Table 1 Baseline characteristics of 4348 men according to marine-derived n-3 fatty acids intake: NIPPON DATA80

	Low intake (<0.35% kcal) n=2111	High intake (≥0.35% kcal) n=2237	p Value
Age—years*	48.6 (13.0)	49.9 (13.1)	<0.001
Ex-smoker—no. (%)	394 (18.7)	389 (17.4)	0.274
Current smoker—no. (%)	1323 (62.7)	1440 (64.4)	0.244
Alcohol drinker—no. (%)	1549 (73.4)	1717 (76.8)	0.010
Body mass index—kg/m²*	23.4 (3.2)	22.5 (2.8)	0.292
Serum total cholesterol—mg/dl*	186.1 (33.3)	186.9 (32.3)	0.260
Blood glucose—mg/dl*	100.2 (31.6)	101.7 (32.6)	0.010
Systolic blood pressure—mm Hg*	137.2 (21.1)	138.6 (20.7)	0.004
Diastolic blood pressure—mm Hg*	83.4 (12.4)	83.5 (12.2)	0.515
Antihypertensive drug user—no. (%)	190 (9.0)	218 (9.7)	0.400
J-point elevation on electrocardiography—no. (%)	140 (6.6)	200 (8.9)	0.005
Heart rate—beats/min*	67.5 (11.2)	67.0 (10.8)	0.317
Left ventricular hypertrophy on electrocardiography—no. (%)†	508 (24.1)	554 (24.8)	0.591
Suspected coronary heart disease on electrocardiography—no. (%)‡	97 (4.6)	109 (4.9)	0.667

*Mean (SD).
†Diagnosis of left ventricular hypertrophy was based on Minnesota Code 3.1 or 3.3.
‡Suspicion of coronary heart disease was based on Minnesota Code 1.1–1.3, 5.1–5.2 or 4.1–4.3.
NIPPON DATA80, National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged, 1980.

The baseline nutritional parameters in both groups of participants are shown in table 2. The mean dietary MDn3FAs intakes in the low and high intake groups were 0.23%kcal (0.62 g/day) and 0.57%kcal (1.49 g/day), respectively. The high intake group had higher intake of sodium, fibre, vegetables, fruit, fish and shellfish, and polyunsaturated fatty acids than the low intake group. In contrast, the high intake group had less total energy intake and had lower intake of meat, total fat, α-linolenic acid (ALA), and trans fatty acids.

During the 24-year follow-up period (mean, 20.4±6.1 years), 1322 participants (30.4%) died from any causes, and 200 participants (4.6%) died from cardiac causes (80 from coronary heart disease, 1.8%; 25 from arrhythmia, 0.6%); they included 94 (4.4%) in the low intake group and 106 (4.7%) in the high intake group.

The results of the Cox proportional hazards models are presented in table 3. In the low MDn3FAs intake group, the risk of cardiac death was significantly higher in men with JPE than in men without JPE (adjusted HR 3.51; 95% CI 1.84 to 6.71; p< 0.001). In contrast, JPE did not increase the risk of cardiac death in the high intake group (adjusted HR 1.09; 95% CI 0.56 to 2.16; p=0.795). The test for a multiplicative interaction between JPE and dietary MDn3FAs intake on the risk of cardiac death was statistically significant (p for interaction=0.006). Because further adjustment for other nutritional parameters (ie, total energy intake and intake of vegetables, fruit, meat, monounsaturated fatty acids, total fat, and trans fatty acids) did not appreciably alter the results, we did not include these factors in the final model. There was no evidence of a multiplicative interaction between JPE and dietary MDn3FAs intake on the risk of all-cause death (p for interaction=0.749).

Figure 1 and online supplementary table S1 indicate the multivariable adjusted HRs and 95% CIs of cardiac death among the groups according to the four categories cross-classified by MDn3FAs (high or low intake) and JPE (absence or presence). Compared with the high intake group without JPE, the low intake group with JPE had a significantly elevated risk of cardiac death (adjusted HR 3.55; p<0.001). However, the high intake group with JPE did not have a significantly elevated risk (adjusted HR 1.12; p=0.736).

In the secondary analyses according to EPA or DHA intake, the risk of cardiac death related to JPE was significantly higher among men with a low intake of EPA (HR 3.27) or DHA (HR 3.44), but not among men with a high intake (p for interaction between JPE and MDn3FAs intake: 0.006 for EPA, 0.005 for DHA) (see online supplementary table S2). However, we observed no evidence of an interaction between JPE and other nutritional parameters on the risk of cardiac death (ie, total calorie intake and intake of vegetables, fruit, meat, ALA, polyunsaturated fatty acids, monounsaturated fatty acids, saturated

Table 2 Baseline nutritional variables among 4348 men according to marine-derived n-3 fatty acids intake: NIPPON DATA80

	Low intake (<0.35%kcal) n=2111	High intake (≥0.35%kcal) n=2237	p Value
Total energy intake—kcal*	2431.3 (470.2)	2384.0 (486.4)	0.001
Vegetables—g/1000 kcal*	117.0 (42.1)	123.0 (45.4)	<0.001
Fruit—g/1000 kcal*	55.9 (37.4)	60.8 (40.8)	<0.001
Meat—g/1000 kcal*	31.7 (16.0)	27.9 (16.8)	<0.001
Fish and shellfish—g/1000 kcal*	38.5 (17.0)	65.2 (24.9)	<0.001
Marine-derived n-3 fatty acids—%kcal*	0.23 (0.07)	0.57 (0.22)	<0.001
α-Linolenic acid—%kcal*	0.66 (0.24)	0.64 (0.25)	0.002
Polyunsaturated fatty acids—%kcal*	5.14 (1.36)	5.41 (1.39)	<0.001
Monounsaturated fatty acids—%kcal*	7.44 (1.94)	7.49 (1.95)	0.870
Saturated fatty acids—%kcal*	5.70 (1.46)	5.65 (1.46)	0.201
Total fat—%kcal*	20.4 (5.2)	19.8 (5.2)	<0.001
Trans fatty acids—%kcal*	0.35 (0.19)	0.29 (0.19)	<0.001
Sodium—g/1000 kcal*	2.31 (0.74)	2.65 (0.87)	<0.001
Fibre—g/1000 kcal*	7.56 (1.72)	7.66 (1.77)	0.009

*Mean (SD).
NIPPON DATA80, National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged, 1980.

Epidemiology

Table 3 HRs and 95% CIs for cardiac and all-cause death according to the presence and absence of J-point elevation by low and high marine-derived n-3 fatty acids intake: a 24-year follow-up of NIPPON DATA80

		J-point elevation (−)	J-point elevation (+)	p Value
Cardiac death				
Low intake (<0.35%kcal)	No. of deaths/no. at risk	82/1971	12/140	
	Model 1*	1.00	3.03 (1.65–5.57)	<0.001
	Model 2*	1.00	3.52 (1.86–6.67)	<0.001
	Model 3*	1.00	3.51 (1.84–6.71)	<0.001
High intake (≥0.35%kcal)	No. of deaths/no. at risk	95/2037	11/200	
	Model 1*	1.00	1.59 (0.85–2.99)	0.149
	Model 2*	1.00	1.13 (0.58–2.20)	0.724
	Model 3*	1.00	1.09 (0.56–2.16)	0.795
p Value for interaction between J-point elevation and marine-derived n-3 fatty acids intake in model 3			0.006	
All-cause death				
Low intake (<0.35%kcal)	No. of deaths/no. at risk	579/1971	31/140	
	Model 1*	1.00	1.01 (0.71–1.46)	0.936
	Model 2*	1.00	1.06 (0.73–1.54)	0.760
	Model 3*	1.00	1.04 (0.71–1.51)	0.843
High intake (≥0.35%kcal)	No. of deaths/no. at risk	646/2037	66/200	
	Model 1*	1.00	1.30 (1.01–1.67)	0.045
	Model 2*	1.00	1.10 (0.85–1.44)	0.466
	Model 3*	1.00	1.10 (0.84–1.44)	0.476
p Value for interaction between J-point elevation and marine-derived n-3 fatty acids intake in model 3			0.749	

Model 1 was adjusted for age. Model 2 was adjusted for age, body mass index, smoking status, drinking habits, medication status, systolic blood pressure, serum total cholesterol, blood glucose, heart rate, left ventricular hypertrophy on electrocardiography (classified according to Minnesota Code 3.1 or 3.3) and suspected coronary heart disease on electrocardiography (classified according to Minnesota Code 1.1–1.3, 5.1–5.2 or 4.1–4.3). Model 3 was adjusted for polyunsaturated fatty acids intake, saturated fatty acids intake, sodium intake and fibre intake in addition to the variables included in model 2.
*HR (95% CI).
NIPPON DATA80, National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged, 1980.

fatty acids, total fat, trans fatty acids, sodium, and fibre) (data not shown). There was no evidence of a multiplicative interaction between JPE and dietary EPA or DHA intake on the risk of all-cause death (p for interaction=0.806 for EPA, 0.712 for DHA) (see online supplementary table S2).
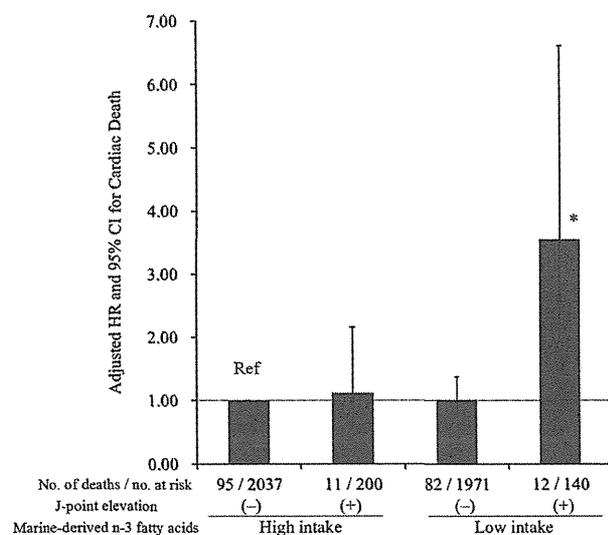

Figure 1 HRs and 95% CIs of cardiac death according to four categories cross-classified by marine-derived n-3 fatty acids (high or low intake) and J-point elevation (absence or presence). The high intake group without J-point elevation served as the reference category. HRs were adjusted for the variables included in model 3 in table 3. Vertical I bars indicate 95% CIs. Significant differences in the HRs: *p<0.001. Ref=reference.

DISCUSSION

In this 24-year prospective study of representative Japanese men who participated in the national surveys, the increased risk of cardiac death associated with JPE was attenuated by higher dietary intake of MDn3FAs, which remained after adjustment for possible confounding factors. This association persisted in secondary analyses of two groups of MDn3FAs, namely, EPA and DHA. To our knowledge, this is the first study to reveal an interaction between dietary MDn3FAs intake and JPE on the risk of cardiac death.

Consistent with previous studies,[9][20] it is possible that ventricular arrhythmia was the main direct cause of cardiac death among participants with JPE in our study. The arrhythmic risks of JPE have mainly been reported in studies of Western populations, where fish intake is lower than in Japan.[11] Japanese tend to consume more fish, and mortality from sudden death is much lower in Japan than in Western countries.[6] Furthermore, some epidemiological[1] and clinical[4] studies have shown that high n-3 fatty acids intake from seafood is associated with a lower risk of sudden death caused by cardiac arrhythmias. Taken together, our data suggest that increased dietary MDn3FAs intake may account for a reduction in ventricular arrhythmias associated with JPE.

The apparent beneficial effect of MDn3FAs on the risk of cardiac death associated with JPE may be partly due to their antiarrhythmic effects, as demonstrated in experimental models.[8] Feasible mechanisms for these antiarrhythmic effects of MDn3FAs include rapid moderation of sodium, potassium and L-type calcium channels without incorporation of MDn3FAs into the cell membranes;[21] inhibition of thromboxane production;[22] decreased levels of inflammatory mediators, such as interleukin-1β and tumour necrosis factor-α;[23] and modulation of autonomic function (increasing heart rate variability).[24] Therefore, MDn3FAs may reduce the risk of sudden

death from cardiac arrhythmias associated with JPE through one or more of these mechanisms. However, we disclosed the benefit of MDn3FAs on the risk of cardiac death associated with JPE, not on the risk of sudden cardiac death from arrhythmia. Accordingly, a potential interaction between dietary MDn3FAs intake and JPE on the risk of sudden cardiac death remains unclear and deserves further investigation.

A favourable risk reduction of cardiac death associated with JPE was observed in men with higher dietary intake of MDn3FAs (EPA and DHA), but not in those with higher dietary intake of plant-derived n-3 fatty acid (ALA). Some studies have suggested that ALA may have biological properties that are independent of its conversion to EPA and DHA,[8] [25] although this beneficial effect remains controversial.[6] However, two principal MDn3FAs—EPA and DHA—may play similarly important roles in protecting against the increased risk of cardiac death associated with JPE.

The strengths of our study include its prospective design and 24-year follow-up of participants in the national circulatory and nutritional surveys from randomly selected health districts in Japan. Although a recent meta-analysis including 20 randomised clinical trials, the majority of which were short-term studies ranged from 1 to 6.2 years, reported that n-3 fatty acids supplementation was unexpectedly weakly associated with a lower risk of cardiac death,[26] we could observe very long-term effects of MDn3FAs against the cardiac risk of JPE. Furthermore, our dietary assessment using weighed food records during 3 days would appear to be well suited for a large-scale prospective study in which a broad evaluation of diet is usually desirable.[27]

There are some limitations to our findings. First, the number of deaths was too small to comprehensively analyse the prognostic significance of arrhythmic deaths associated with JPE and the dose–response effects between intake of MDn3FAs and death among men with JPE. During the 24-year follow-up period, we observed a quite low prevalence of JPE (n=340, 7.8%), particularly with only 140 in the low MDn3FAs intake group, and a low cardiac mortality. Second, our definition of JPE, which is in accordance with Minnesota Code 9.2, is different from that used in other studies. However, JPE has still not been clearly defined.[10] [28] [29] Olson and coworkers used a similar definition to ours (including JPE in the anterior leads and one lead affection) and reported that JPE was associated with an increased risk of sudden cardiac death.[10] Third, the use of death certificate data may lead to misclassification in the causes of deaths. It was reported that most cases of sudden cardiac death tend to be described as coronary heart disease or heart failure on Japanese death certificates.[30] However, in our study, we addressed this problem by incorporating coronary heart disease and heart failure deaths into the category of cardiac death. Fourth, nutrient intake was based on a baseline measurement for 3 days, and it may not accurately reflect long-term MDn3FAs intake in the follow-up period. Fifth, our analyses were limited to men, and our results should not be generalised to women. Finally, the interaction between dietary MDn3FAs intake and JPE on the risk of cardiac death could be due to residual confounding by other unmeasured dietary or lifestyle factors.

In conclusion, in this long-term prospective observation study of Japanese men, the increased risk of cardiac death associated with JPE was attenuated in those with higher dietary MDn3FAs intake. These results suggest that higher dietary MDn3FAs intake may prevent cardiac deaths associated with JPE. Further studies are necessary to confirm these findings in other populations, particularly in women, and to identify the cellular mechanisms underlying the influence of MDn3FAs intake on

cardiac deaths associated with JPE. If the observed association is indeed causal, increased intake of MDn3FAs by eating more fish or by taking dietary supplements may be a useful, low cost intervention for people with JPE.

Author affiliations
[1]Center for Epidemiologic Research in Asia, Shiga University of Medical Science, Otsu, Japan
[2]Department of Health Science, Shiga University of Medical Science, Otsu, Japan
[3]Department of Cardiovascular and Respiratory Medicine, Shiga University of Medical Science, Otsu, Japan
[4]Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan
[5]Department of School Nursing and Health Education, Osaka Kyoiku University, Osaka, Japan
[6]Section of Shokuiku, Department of Nutritional Education, National Institute of Health and Nutrition, Tokyo, Japan
[7]Faculty of Health and Nutrition, Bunkyo University, Chigasaki, Japan
[8]Department of Food Science and Nutrition, Osaka City University, Osaka, Japan
[9]Department of Medical Statistics, Shiga University of Medical Science, Otsu, Japan
[10]Cardiovascular Epidemiology, Kyoto Women's University, Kyoto, Japan
[11]Department of Preventive Medicine and Public Health, Keio University, Tokyo, Japan
[12]First Institute for Health Promotion and Health Care, Tokyo, Japan

REFERENCES
1 Albert CM, Hennekens CH, O'Donnell CJ, et al. Fish consumption and risk of sudden cardiac death. JAMA 1998;279:23–8.
2 Hu FB, Bronner L, Willett WC, et al. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. JAMA 2002;287:1815–21.
3 Leaf A, Kang JX, Xiao YF, et al. Clinical prevention of sudden cardiac death by n-3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by n-3 fish oils. Circulation 2003;107:2646–52.
4 GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Lancet 1999;354:447–55.
5 Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1223–30.
6 De Caterina R. n-3 Fatty acids in cardiovascular disease. N Engl J Med 2011;364:2439–50.
7 Mozaffarian D, Wu JH. Omega-3 Fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol 2011;58:2047–67.
8 Billman GE, Kang JX, Leaf A. Prevention of sudden cardiac death by dietary pure omega-3 polyunsaturated fatty acids in dogs. Circulation 1999;99:2452–7.
9 Tikkanen JT, Anttonen O, Junttila MJ, et al. Long-term outcome associated with early repolarization on electrocardiography. N Engl J Med 2009;361:2529–37.
10 Olson KA, Viera AJ, Soliman EZ, et al. Long-term prognosis associated with J-point elevation in a large middle-aged biracial cohort: the ARIC study. Eur Heart J 2011;32:3098–106.

11 Ueshima H, Stamler J, Elliott P, et al. Food omega-3 fatty acid intake of individuals (total, linolenic acid, long-chain) and their blood pressure: INTERMAP study. Hypertension 2007;50:313–19.

12 Okamura T, Hayakawa T, Kadowaki T, et al. Resting heart rate and cause-specific death in a 16.5-year cohort study of the Japanese general population. Am Heart J 2004;147:1024–32.

13 Nakamura Y, Okamura T, Higashiyama A, et al. Prognostic values of clockwise and counterclockwise rotation for cardiovascular mortality in Japanese subjects: a 24-year follow-up of the national integrated project for prospective observation of noncommunicable disease and its trends in the aged, 1980–2004 (NIPPON DATA80). Circulation 2012;125:1226–33.

14 Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation 2005;111:659–70.

15 Nakamura Y, Okuda N, Turin TC, et al. Comparison of the National Nutritional Survey in Japan estimated individual-based nutritional data and NIPPON DATA80 food frequency questionnaires. J Epidemiol 2010;20(Suppl 3):S582–6.

16 Ministry of Health and Welfare. Annual report of the National Nutrition Survey in 1980. Tokyo: Daiichi Shuppan Publishing, 1982.

17 Okuda N, Miura K, Yoshita K, et al. Integration of data from NIPPON DATA80/90 and National Nutrition Survey in Japan: for cohort studies of representative Japanese on nutrition. J Epidemiol 2010;20(Suppl 3):S506–14.

18 Iwaoka H, Yoshiike N, Date C, et al. A validation study on a method to estimate nutrient intake by family members through a household-based food-weighing survey. J Nutr Sci Vitaminol (Tokyo) 2001;47:222–7.

19 Rumana N, Turin TC, Miura K, et al. Prognostic value of ST-T abnormalities and left high R waves with cardiovascular mortality in Japanese (24-year follow-up of NIPPON DATA80). Am J Cardiol 2011;107:1718–24.

20 Haissaguerre M, Derval N, Sacher F, et al. Sudden cardiac arrest associated with early repolarization. N Engl J Med 2008;358:2016–23.

21 Kang JX, Leaf A. Antiarrhythmic effects of polyunsaturated fatty acids. Recent studies. Circulation 1996;94:1774–80.

22 Nair SS, Leitch JW, Falconer J, et al. Prevention of cardiac arrhythmia by dietary (n-3) polyunsaturated fatty acids and their mechanism of action. J Nutr 1997;127:383–93.

23 Endres S, Ghorbani R, Kelley VE, et al. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. N Engl J Med 1989;320:265–71.

24 Christensen JH, Skou HA, Fog L, et al. Marine n-3 fatty acids, wine intake, and heart rate variability in patients referred for coronary angiography. Circulation 2001;103:651–7.

25 Kromhout D, Giltay EJ, Geleijnse JM. n-3 fatty acids and cardiovascular events after myocardial infarction. N Engl J Med 2010;363:2015–26.

26 Rizos EC, Ntzani EE, Bika E, et al. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. JAMA 2012;308:1024–33.

27 Thompson FE, Subar AF. Dietary assessment methodology. In: Coulson AM, Rock CL, Monsen ER, eds. Nutrition in the prevention and treatment of disease. San Diego, CA: Academic Press, 2001:3–39.

28 Uberoi A, Jain NA, Perez M, et al. Early repolarization in an ambulatory clinical population. Circulation 2011;124:2208–14.

29 Turagam MK, Velagapudi P, Kocheril AG. Early repolarization on electrocardiogram: benign or not? Am J Cardiol 2011;108:1841.

30 Saito I, Folsom AR, Aono H, et al. Comparison of fatal coronary heart disease occurrence based on population surveys in Japan and the USA. Int J Epidemiol 2000;29:837–44.

8. 体格指数（body mass index）・過体重・肥満が冠動脈疾患と脳卒中に及ぼす作用とその代謝性媒介危険因子—97の前向きコホート，180万人のプール解析

（NIPPON DATA研究グループとして国際的メタ解析研究に参加）

【背景】

　世界的には、糖尿病患者数と集団におけるBMIレベルの増加が認められる一方、平均血圧およびコレステロール値は不変、または減少傾向がみられる。本研究では、BMIが血圧・コレステロール・血糖の上昇を通じて、あるいはそれらとは独立して、脳心血管疾患発症にどの程度影響を与えるか検討した。

【方法】

　1948〜2005年に実施された97の前向きコホート研究より、180万人のデータをプールした。冠動脈疾患は57,161名、脳卒中は31,093名であった。各コホートにおいて、18歳未満、BMI 20 kg/m² 未満、脳心血管既往歴のある対象者は除外した。BMIの冠動脈疾患と脳卒中におけるハザード比を算出した。ハザード比はすべて、性・年齢・喫煙習慣の有無で調整した。また、肥満と上記疾患を媒介する危険因子である血圧・コレステロール・血糖の3危険因子について、可能なすべての組み合わせによる調整を加えたハザード比も算出した。各コホートのハザード比をプールし、ランダム効果モデルを用いて推定した。BMIに上記の3危険因子を加えることによるハザード比の減少量も算出した。

【結果】

　BMI 5 kg/m² 増加ごとのハザード比は、冠動脈疾患において1.27（95%信頼区間：1.23-1.31）、脳卒中において1.18（95%信頼区間：1.14-1.22）であった（図1）。上記3つの媒介危険因子すべてで調整したハザード比は、冠動脈疾患において1.15（95%信頼区間：1.12-1.18）、脳卒中において1.04（95%信頼区間：1.01-1.08）であった。すなわち、BMI増加による疾患リスクの上昇のうち、冠動脈疾患では46%（95%信頼区間：42-50%）、脳卒中では76（65-91）%がこれら危険因子を介して説明された。3危険因子のうち血圧の寄与率が最も大きく、冠動脈疾患で31%（28-35）、脳卒中で65%（56-75）であった。これら危険因子の各疾患への寄与について、アジアと西洋とのコホート間に有意な差はみられなかった。正常体重（BMI 25未満）に比べると過体重（BMI 25以上30未満）、および肥満（BMI 30以上）についてもリスク増加がみられた。3危険因子が媒介する割合について、冠動脈疾患では正常体重を基準とした過体重者のリスク上昇の50%（44-58）、肥満者のリスク上昇の44%（41-48）が、これらの危険因子を介して説明された。同様に、脳卒中では過体重者のリスク上昇の98%（69-155）、肥満者のリス

ク上昇の 69％（64-77）が、3 つの危険因子を介して説明された。

【結論】
BMI 高値による冠動脈疾患リスク上昇の約 5 割、および脳卒中リスク上昇の約 4 分の 3 が高血圧・脂質高値・高血糖の 3 危険因子を介して生じることが明らかとなった。脳心血管疾患予防効果を最大限得るためには、適正体重を維持することが必要と考えられる。

Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1·8 million participants

The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effects)*

Summary

Background Body-mass index (BMI) and diabetes have increased worldwide, whereas global average blood pressure and cholesterol have decreased or remained unchanged in the past three decades. We quantified how much of the effects of BMI on coronary heart disease and stroke are mediated through blood pressure, cholesterol, and glucose, and how much is independent of these factors.

Methods We pooled data from 97 prospective cohort studies that collectively enrolled 1·8 million participants between 1948 and 2005, and that included 57 161 coronary heart disease and 31 093 stroke events. For each cohort we excluded participants who were younger than 18 years, had a BMI of lower than 20 kg/m², or who had a history of coronary heart disease or stroke. We estimated the hazard ratio (HR) of BMI on coronary heart disease and stroke with and without adjustment for all possible combinations of blood pressure, cholesterol, and glucose. We pooled HRs with a random-effects model and calculated the attenuation of excess risk after adjustment for mediators.

Findings The HR for each 5 kg/m² higher BMI was 1·27 (95% CI 1·23–1·31) for coronary heart disease and 1·18 (1·14–1·22) for stroke after adjustment for confounders. Additional adjustment for the three metabolic risk factors reduced the HRs to 1·15 (1·12–1·18) for coronary heart disease and 1·04 (1·01–1·08) for stroke, suggesting that 46% (95% CI 42–50) of the excess risk of BMI for coronary heart disease and 76% (65–91) for stroke is mediated by these factors. Blood pressure was the most important mediator, accounting for 31% (28–35) of the excess risk for coronary heart disease and 65% (56–75) for stroke. The percentage excess risks mediated by these three mediators did not differ significantly between Asian and western cohorts (North America, western Europe, Australia, and New Zealand). Both overweight (BMI ≥25 to <30 kg/m²) and obesity (BMI ≥30 kg/m²) were associated with a significantly increased risk of coronary heart disease and stroke, compared with normal weight (BMI ≥20 to <25 kg/m²), with 50% (44–58) of the excess risk of overweight and 44% (41–48) of the excess risk of obesity for coronary heart disease mediated by the selected three mediators. The percentages for stroke were 98% (69–155) for overweight and 69% (64–77) for obesity.

Interpretation Interventions that reduce high blood pressure, cholesterol, and glucose might address about half of excess risk of coronary heart disease and three-quarters of excess risk of stroke associated with high BMI. Maintenance of optimum bodyweight is needed for the full benefits.

Funding US National Institute of Health, UK Medical Research Council, National Institute for Health Research Comprehensive Biomedical Research Centre at Imperial College Healthcare NHS Trust, Lown Scholars in Residence Program on cardiovascular disease prevention, and Harvard Global Health Institute Doctoral Research Grant.

Introduction

Cardiovascular diseases, especially coronary heart disease and stroke, are the leading causes of death worldwide.[1] High body-mass index (BMI) is an important cardiovascular disease risk factor,[2–4] and raised blood pressure, cholesterol, and glucose partly mediate its effects.[5,6] Present behavioural interventions for weight management are only effective in the short term,[7,8] most weight-loss drugs lack either sustained efficacy or an acceptable safety profile,[9,10] and surgical methods are recommended only for very obese individuals.[11,12] This situation has created concerns about a potentially massive worldwide increase in cardiovascular diseases as a result of increased BMI and prevalence of overweight and obesity in most countries.[13–15] By contrast, effective clinical and public health interventions for blood pressure and cholesterol are available, as evidenced by large decreases in these measures in some countries despite rises in obesity.[14,16,17] Therefore, an important clinical and public health question is: to what extent can the adverse effects of high BMI be mitigated by targeting its metabolic mediators?

To answer this question we need a detailed understanding of how much of the effect of excess weight on cardiovascular disease is mediated by these metabolic factors, separately and in combinations, which are relevant for individual patients or populations. Whether the extent

of mediation differs by population characteristics is also important to understand—eg, Asian versus western populations (North America, western Europe, Australia, and New Zealand)—because of physiological differences in how BMI affects intermediate metabolic risks or differences in the extent to which health-care systems have addressed the mediating metabolic risks.

Some researchers have investigated the mediated effects of BMI on coronary heart disease through blood pressure, cholesterol, and diabetes together;[3,18–21] fewer studies have been done for stroke,[3,19,22,23] which is the largest cause of death in Asian populations.[1] However, these studies did not assess whether characteristics of study populations affect the extent of mediation because the number of events was insufficient or data were comprised of participants from one or two regions. Importantly, these studies did not quantify the role of individual mediators or all possible combinations of two mediators that are needed to select clinical and public health interventions.

We quantified how much of the effects of high BMI, overweight, and obesity, on coronary heart disease and stroke are mediated through blood pressure, serum cholesterol, and glucose, individually and in all possible combinations by analysing data from 97 prospective cohort studies. We also assessed whether the extent of mediation was modified by geographical region, study period, and other characteristics of study populations.

Methods

Cohort identification and selection

We identified cohorts through a review of published articles and through the National Heart, Lung, and Blood Institute (NHLBI, Bethesda, MD, USA), and through personal communication with researchers.

Two reviewers independently assessed the studies and deemed them eligible if they met the following criteria: prospective design with at least 1 year of follow-up; participants were not selected based on previous history

	Number of cohorts
Blood pressure	
Systolic blood pressure	95
Hypertension	2
Cholesterol	
Total serum cholesterol	86
HDL cholesterol	1
Hypercholesterolaemia	1
Blood glucose	
Fasting glucose	39
Postprandial glucose*	18
Haemoglobin A_{1c}	1
Diabetes	19

*One cohort reported casual (or random) glucose. For each cohort, only one metric was extracted for each mediator in the main analysis.

Table 1: Mediators analysed by participating cohorts in the main analysis

of coronary heart disease or stroke; height and weight were measured at baseline; at least one of the mediators (blood pressure, serum cholesterol, and blood glucose, or diabetes) was also measured at baseline; fatal or non-fatal coronary heart disease or both, or stroke were ascertained during follow-up.

We contacted investigators from 126 eligible cohorts, of which 68 (54%) agreed to participate. Seven of these cohorts were subsequently excluded because the participants all had previous cardiovascular disease (three studies), the reported outcome was only total cardiovascular disease (three studies), or the analysis could not adjust for smoking (one study). Collaborating Group members of the other 61 cohorts reanalysed their data with a consistent protocol. We obtained additional data from nine cohorts through a special request to the NHLBI and from 27 cohorts in the Asia Pacific Cohort Studies Collaboration (APCSC) through its participation in the Global Burden of Metabolic Risk Factors for Chronic Diseases Study.[14–17]

We analysed data from 97 prospective cohort studies. Of these, nine studies were not included in the coronary heart disease analysis and 11 in the stroke analysis because they did not report the corresponding disease outcome or had fewer than five events. All data were de-identified, and the study protocol was approved by the institutional review board at the Harvard School of Public Health (Boston, MA, USA).

Eligibility, exposure definition, mediators, and potential confounders

In each cohort, we excluded participants who were younger than 18 years; had a BMI of lower than 20 kg/m²; had a history of coronary heart disease or stroke before enrolment; were missing data for age, sex, smoking status, height, or weight; or did not have data for mediators at baseline. We used BMI as the main measure of adiposity because it was measured in every cohort; data for waist circumference or waist-to-hip ratio were available in 17 cohorts and were analysed in sensitivity analyses. In the primary analysis, we accepted different metrics for mediators, including systolic blood pressure or hypertension status for blood pressure; total, HDL and LDL cholesterol concentrations, or hypercholesterolaemia for serum cholesterol; and fasting and postprandial glucose, haemoglobin A_{1c}, or diabetes status for blood glucose. Table 1 shows the number of cohorts providing each measure and the appendix (pp 8–14) provides cohort details. We adjusted for age, sex, and smoking status as the minimum set of potential confounders, and for additional variables in individual cohorts as available (appendix, pp 8–14). We obtained data for BMI, mediators, and potential confounder from baseline examinations.

Follow-up and outcome definitions

Our primary outcomes were the first occurrence of coronary heart disease or stroke event. Coronary heart

disease included fatal or non-fatal ischaemic heart disease, including acute myocardial infarction and angina pectoris; stroke included fatal or non-fatal cerebral infarction, and intracerebral or subarachnoid haemorrhage. We followed up each participant until the first occurrence of the corresponding outcome, death, or loss to follow-up, whichever occurred first.

Statistical analysis

We used Cox proportional hazards regression to estimate the hazard ratios (HRs) in each cohort. We analysed BMI as a continuous variable in relation to risk of coronary heart disease and stroke after excluding participants with a BMI of less than 20 kg/m² at baseline because the associations of BMI with the risks of death from coronary heart disease and stroke are continuous and roughly log-linear except at low BMIs.[2,3,24] We first estimated the effect of 5 kg/m² higher baseline BMI on coronary heart disease or stroke with adjustment for confounders. We then added the mediators to the model, separately, in all combinations of two, and all three together. We did not incorporate interaction between BMI and mediators in the continuous analysis. We also analysed categories of overweight (BMI ≥25–<30 kg/m²) and obesity (BMI ≥30 kg/m²) as compared with normal weight (BMI ≥20–<25 kg/m²) with the same methods as continuous analysis. We pooled HRs across cohorts with a random-effects model with inverse variance weights.[25] We assessed heterogeneity with Cochran Q test and I^2 statistic.[26]

We estimated the percentage of excess risk mediated (PERM)[27] with pooled HRs as:

$$PERM = \frac{HR_{(confounder\ adjusted)} - HR_{(confounder\ and\ mediator\ adjusted)}}{HR_{(confounder\ adjusted)} - 1} \times 100$$

PERM is not additive across multiple mediators. To calculate the uncertainty of PERM, we randomly drew 5000 pairs of $HR_{(confounder\ adjusted)}$ and $HR_{(confounder\ and\ mediator\ adjusted)}$ from their corresponding uncertainty distributions while accounting for their correlations; estimated PERM for each pair of HRs and quantified its variability across all 5000 estimates (appendix pp 5–7). We used the median of these 5000 estimates as the point estimate of PERM, and its 2·5th and 97·5th percentiles as the 95% CI.

Subgroup and sensitivity analyses

We tested whether the extent of mediation differed by selected cohort characteristics including event types (fatal vs fatal and non-fatal combined), median age of participants at baseline, baseline study year, region of the study, and follow-up duration. In sensitivity analyses, we examined whether the results depended on how the mediators were measured, with use of total versus LDL cholesterol or glucose versus diabetes as the metric of mediator. In sensitivity analyses, we also estimated PERM for waist circumference and

waist-to-hip ratio in 17 cohorts that had measured either of them in addition to BMI. We compared PERM per 10 cm waist circumference and 0·1 waist-to-hip ratio (roughly equivalent to 1 standard deviation increment of these metrics in a pooled sample of 58 prospective cohorts)[3] with that for 5 kg/m² BMI in the same cohorts. For simplicity of presentation, we report results of these secondary analyses only for all three mediators together; results for one or two mediators are available from the authors by request. All statistical analyses were done with Stata 11·0 and R 2·11. All reported p values were two-sided and were deemed significant if less than 0·05.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The members of the Cohort Collaborating Group had access to the original data, which were re-analysed for this report. The corresponding author had final responsibility for the decision to submit.

Results

We included 97 prospective cohorts in the analysis. These studies collectively enrolled 1·8 million participants between 1948 and 2005. During follow-ups that ranged between 2·7 and 57·5 years (median time across all cohorts was 13·3 years), 57161 coronary heart disease and 31093 stroke events were reported (appendix pp 8–14). Western European cohorts (32 cohorts) had the largest number of coronary heart disease and stroke events, contributing 31289 (55%) of coronary heart disease and 13591 (44%) of stroke events. Cohorts from east and southeast Asia (33 cohorts) contributed 10163 (33%) of stroke but only 3763 (7%) of coronary heart disease events, showing the importance of stroke in Asia compared with coronary heart disease (table 2). 72 cohorts measured all three mediators and 21 measured two mediators.

After we adjusted for confounders, each 5 kg/m² higher BMI was associated with a HR of 1·27 (95% CI 1·23–1·31) for coronary heart disease and 1·18 (1·14–1·22) for stroke (figure 1; appendix pp 19–36 shows cohort-specific HRs). Blood pressure was the most

	Number of cohorts (%)	Number of participants (%)	Number of CHD events (%)	Number of stroke events (%)
East and southeast Asia	33 (34·0%)	479736 (26·7%)	3763 (6·6%)	10163 (32·7%)
Western Europe	32 (33·0%)	1055454 (58·7%)	31289 (54·7%)	13591 (43·7%)
North America	15 (15·5%)	157136 (8·7%)	16183 (28·3%)	5485 (17·7%)
Australia or New Zealand	10 (10·3%)	84632 (4·7%)	3207 (5·6%)	1067 (3·4%)
Latin America, central and eastern Europe, North Africa, and Middle East	7 (7·2%)	21110 (1·2%)	2719 (4·8%)	787 (2·5%)
Total	97 (100%)	1798068 (100%)	57161 (100%)	31093 (100%)

CHD=coronary heart disease.

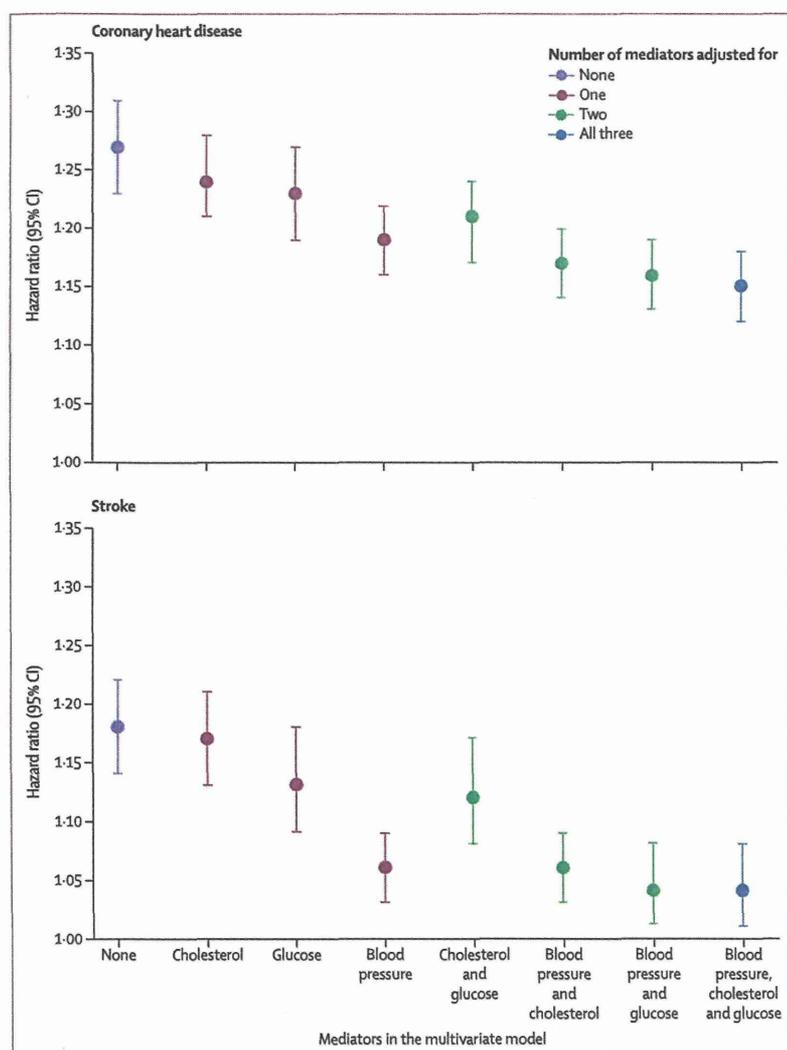Table 2: Number of analysed cohorts, participants, and events by region

Figure 1: Hazard ratios per 5 kg/m² higher body-mass index adjusted for different combinations of mediators in coronary heart disease and stroke
All hazard ratios were also adjusted for confounders as described in Methods. The appendix (pp 19–36) shows cohort-specific hazard ratios.

important mediator for the effects of BMI on both coronary heart disease and stroke; the HR for coronary heart disease fell to 1·19 (1·16–1·22) and for stroke to 1·06 (1·03–1·09) after we adjusted for blood pressure. The second most important mediator was glucose, adjustment for which lowered HRs to 1·23 (1·19–1·27) for coronary heart disease and 1·13 (1·09–1·18) for stroke. Adjustment for any combinations of two or three mediators further reduced HRs of coronary heart disease and stroke compared with adjustment for one mediator (figure 1). When we adjusted for all three mediators, the HR for coronary heart disease decreased to a significantly lower value of 1·15 (1·12–1·18), and for stroke to 1·04 (1·01–1·08; figure 1).

Being overweight, compared with normal weight, was associated with an HR of 1·26 (1·22–1·30) for coronary heart disease and 1·13 (1·08–1·18) for stroke after adjustment for confounders (table 3; appendix pp 37–72 shows cohort-specific HRs). Obesity had a significantly larger association with both coronary heart disease and stroke than did overweight: the confounder-adjusted HR of obesity versus normal weight was 1·69 (1·58–1·81) for coronary heart disease and 1·47 (1·36–1·59) for stroke. We noted associations between both overweight and obesity and the risk of CHD and stroke in both Asian and western cohorts, and in both older (enrolment before 1990) and more recent cohorts (enrolment in or after 1990; appendix pp 15–16).

Similar to analysis using continuous BMI, blood pressure was the most important mediator for the association of overweight and obesity with both coronary heart disease and stroke (table 3). After adjustment for all three mediators, the HR of overweight versus normal weight for coronary heart disease decreased to 1·13 (1·09–1·16) and its association with stroke became null with an HR of 1·00 (0·96–1·05). The HR of obesity versus normal weight for coronary heart disease decreased to 1·39 (1·32–1·47) and that of stroke to 1·14 (1·08–1·21).

We recorded higher HRs per 5 kg/m² BMI for both coronary heart disease and stroke in east and south-east Asia than HRs in western cohorts (North America, western Europe, Australia, and New Zealand; figure 2, appendix pp 73–90). Asian cohorts had an HR of 1·40 (1·29–1·52) for coronary heart disease versus 1·24 (1·20–1·28) in western cohorts (p value for comparison of the two HRs=0·01), and 1·29 (1·20–1·38) for stroke versus 1·14 (1·09–1·18) in western cohorts (p=0·002). After we adjusted for all three mediators, the HRs for coronary heart disease were 1·23 (1·12–1·36) in Asian cohorts and 1·13 (1·10–1·16) in western cohorts (p=0·10); the HRs for stroke became almost identical between regions (figure 2). The HRs for both coronary heart disease and stroke were larger in cohorts that enrolled younger participants (median age at baseline <55 years compared with ≥55 years), both before and after adjustment for mediators (figure 2).

After we adjusted for blood pressure, the excess risk of coronary heart disease associated with 5 kg/m² higher BMI decreased by 31% (95% CI 28–35) (figure 3). This figure was three times larger than the proportion mediated by serum cholesterol (10%, 5–15), and more than twice that of glucose (15%, 10–21). Blood pressure alone accounted for a higher percentage of excess risk of BMI than did cholesterol and glucose together (23%, 19–28). The three mediators collectively explained 46% (42–50) of excess risk for coronary heart disease. Blood pressure was a stronger mediator for stroke risk than for coronary heart disease. Adjustment for blood pressure lowered the excess risk of stroke by 65% (56–75). The corresponding percentages were only 24% (15–36) for glucose and