB, Hankey G, Hassen HY, Abate KH, Havmoeller R, Hay SI, Horino M, Hotez PJ, Jacobsen K, James S, Javanbakht M, Jeemon P, John D, Jonas J, Kalkonde Y, Karimkhani C, Kasaeian A, Khader Y, Khan A, Khang YH, Khera S, Khoja AT, Khubchandani J, Kim D, Kolte D, Kosen S, Krohn KJ, Kumar GA, Kwan GF, Lal DK, Larsson A, Linn S, Lopez A, Lotufo PA, El Razek HMA, Malekzadeh R, Mazidi M, Meier T, Meles KG, Mensah G, Meretoja A, Mezgebe H, Miller T, Mirrakhimov E, Mohammed S, Moran AE, Musa KI, Narula J, Neal B, Ngalesoni F, Nguyen G, Obermeyer CM, Owolabi M, Patton G, Pedro J, Qato D, Qorbani M, Rahimi K, Rai RK, Rawaf S, Ribeiro A, Safiri S, Salomon JA, Santos I, Santric Milicevic M, Sartorius B, Schutte A, Sepanlou S, Shaikh MA, Shin MJ, Shishehbor M, Shore H, Silva DAS, Sobngwi E, Stranges S, Swaminathan S, Tabares-Seisdedos R, Tadele Atnafu N, Tesfay F, Thakur JS, Thrift A, Topor-Madry R, Truelsen T, Tyrovolas S, Ukwaja KN, Uthman O, Vasankari T, Vlassov V, Vollset SE, Wakayo T, Watkins D, Weintraub R, Werdecker A, Westerman R, Wiysonge CS, Wolfe C, Workicho A, Xu G, Yano Y, Yip P, Yonemoto N, Younis M, Yu C, Vos T, Naghavi M, Murray C. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. J Am Coll Cardiol, 2017; 70: 1-25
7) Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, Mossialos EA, Maggioni AP, Kazakiewicz D, May HT, De Smedt D, Flather M, Zuhlke L, Beltrame JF, Huculeci R, Tavazzi L, Hindricks G, Bax J, Casadei B, Achenbach S, Wright L, Vardas P, European Society of C. European Society of Cardiology: Cardiovascular Disease Statistics 2019. Eur Heart J, 2020; 41: 12-85
8) Andersson C, Vasan RS. Epidemiology of cardiovascular disease in young individuals. Nat Rev Cardiol, 2018; 15: 230-240
9) Ford ES, Capewell S. Coronary heart disease mortality among young adults in the U.S. from 1980 through 2002: concealed leveling of mortality rates. J Am Coll Cardiol, 2007; 50: 2128-2132
10) George MG, Tong X, Kuklina EV, Labarthe DR. Trends in stroke hospitalizations and associated risk factors among children and young adults, 1995-2008. Ann Neurol, 2011; 70: 713-721
11) Kissela BM, Khoury JC, Alwell K, Moomaw CJ, Woo D, Adeoye O, Flaherty ML, Khatri P, Ferioli S, De Los Rios La Rosa F, Broderick JP, Kleindorfer DO. Age at stroke: temporal trends in stroke incidence in a large, biracial population. Neurology, 2012; 79: 1781-1787
12) Kaneko H, Itoh H, Kiriyama H, Kamon T, Fujiu K, Morita K, Michihata N, Jo T, Takeda N, Morita H, Yasunaga H, Komuro I. Lipid Profile and Subsequent Cardiovascular Disease among Young Adults Aged <50 Years. Am J Cardiol, 2021; 142: 59-65
13) Yandrapalli S, Nabors C, Goyal A, Aronow WS, Frishman WH. Modifiable Risk Factors in Young Adults With First Myocardial Infarction. J Am Coll Cardiol, 2019; 73: 573-584
14) Goto A, Goto M, Terauchi Y, Yamaguchi N, Noda M. Association Between Severe Hypoglycemia and Cardiovascular Disease Risk in Japanese Patients With Type 2 Diabetes. J Am Heart Assoc, 2016; 5: e002875
15) Wake M, Onishi Y, Guelfucci F, Oh A, Hiroi S, Shimasaki Y, Teramoto T. Treatment patterns in hyperlipidaemia patients based on administrative claim databases in Japan. Atherosclerosis, 2018; 272: 145-152
16) Kawasaki R, Konta T, Nishida K. Lipid-lowering medication is associated with decreased risk of diabetic retinopathy and the need for treatment in patients with type 2 diabetes: A real-world observational analysis of a health claims database. Diabetes Obes Metab, 2018; 20: 2351-2360
17) Kaneko H, Itoh H, Yotsumoto H, Kiriyama H, Kamon T, Fujiu K, Morita K, Michihata N, Jo T, Morita H, Yasunaga H, Komuro I. Association of body weight gain with subsequent cardiovascular event in non-obese general population without overt cardiovascular disease. Atherosclerosis, 2020; 308: 39-44
18) Davis KL, Meyers J, Zhao Z, McCollam PL, Murakami M. High-Risk Atherosclerotic Cardiovascular Disease in a Real-World Employed Japanese Population: Prevalence, Cardiovascular Event Rates, and Costs. J Atheroscler Thromb, 2015; 22: 1287-1304

19) Dixon JR, Jr. The International Conference on Harmonization Good Clinical Practice guideline. Qual Assur, 1998; 6: 65-74
20) Matsuzawa Y. Metabolic syndrome--definition and diagnostic criteria in Japan. J Atheroscler Thromb, 2005; 12: 301
21) Yagi M, Yasunaga H, Matsui H, Morita K, Fushimi K, Fujimoto M, Koyama T, Fujitani J. Impact of Rehabilitation on Outcomes in Patients With Ischemic Stroke: A Nationwide Retrospective Cohort Study in Japan. Stroke, 2017; 48: 740-746
22) Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. Stat Med, 1991; 10: 585-598
23) Aloisio KM, Swanson SA, Micali N, Field A, Horton NJ. Analysis of partially observed clustered data using generalized estimating equations and multiple imputation. Stata J, 2014; 14: 863-883
24) Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Caggiula AW, Wing RR. Menopause and risk factors for coronary heart disease. N Engl J Med, 1989; 321: 641-646
25) Godsland IF, Wynn V, Crook D, Miller NE. Sex, plasma lipoproteins, and atherosclerosis: prevailing assumptions and outstanding questions. Am Heart J, 1987; 114: 1467-1503
26) Matthews KA, Crawford SL, Chae CU, Everson-Rose SA, Sowers MF, Sternfeld B, Sutton-Tyrrell K. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? J Am Coll Cardiol, 2009; 54: 2366-2373
27) Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. Lancet, 2011; 378: 1297-1305
28) Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ, 2006; 332: 73-78
29) Peters SA, Huxley RR, Woodward M. Comparison of the sex-specific associations between systolic blood pressure and the risk of cardiovascular disease: a systematic review and meta-analysis of 124 cohort studies, including 1.2 million individuals. Stroke, 2013; 44: 2394-2401
30) Prospective Studies Collaboration, Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet, 2007; 370: 1829-1839
31) Emerging Risk Factors Collaboration, Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, Wood AM, Lewington S, Sattar N, Packard CJ, Collins R, Thompson SG, Danesh J. Major lipids, apolipoproteins, and risk of vascular disease. JAMA, 2009; 302: 1993-2000
32) Eslami A, Mozaffary A, Derakhshan A, Azizi F, Khalili D, Hadaegh F. Sex-specific incidence rates and risk factors of premature cardiovascular disease. A long term follow up of the Tehran Lipid and Glucose Study. Int J Cardiol, 2017; 227: 826-832
33) Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, Lindley KJ, Vaccarino V, Wang TY, Watson KE, Wenger NK, American Heart Association Cardiovascular Disease in W, Special Populations Committee of the Council on Clinical Cardiology CoE, Prevention CoC, Stroke N, Council on Quality of C, Outcomes R. Acute Myocardial Infarction in Women: A Scientific Statement From the American Heart Association. Circulation, 2016; 133: 916-947
34) Anderson ML, Peterson ED, Brennan JM, Rao SV, Dai D, Anstrom KJ, Piana R, Popescu A, Sedrakyan A, Messenger JC, Douglas PS. Short- and long-term outcomes of coronary stenting in women versus men: results from the National Cardiovascular Data Registry Centers for Medicare & Medicaid services cohort. Circulation, 2012; 126: 2190-2199
35) Saito I, Yamagishi K, Kokubo Y, Yatsuya H, Iso H, Sawada N, Inoue M, Tsugane S. Association between mortality and incidence rates of coronary heart disease and stroke: The Japan Public Health Center-based prospective (JPHC) study. Int J Cardiol, 2016; 222: 281-286
36) Kokubo Y, Watanabe M, Higashiyama A, Nakao YM, Kusano K, Miyamoto Y. Development of a Basic Risk Score for Incident Atrial Fibrillation in a Japanese General Population- The Suita Study. Circ J, 2017; 81: 1580-1588
37) Yamana H, Moriwaki M, Horiguchi H, Kodan M, Fushimi K, Yasunaga H. Validity of diagnoses, procedures, and laboratory data in Japanese administrative data. J Epidemiol, 2017; 27: 476-482

Supplementary Table 1. The Frequency of Events, Corresponding Incidence Rates, and Hazard Ratios for Cardiovascular Disease Events in 20-45 age

	Men Number of Abnormal Lipid Profiles					Women Number of Abnormal Lipid Profiles				
	0	1	2	3	*P* for trend	0	1	2	3	*P* for trend
Number	509,222	233,429	92,177	11,109		564,085	87,800	12,218	732	
Myocardial Infarction										
No. of Events	439	406	302	80	-----	272	67	18	0	-----
Incidence	2.6 (2.4-2.9)	5.0 (4.5-5.5)	9.2 (8.3-10.3)	20.5 (16.5-25.5)	-----	1.6 (1.4-1.8)	2.5 (2.0-3.2)	4.8 (3.0-7.6)	0.0 (0.0-17.2)	-----
Model 1	1 [Reference]	1.89 (1.66-2.17)	3.50 (3.03-4.06)	7.84 (6.17-9.94)	<0.001	1 [Reference]	1.59 (1.22-2.07)	3.06 (1.90-4.94)	-----	<0.001
Model 2	1 [Reference]	1.71 (1.50-1.96)	3.10 (2.68-3.60)	7.01 (5.52-8.89)	<0.001	1 [Reference]	1.51 (1.15-1.97)	2.88 (1.79-4.64)	-----	<0.001
Model 3	1 [Reference]	1.43 (1.24-1.64)	2.14 (1.83-2.51)	4.27 (3.33-5.49)	<0.001	1 [Reference]	1.31 (0.99-1.73)	1.76 (1.04-2.95)	-----	0.024
Angina Pectoris										
No. of Events	5,500	3,595	1,841	247	-----	4,768	1,055	199	16	-----
Incidence	33.1 (32.2-33.9)	44.7 (43.2-46.2)	57.1 (54.5-59.7)	64.1 (56.6-72.6)	-----	27.7 (26.9-28.5)	39.6 (37.2-42.0)	53.9 (46.9-61.9)	73.2 (45.1-119.0)	-----
Model 1	1 [Reference]	1.35 (1.29-1.40)	1.72 (1.63-1.81)	1.94 (1.71-2.20)	<0.001	1 [Reference]	1.43 (1.34-1.53)	1.95 (1.69-2.24)	2.66 (1.63-4.34)	<0.001
Model 2	1 [Reference]	1.24 (1.19-1.30)	1.56 (1.48-1.64)	1.77 (1.56-2.01)	<0.001	1 [Reference]	1.34 (1.26-1.44)	1.81 (1.57-2.08)	2.46 (1.51-4.02)	<0.001
Model 3	1 [Reference]	1.11 (1.07-1.16)	1.26 (1.19-1.34)	1.39 (1.22-1.58)	<0.001	1 [Reference]	1.24 (1.16-1.33)	1.41 (1.21-1.63)	1.72 (1.05-2.83)	<0.001
Stroke										
No. of Events	2,008	1,325	621	100	-----	1,938	439	77	5	-----
Incidence	12.0 (11.5-12.5)	16.3 (15.5-17.2)	19.1 (17.6-20.6)	25.6 (21.1-31.2)	-----	11.2 (10.7-11.7)	16.4 (14.9-18.0)	20.6 (16.5-25.8)	22.4 (9.6-52.5)	-----
Model 1	1 [Reference]	1.35 (1.26-1.45)	1.57 (1.44-1.72)	2.13 (1.74-2.61)	<0.001	1 [Reference]	1.46 (1.32-1.62)	1.84 (1.47-2.31)	2.00 (0.83-4.81)	<0.001
Model 2	1 [Reference]	1.22 (1.14-1.31)	1.39 (1.27-1.52)	1.90 (1.55-2.32)	<0.001	1 [Reference]	1.32 (1.19-1.46)	1.63 (1.30-2.05)	1.78 (0.74-4.27)	<0.001
Model 3	1 [Reference]	1.07 (1.00-1.15)	1.09 (0.99-1.20)	1.43 (1.17-1.76)	0.002	1 [Reference]	1.17 (1.05-1.31)	1.16 (0.91-1.47)	1.08 (0.45-2.62)	0.007
Heart Failure										
No. of Events	4,986	3,319	1,722	238	-----	4,892	1,010	218	20	-----
Incidence	29.9 (29.1-30.8)	41.1 (39.8-42.6)	53.2 (50.8-55.8)	61.6 (54.3-70.0)	-----	28.4 (27.6-29.2)	37.8 (35.6-40.2)	59.0 (51.6-67.3)	91.3 (59.1-141.0)	-----
Model 1	1 [Reference]	1.37 (1.31-1.43)	1.77 (1.67-1.87)	2.06 (1.81-2.34)	<0.001	1 [Reference]	1.33 (1.25-1.43)	2.08 (1.82-2.38)	3.22 (2.07-4.99)	<0.001
Model 2	1 [Reference]	1.27 (1.21-1.33)	1.62 (1.53-1.71)	1.89 (1.66-2.16)	<0.001	1 [Reference]	1.25 (1.17-1.33)	1.92 (1.68-2.20)	2.98 (1.92-4.62)	<0.001
Model 3	1 [Reference]	1.07 (1.03-1.12)	1.18 (1.11-1.25)	1.33 (1.16-1.51)	<0.001	1 [Reference]	1.08 (1.00-1.15)	1.26 (1.09-1.46)	1.67 (1.07-2.60)	<0.001

The incidence rate was per 10000 person-years. Unadjusted and adjusted odds ratios (95% confidence intervals) associated with the number of abnormal lipid profiles are shown. Model 1 is unadjusted. Model 2 includes adjustment for age. Model 3 includes adjustment for age, obesity, high waist circumference, hypertension, diabetes mellitus, and cigarette smoking.