介入項目：生活習慣全般　No.16

筆頭著者：石田 さくらこ

論文タイトル：職域での健康教育プログラムの効果−中高年前の高脂血症症例への対策−

雑誌名（Vol, No, Page, year）：糖尿病（47, 9, 707−713, 2004）

論文種類：

☑ 原著

研究デザイン：

☐ 無作為化比較対照試験　☑ 比較対照試験　☐ (無作為化)比較対照試験のメタアナリシス　☐ その他　（　　）

実施された場所・地域：

広島県原爆障害対策協議会健康管理・増進センターの糖尿病予防事業（老人保健法による健康診査）

対象集団の特性：

☐ 地域住民　☐ 職域　☐ 地域と職域の混合集団　☑ その他　（実施施設の健診受診者）

人数：（介入群　男性59人、女性43人、対照群　男性59人、女性43人、総計：204人）

年齢(才)：（範囲：　平均or中央値：　介入群　65.3±6.7、対照群　65.6±6.5 ）

BMI(kg/m^2)：（範囲　平均or中央値：　介入群　23.9±3.0、対照群　23.5±2.6 ）

腹囲(cm)：（範囲：　平均or中央値：　）

介入実施期間：　1998年8月～　登録終了 2002年ごろ（期間：介入を行った時期は異なるが全て1年間）

介入後観察期間：　月～　年　月（期間(年数or月数or日数)：　）　☑ 介入後観察期間無

介入の内容(具体的に箇条書きで書いてください)：

1）介入群：老人保健法にもとづく健診で、糖尿病要精査と判定された者に75gOGTTを実施し境界型と判定された者に、個別に①医師によるガイダンス②臨床検査③食事調査および栄養指導④体力測定・生活活動量の調査と運動指導を行った。
①医師によるガイダンス：身体理学所見、OGTT結果の解説や境界型の臨床的意義に関する説明、生活習慣改善への動機づけ、②臨床検査：身長、体重、体脂肪率、血圧、血糖、HbA1c、肝機能、眼底など　③食事：食物摂取頻度法による質問票から、平均栄養素等摂取量、充足率と食品群別バランスチャートを作成し、食生活の改善点をみつけて対象者本人が目標を設定　④運動：運動指導士による基礎体力測定、生活体力測定や問診により、労働や余暇による消費エネルギー量を出し、必要に応じて運動負荷検査も行い、個人にあわせた運動指導を実施。運動量の増大と持続を目標とし、内容は対象者が自発的に決定。　以上の生活指導を6か月ごとに繰り返し、1年毎にOGTTを実施した。
2）対照群：個別生活指導を開始する前の1994～98年までの受診者データから、介入群と性・年齢をマッチングして抽出。

アウトカム：

1）BMI、体脂肪率　2）OGTT、糖尿病発症率　3）食事調査項目（エネルギー充足率、食品群別エネルギー摂取状況）　4）運動調査項目　5）生活習慣改善と糖尿病発症率（介入群のうちBMI≧22.0で検討）

BMIや腹囲で対象者を限定または層化した分析：

☑ あり　（カットオフ値：　）☐ なし

結果：介入前後のアウトカムの変化を検定方法、P値・信頼区間、共変量とともに記載してください。非肥満者に限定または層化した解析結果があれば必ず記載してください。

介入前の測定値は介入群、対照群で有意差なし。
介入後の変化　1）BMI、体脂肪率：対照群ではBMIや体脂肪率に変化はなかったが、介入群ではBMIで男女とも有意に低下し（男性24.2±2.9→23.6±2.9、p<0.001、女性23.5±3.1→22.5±3.1、p<0.001）、女性では体脂肪率も有意に低下した（29.3±5.7→27.6±6.0、p<0.001）。 2）OGTT：介入群では血糖値、インスリン値とも全般に介入前よりも低く、120分値は有意に低値であったが、対照群では血糖値、インスリン値ともに介入前後で有意な差はなかった。 糖尿病発症率：対照群は19.6%で、介入群は6.9%と有意に低かった（p<0.05）。BMI 22.0kg/m2以上例と22.0kg/m2未満例にわけて比較したところ、22.0未満例では例数が少なく有意差を認めないものの、介入群では約1/3に低下していた。3）食事調査項目（介入群のみデータあり）：介入群ではエネルギー充足率が122.3±17.8→109.4±15.9%、p<0.001と過剰摂取に関して有意に改善した。食品群別エネルギー摂取状況では、穀類・いも類・菓子類で有意に減少した（穀類・いも類　891.0±211.1→839.2±174.9kcal、p<0.05、菓子類　144.6±139.5→87.5±87.3kcal、p<0.001）。 4）運動調査項目（介入群のみ）：運動しない者の頻度は、介入前は41.8%であったが、1年後は19.2%と有意に減少した。 5）生活習慣改善と糖尿病発症率（BMI22.0以上の者のみのデータ）：①1年後に1kg以上減量した者の糖尿病発症率は5.7%、減量できなかった者では15.0%であり有意に低率であった（p<0.05）。BMI22.0以上の対照群では、1kg以上減量できた者の糖尿病発症率は15.4%、体重減少を認めなかった者では27.7%であり、有意差は認めないが更に高率であった。②摂取エネルギー充足率の5%以上減少を達成した者の糖尿病発症率は3.8%で、達成しなかった者の19.0%に比べ低率であったが有意差はなかった。③運動消費エネルギー量50kcal/日増を達成した者の糖尿病発症率は2.95であり、達成できなかった者の12.8%に比して有意に低率（p<0.01）であった。①～③の指標のうち1つ達成するごとに1pointとし、0～3pointについて糖尿病発症率をみると0pで33.3%、1pで12.5%、2pで6.7%、3pで0%であった（p<0.01）。

結論：

糖負荷検査を受け境界型と判定された平均BMI23の健診受診者において、食事と運動の個別指導により負荷後2時間の血糖値やインスリン値が改善し、対照群と比べ1年後の糖尿病発症率は低かった。

備考：

介入項目:禁煙　No.1

筆頭著者: Masahiko Iwaoka

論文タイトル: 職域での健康教育プログラムの効果-中高年前の高脂血症症例への対策-

雑誌名(Vol, No, Page, year): Journal of Cardiology (64, 3-4, 318-323, 2014)

論文種類:

☑ 原著

研究デザイン:

☐ 無作為化比較対照試験　☑ 比較対照試験　☐ (無作為化)比較対照試験のメタアナリシス　☐ その他　(　　)

実施された場所・地域:

Tokyo Kita Social Insurance Hospital

対象集団の特性:

☐ 地域住民　☐ 職域　☐ 地域と職域の混合集団　☑ その他　(禁煙外来受診者)

人数:(男性: 53　女性: 33　総計: 86)

年齢(才):(範囲:　平均or中央値:禁煙成功群 60.2±11.3, 失敗群 60.4±11.7)

BMI(kg/m^2) :(範囲:　平均or中央値:禁煙成功群 G 23.5±3.6, 失敗群　22.9±3.9)

腹囲(cm):(範囲:　平均or中央値:)

介入実施期間: 2010年　8月～2013年 4月 (期間(年数or月数or日数):)

介入後観察期間:　年　月～　年　月 (期間(年数or月数or日数):) ☐ 介入後観察期間無

介入の内容(具体的に箇条書きで書いてください):

Varenicklineを用いた12 週間の禁煙プログラム
・Varenicklineは 1.0mg 1日2回で用いた。(最初の3日間は, 0.5mg1日1回、次の4日間は0.5mg1日2回、それからは11週間の、1.0mg1日2回)

アウトカム:

・定期的なフォローは1, 15, 29, 57, そして85日目に行われた。
・Self-reported smoking status と 呼気CO濃度 は毎回の受診で評価。
・禁煙成功の定義は、9～12週の中で呼気CO濃度で4週間連続した禁煙が確認された時。
・血液検査は、最初と最後の受診で施行し、総コレステロール、トリグリセリド、HDLコレステロール、CRP、空腹時血糖、HbA1c、apo A-I。

BMIや腹囲で対象者を限定または層化した分析:

☐ あり (カットオフ値:) ☑ なし

結果:介入前後のアウトカムの変化を検定方法、P値・信頼区間、共変量とともに記載してください。非肥満者に限定または層化した解析結果があれば必ず記載してください。

・89例中、69例が禁煙に成功した。
各群の変化
・禁煙成功群では、12週間の間で体重が有意に増加(P<0.01, paired t検定)、HDLコレステロールは増加(P<0.01, paired t検定)、血清ApoA-Iは増加(P<0.01, paired t検定)、CRPは有意に減少(P=0.04, paired t検定)した。
・失敗群では、CRPが有意に増加した(P=0.04, paired t検定)

結論:

Varenicklineを用いた禁煙に成功した群は血清ApoA-I、HDL-コレステロールが改善した。

備考:

本研究は、Varenicklineを用いた禁煙介入に成功した群と失敗群を比較したものである

介入項目：禁煙　No.2

筆頭著者：関 奈緒

論文タイトル：職域での健康教育プログラムの効果−中高年前の高脂血症症例への対策−

雑誌名（Vol, No, Page, year）：新潟医学会雑誌(118(1), 21−30, 2004)

論文種類：

☑ 原著

研究デザイン：

☐ 無作為化比較対照試験　☑ 比較対照試験　☐ (無作為化)比較対照試験のメタアナリシス　☐ その他　（　　）

実施された場所・地域：

日本（新潟　長野　秋田　山形）

対象集団の特性：

☐ 地域住民　☑ 職域　☐ 地域と職域の混合集団　☐ その他　（詳細不明）

人数：（男性：53　女性：0　総計：53）

年齢(才)：（範囲：　平均or中央値：禁煙群：45.3±10.4　対照群：N/A

BMI(kg/m^2)：（範囲：　−　平均or中央値：禁煙群：23.3±2.2　対照群：24.0±4.1

腹囲(cm)：（範囲：　−　平均or中央値：N/A

介入実施期間：時期の詳細不明（期間(年数or月数or日数)：1ヶ月　）

介入後観察期間：　年　月～　年　月（期間(年数or月数or日数)：　）☑ 介入後観察期間無

介入の内容(具体的に箇条書きで書いてください)：

禁煙教室に参加し1ヶ月後に完全に禁煙できた禁煙群と、禁煙教室に不参加のボランティア対照群の1ヶ月間の検査所見を比較

アウトカム：

BMI、総コレステロール、中性脂肪、HDLコレステロール

BMIや腹囲で対象者を限定または層化した分析：

☐ あり（カットオフ値：　）☑ なし

結果：介入前後のアウトカムの変化を検定方法、P値・信頼区間、共変量とともに記載してください。非肥満者に限定または層化した解析結果があれば必ず記載してください。

■介入前後および群間のアウトカム：

BMI(kg/m2)；禁煙群で23.3==>23.9(0.5増加：p＜0.01)、対照群で24.0==>24.1(0.1増加：n.s.)(群間比較p＜0.05)

総コレステロール(mg/dl)；禁煙群で191.5==>193.3(1.8増加：n.s.)、対照群で193.3==>191.6(1.7減少：n.s.)(群間比較n.s.)

中性脂肪(mg/dl)；禁煙群で144.4==>137.4(7.0減少：n.s.)、対照群で98.3==>110.8(12.5増加：n.s)(群間比較n.s)

HDLコレステロール(mg/dl)；禁煙群で48.8==>54.0(5.2増加：p＜0.01)、対照群で52.5==>53.3(0.7増加：n.s)(群間比較p＜0.05)

結論：

中高年者における禁煙は、HDLコレステロール値の改善をもたらすことが示唆された。

備考：

介入項目：禁酒・減酒　No.1

筆頭著者：Makoto Ayaopri

論文タイトル：職域での健康教育プログラムの効果−中高年前の高脂血症症例への対策−

雑誌名（Vol, No, Page, year）：Journal of Nutritional Science and Vitaminology (46, 4, 171−174, 2000)

論文種類：

☑ 原著

研究デザイン：

☑ 無作為化比較対照試験　☐ 比較対照試験　☐ (無作為化)比較対照試験のメタアナリシス　☐ その他　(　　)

実施された場所・地域：

海上自衛隊下総基地

対象集団の特性：

☐ 地域住民　☑ 職域　☐ 地域と職域の混合集団　☐ その他　(　　)

人数：(男性：40　女性：　　総計：　　)

年齢(才)：(範囲：35−56　　)

BMI(kg/m^2)：(平均：介入群24.4±3.0　対照群24.0±2.0　　)

腹囲(cm)：(範囲：　　平均or中央値：　　)

介入実施期間： 4週間

介入後観察期間：　年　月～　年　月 (期間(年数or月数or日数)：　　)　☑ 介入後観察期間無

介入の内容(具体的に箇条書きで書いてください)：

・4週間の禁酒。
・他の生活習慣は変えない

アウトカム：

総コレステロール、中性脂肪、HDLコレステロール

BMIや腹囲で対象者を限定または層化した分析：

☐ あり (カットオフ値：　　) ☑ なし

結果：介入前後のアウトカムの変化を検定方法、P値・信頼区間、共変量とともに記載してください。非肥満者に限定または層化した解析結果があれば必ず記載してください。

対応のあるt検定により介入群、コントロール群それぞれの前後比較を行った。

アウトカム
介入前の平均値(標準偏差)→介入後の平均値(標準偏差) (P値)
は下記である。

*p<0.05

・総コレステロール, μmol/L
　介入群 5.39(0.74)→5.16(0.64)　　対照群 5.35(0.83)→5.28(0.78)
・HDLコレステロール, μmol/L
　介入群 1.30(0.23)→1.17(0.36)*　　対照群 1.28(0.35)→1.38(0.36)
・中性脂肪, μmol/L
　介入群 2.76(1.79)→1.87(0.97) *　　対照群 2.50(1.48)→2.63(2.01)

結論：

4週間の禁酒により、中性脂肪値は有意に減少した。一方HDLコレステロール値も有意に減少した。

備考：

Ⅲ．研究成果の刊行に関する一覧表

書籍

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
該当なし					

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Bouchi Ryotaro et al.	Is visceral adiposity a modifier for the impact of blood pressure on arterial stiffness and albuminuria in patients with type 2 diabetes?	Cardiovascular Diabetology	15	10	2016
Nagai M, Ohkubo T, Miura K, Fujiyoshi A, Okuda N, Hayakawa T, Yoshita K, Arai Y, Nakagawa H, Nakamura K, Miyagawa N, Takashima N, Kadota A, Murakami Y, Nakamura Y, Abbott RD, Okamura T, Okayama A, Ueshima H.	Association of Total Energy Intake with 29-Year Mortality in the Japanese: NIPPON DATA80.	J Atheroscler	2016 Mar 1;23(3)	339-54	2016
Kawabe Y, Nakamura Y, Kikuchi S, Suzukamo Y, Murakami Y, Tanaka T, Takebayashi T, Okayama A, Miura K, Okamura T, Fukuhara S, Ueshima H.	Relationship of type of work with health-related quality of life	Qual Life Res	2015 Dec;24(12)	2927-32	2015
Kokubo Y, Watanabe M, Higashiyama A, Nakao YM, Kobayashi T, Watanabe T, Okamura T, Okayama A, Miyamoto Y.	Interaction of Blood Pressure and Body Mass Index With Risk of Incident Atrial Fibrillation in a Japanese Urban Cohort: The Suita Study.	Am J Hypertens	2015 Nov;28(11)	1355-61	2015

Ⅳ. 研究成果の刊行物・別刷

Bouchi et al. Cardiovasc Diabetol (2016) 15:10
DOI 10.1186/s12933-016-0335-3

Cardiovascular Diabetology

ORIGINAL INVESTIGATION Open Access

Is visceral adiposity a modifier for the impact of blood pressure on arterial stiffness and albuminuria in patients with type 2 diabetes?

Ryotaro Bouchi[1*], Norihiko Ohara[1], Masahiro Asakawa[1], Yujiro Nakano[1], Takato Takeuchi[1], Masanori Murakami[1], Yuriko Sasahara[1], Mitsuyuki Numasawa[1], Isao Minami[1], Hajime Izumiyama[1,2], Koshi Hashimoto[1,3], Takanobu Yoshimoto[1] and Yoshihiro Ogawa[1,4]

Abstract

Background: We aimed to investigate whether visceral adiposity could modify the impact of blood pressure on arterial stiffness and albuminuria in patients with type 2 diabetes.

Methods: This cross-sectional study examines the interaction of visceral adiposity with increased blood pressure on arterial stiffness and albuminuria. 638 patients with type 2 diabetes (mean age 64 ± 12 years; 40 % female) were enrolled. Visceral fat area (VFA, cm^2) was assessed by a dual-impedance analyzer, whereby patients were divided into those with VFA < 100 (N = 341) and those with VFA ≥ 100 (N = 297). Albuminuria was measured in a single 24-h urine collection (UAE, mg/day) and brachial-ankle pulse wave velocity (ba-PWV, cm/s) was used for the assessment of arterial stiffening. Linear regression analyses were used to investigate the association of systolic blood pressure (SBP) and VFA with UAE and baPWV.

Results: Patients with VFA ≥ 100 were significantly younger, had higher SBP, HbA1c, triglycerides, UAE, alanine aminotransferase, C-reactive protein and lower high-density lipoprotein and shorter duration of diabetes than those with VFA < 100. SBP was significantly and almost equivalently associated with ba-PWV both in VFA < 100 (standardized β 0.224, p = 0.001) and VFA ≥ 100 (standardized β 0.196, p = 0.004) patients in the multivariate regression analysis adjusting for covariates including age, gender, HbA1c, diabetic complications and the use of insulin and anti-hypertensive agents. By contrast, the association of SBP with UAE was stronger in patients with VFA ≥ 100 (standardized β 0.263, p = 0.001) than that in patients with VFA < 100 (standardized β 0.140, p = 0.080) in the multivariate regression model. In the whole cohort, the significant interaction between SBP and VFA on UAE (standardized β 0.172, p = 0.040) but not on ba-PWV (standardized β −0.008, p = 0.916) was observed.

Conclusions: The effect of increased blood pressure on arterial stiffness is almost similar in type 2 diabetic patients with both low and high visceral adiposity, while its association with albuminuria is stronger in the latter.

Keywords: Visceral adiposity, Blood pressure, Arterial stiffness, Albuminuria, Type 2 diabetes

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Background

Blood pressure is a strong risk factor for cardiovascular disease (CVD) [1, 2] and chronic kidney disease (CKD) [3–5]. Among patients with diabetes, hypertension is associated with the incidence of CVD and CKD as well [6–9]. The reduction of blood pressure could reduce the risks both for CVD and CKD.

Obesity, especially increased visceral adiposity is a major cause of hypertension, accounting for 65–75 % of the risk for human essential hypertension [10]. In addition, obesity has been reported to be associated with various cardio-metabolic risks including insulin resistance and dyslipidemia, and also be directly associated with CVD [11–14]. Furthermore, abdominal obesity is a strong risk factor for CKD both in general population and patients with diabetes [15, 16]. Therefore, abdominal adiposity is thought to be an important determinant that can account for the association of cardio-metabolic risks with CVD and CKD.

Regarding the association between blood pressure and CVD, the impact of elevated blood pressure on CVD events has been reported to be stronger among people without obesity than those with [17–19]. Also, it has been suggested that normal-weight patients with essential hypertension have increased arterial stiffness [20] and systemic vascular resistance. We recently reported that increased visceral adiposity with normal weight is strongly associated with cardio-metabolic risks and arterial stiffness in patients with type 2 diabetes [21]. These studies imply that visceral adiposity could modify the impact of blood pressure on CVD; however, it is uncertain whether increased blood pressure could more strongly affect arterial stiffening in people with low visceral adiposity than in those with high visceral adiposity. On the other hand, among obese people, especially those with high visceral adiposity, intra-renal renin-angiotensin-aldosterone system is activated [22–24], leading to the glomerular hyperfiltration at the early stage of obesity-hypertension. Hyperglycemia also induces renal damage directly or through hemodynamic modifications including glomerular hyperfiltration [25]. Therefore, it is possible that increase in systemic blood pressure could more strongly affect the renal hemodynamics in obese, especially in obese patients with diabetes, than in non-obese people, resulting in more severe renal manifestations such as increased albuminuria and decreased glomerular filtration rate (GFR). Taken together, we conducted this cross-sectional study to investigate the interaction of visceral adiposity with blood pressure on the increased risk for arterial stiffening and albuminuria in patients with type 2 diabetes.

Methods

Subjects

Patients with type 2 diabetes who admitted to Tokyo Medical and Dental University Hospital for the purpose of glycemic control and/or evaluation of diabetic complications participated in this cross-sectional study. Patients were eligible, if they were aged ≥20 years, and patients who measured both brachia-ankle pulse wave velocity (ba-PWV) and visceral fat area (VFA) and subcutaneous fat area (SFA) by a dual bioelectrical impedance analyzer were enrolled. Patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <15 mL/min/1.73 m^2 or undergoing renal replacement therapy), pregnant women, and those with infectious or malignant diseases were excluded. Type 2 diabetes was diagnosed according to the criteria of the Japan Diabetes Society (JDS) [26]. As shown in Fig. 1, 638 patients were finally enrolled in this study. This study complies with the principles laid by Declaration of Helsinki and has been approved by the ethical committee of Tokyo Medical and Dental University (No. 1924).

Clinical and biochemical analysis

Standardized questionnaires were used to obtain information on smoking, medication and past history. Smoking history was classified as either current smoker or non-smoker. CVD was defined as the presence of a previous stroke, myocardial infarction, coronary revascularization procedure. Blood pressure was measured in the sitting position after at least 5 min rest, using an electronic sphygmomanometer (ES-H55, Terumo Inc.,

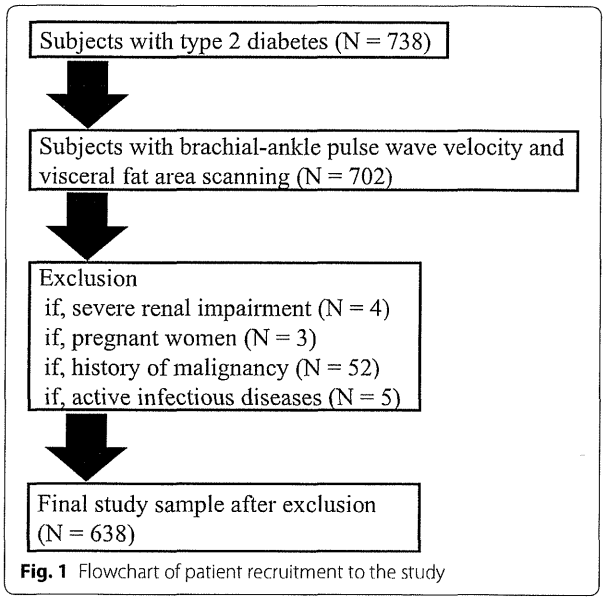

Fig. 1 Flowchart of patient recruitment to the study

Tokyo, Japan). HbA1c was measured by the latex agglutination method. HbA1c levels were expressed in accordance with the National Glycohemoglobin Standardization Programs recommended by the Japanese Diabetes Society [26]. Urinary albumin (UAE) and creatinine excretion were measured by the turbidimetric immunoassay and enzymatic method, respectively, in a single 24-h urine collection. GFR was estimated using the following equation for the Japanese, as proposed by the Japanese Society of Nephrology [27]; GFR = $194 \times SCr^{-1.094} \times age^{-0.287}$ [(if female) $\times$ 0.739], where SCr stands for serum creatinine in mg/dl, measured by an enzymatic method. Coefficient of variation of R–R intervals (CV-RR) was used for the assessment of diabetic neuropathy. BMI was calculated as weight divided by the square of height (kg/m^2). VFA and SFA were measured at the level of umbilicus by dual bioelectrical impedance analyzer (DUALSCAN, Omron Healthcare Co., Kyoto, Japan). Patients were divided into those with VFA < 100 cm^2 (low-V) and those with VFA $\geq$ 100 cm^2 (high-V). Brachial-ankle pulse wave velocity (ba-PWV) was measured using a volume-plethysmographic apparatus (BP-203RPE II form PWV/ABI, Omron Healthcare Co., Kyoto, Japan), with subjects in the supine position after at least 5 min of rest [28, 29]. The ba-PWV was calculated as reported previously [30]. We simultaneously measured ba-PWV on both the right and left sides and the averaged values from each individual were subjected to statistical analysis.

Statistical analysis

Statistical analysis was performed using programs available in the SPSS version 21.0 statistical package (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± SD, median with interquartile range (IQR), or percent as appropriate according to data distribution. Normality was tested by the Kolmogorov–Smirnov test. Differences between low-V and high-V patients were tested with a *t* test or Mann–Whitney U test for continuous variables and Chi square test for categorical variables. Linear regression analyses were used to investigate the association of SBP and VFA with ba-PWV and UAE. We determined the linear relationship and multicollinearity for regression assumptions. We removed one variable if a strong correlation (coefficient of correlation >0.8) was observed between the two independent variables. In order to check the multicollinearity, we evaluated variance infiltration factors. If multicollinearity was found in the data, one variable was removed from the multivariate regression analysis. The following covariates were incorporated into the analysis with a stepwise procedure; duration of diabetes, smoking status, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, HbA1c, eGFR, log CRP and the usage of insulin, calcium channel blockers (CCB), angiotensin receptor blockers (ARB), statins and anti-platelet agents. Age and gender were forced into the model. The interaction between SBP and VFA was also investigated in the multiple linear regression analyses. Differences were considered to be statistically significant at p value less than 0.05.

Results

Clinical characteristics of patients with low-V and high-V

Among 638 patients, 341 and 297 were classified as low-V and high-V patients. As shown in Table 1, high-V patients were significantly younger, had significantly higher SBP and DBP, lower HDL-C, higher triglycerides levels and a shorter duration of diabetes than the low-V patients. Urinary C-peptide and UAE levels in high-V patients were significantly higher than those in low-V patients. BMI, WC, VFA and SFA levels in high-V patients were significantly higher than in those with low-V. The high-V patients were more frequently receiving CCBs, ARBs and statin therapy and were less likely to receive insulin than low-V patients. baPWV in high-V patients was significantly lower than that in low-V patients.

Association between SBP and baPWV according to VFA categories

Table 2 shows the linear regression analyses to investigate the association between SBP and ba-PWV in patients with low-V and those with high-V. In the univariate model, SBP was significantly and equivalently associated with ba-PWV. After adjusting for age and gender, the statistical significance of SBP with ba-PWV was unchanged both in patients with low-V and those with high-V. In the multivariate model including covariates such as eGFR and anti-hypertensive agents, the association of SBP with ba-PWV remained significant regardless of visceral adiposity (standardized β 0.224, p = 0.001 in low-V and standardized β 0.196, p = 0.004 in high-V). Among patients with high-V, SFA was inversely associated with ba-PWV (standardized β −0.199, p = 0.007). eGFR was a significant covariate regardless of visceral adiposity.

Association between SBP and UAE according to VFA categories

Table 3 shows the association between SBP and UAE according to VFA categories among patients with type 2 diabetes. In the univariate model, SBP was significantly associated with UAE both in patients with low-V and those with high-V. The association of SBP with UAE was unchanged in age- and gender-adjusted model regardless of visceral adiposity (standardized β 0.205, p = 0.001 in patients with low-V and standardized β 0.290, p < 0.001 in patients with high-V). In the multivariate model

Table 1 Clinical characteristics according to VFA levels

	VFA < 100 cm^2 (N = 341)	VFA ≥ 100 cm^2 (N = 297)	p values
Age (years)	66 ± 12	62 ± 13	<0.001
Gender (% male)	57	63	0.196
SBP (mmHg)	128 ± 20	132 ± 17	0.016
DBP (mmHg)	73 ± 12	78 ± 12	<0.001
HbA1c (mmol/mol)	71.6 ± 20.2	75.0 ± 19.5	0.029
HbA1c (%)	8.7 ± 1.8	9.0 ± 1.8	
HDL-cholesterol (mmol/l)	1.32 ± 0.42	1.19 ± 0.31	<0.001
LDL-cholesterol (mmol/l)	2.87 (2.29–3.56)	2.79 (2.26–3.44)	0.515
Triglycerides (mmol/l)	1.31 (0.98–1.86)	1.61 (1.19–2.26)	<0.001
Urinary C-peptide (μg/day)	42 (27–67)	60 (35–99)	<0.001
Duration of diabetes (years)	12 (5–20)	10 (4–16)	0.044
Current smoker (%)	22	25	0.452
History of CVD	13	17	0.183
UAE (mg/day)	11 (7–26)	19 (10–58)	0.001
eGFR (ml/min/1.73 m^2)	72.0 ± 23.3	71.5 ± 25.6	0.791
AST (U/l)	22 (17–28)	24 (19–41)	<0.001
ALT (U/l)	19 (14–30)	28 (18–48)	<0.001
C-reactive protein (mg/l)	0.80 (0.40–1.95)	1.60 (0.80–3.60)	<0.001
PDR (%)	19	12	0.536
CV-RR (%)	3.3 (2.2–4.8)	3.6 (2.3–5.3)	0.109
ba-PWV (cm/s)	1711 (1459–1906)	1582 (1411–1785)	0.007
Body mass index (kg/m^2)	23.5 ± 3.2	29.4 ± 4.4	<0.001
Waist circumference (cm)	86 ± 9	102 ± 11	<0.001
Visceral fat area (cm^2)	74 (57–87)	133 (114–152)	<0.001
Subcutaneous fat area (cm^2)	144 (120–178)	236 (194–284)	<0.001
Insulin (%)	75	61	0.002
CCBs (%)	29	39	0.023
ARBs (%)	35	53	<0.001
Statin (%)	42	52	0.050
Anti-platelets (%)	17	22	0.322

ALT alanine aminotransferase, *ARB* angiotensin receptor blocker, *AST* asparatate aminotransferase, *baPWV* brachial-ankle pulse wave velocity, *CCB* calcium channel blocker, *CVD* cardiovascular disease, *CV-RR* coefficient of variation of R–R intervals, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *PDR* proliferative diabetic retinopathy, *SBP* systolic blood pressure

adjusting for covariates including age, gender, diabetic complications such as neuropathy and retinopathy and HbA1c level, SBP remained significantly associated with UAE in patients with high-V (standardized β 0.263, p = 0.001); whereas, its association with UAE was attenuated in those patients with low-V (standardized β 0.140, p = 0.080).

Interaction between SBP and VFA accounting for the risk of arterial stiffening and albuminuria

Table 4 shows the multivariate linear regression analyses to investigate whether binary interaction between SBP and VFA could account for the risks of arterial stiffening and albuminuria in the whole cohort. The significant interaction between SBP and VFA was observed in the model where UAE was used for a dependent variable; whereas, no significant interaction of SBP with VFA was found as for ba-PWV.

Discussion

Both increased arterial stiffness and albuminuria are strong predictors for mortality, CVD and CKD in patients with diabetes [31–36]. Therefore, it is important to elucidate the high risk groups both for increased arterial stiffness and albuminuria among diabetic patients. This study clearly demonstrates that increased SBP can equivalently account for the risk for arterial stiffening regardless of visceral adiposity; whereas, the impact of SBP on albuminuria is stronger in diabetic patients with high visceral adiposity than those with low visceral adiposity.

Table 2 Linear regression analysis to investigate the association of blood pressure and visceral adiposity with arterial stiffness in patients with type 2 diabetes

	VFA < 100 cm^2		VFA ≥ 100 cm^2	
	Standardized β	p values	Standardized β	p values
Univariate				
Systolic blood pressure	0.183	0.001	0.215	
Age- and gender-adjusted				
Systolic blood pressure	0.172	0.001	0.253	
Age	0.426	<0.001	0.421	
Gender (male versus female)	0.071	0.151	0.044	
Multivariate				
Systolic blood pressure	0.224	0.001	0.196	0.004
Age	0.430	<0.001	0.383	<0.001
Gender (male versus female)	0.130	0.051	0.007	0.920
eGFR	−0.087	0.055	−0.199	0.042
SFA	NA		0.149	0.007
CCB	NA		−0.155	0.031

CCB calcium channel blocker, *eGFR* estimated glomerular filtration rate, *SFA* subcutaneous fat area, *VFA* visceral fat area

Table 3 Linear regression analysis to investigate the association of blood pressure and visceral adiposity with albuminuria in patients with type 2 diabetes

	VFA < 100 cm^2		VFA ≥ 100 cm^2	
	Standardized β	p values	Standardized β	p values
Univariate				
Systolic blood pressure	0.203	0.001	0.280	<0.001
Age- and gender-adjusted				
Systolic blood pressure	0.205	0.001	0.290	<0.001
Age	0.079	0.188	0.172	0.172
Gender (male versus female)	0.074	0.219	0.087	0.087
Multivariate				
Systolic blood pressure	0.140	0.080	0.263	0.001
Age	−0.042	0.649	−0.090	0.236
Gender (male versus female)	0.120	0.122	0.166	0.28
eGFR	−0.191	0.042	NA	
Insulin	0.145	0.064	NA	
PDR	0.177	0.024	NA	
CV-RR	−0.142	0.075	−0.161	0.034
HbA1c			0.135	0.076

CV-RR Coefficient of variation of RR intervals, *eGFR* estimated glomerular filtration rate, *PDR* proliferative diabetic retinopathy, *VFA* visceral fat area

Association of blood pressure and visceral adiposity with organ damage

Visceral adiposity has been reported to be associated with incident hypertension [37, 38] and albuminuria [39, 40]. More recently, we found that high visceral fat with low subcutaneous fat accumulation is an important determinant of carotid atherosclerosis and high subcutaneous fat could be protective against atherosclerosis in patients with type 2 diabetes [41], and others reported that subcutaneous fat thickness assessed by ultrasound is inversely associated with carotid atherosclerosis in diabetic patients, particularly in men [42]. Moreover, visceral adiposity is strongly associated with the alteration of myocardial glucose uptake and its association further relates to type 2 diabetes [43]. These studies suggest that visceral and subcutaneous adiposities are directly associated not only cardio-metabolic risks but also target organ damage including heart and arterial wall injuries. We found in this study a stronger association of blood pressure with albuminuria in patients with high visceral adiposity than those with low visceral adiposity, suggesting that visceral adiposity could modify the association of blood pressure at least with albuminuria in patients with type 2 diabetes.

Potential mechanisms regarding the interaction between blood pressure and adiposity on albuminuria

By which mechanisms are involved in the greater impact of elevated blood pressure on albuminuria in patients with high visceral adiposity than in those with low visceral adiposity? Sympathetic activity and local (renal) renin-angiotensin-aldosterone system could account for the association. Obesity increases sympathetic activity in the kidneys and skeletal muscle; however, cardiac sympathetic activity may not be elevated [44–46]. Furthermore, excessive weight gain, especially visceral adiposity increases leptin level, promotes renal compression, activates renal renin-angiotensin-aldosterone system [47], all of which could impair renal-pressure natriuresis, increase glomerular pressure, leading to progression of albuminuria. These observations could at least partly explain why elevated blood pressure is more strongly associated with albuminuria among patients with high visceral adiposity than among patients with low visceral adiposity.

Strengths and limitations

The strength of our study is that we directly measured VFA by a dual-impedance analyzer for the assessment

Table 4 Interaction between blood pressure and visceral adiposity accounting for the risk of arterial stiffening and albuminuria in patients with type 2 diabetes

	ba-PWV		UAE	
	Standardized β	p values	Standardized β	p values
SBP × VFA	−0.008	0.916	0.172	0.040
Systolic blood pressure	0.177	<0.001	0.171	0.001
Visceral fat area	0.149	0.149	−0.060	0.471
Age	0.430	<0.001	NA	
Body mass index	−0.299	0.001	NA	
eGFR	−0.146	0.008	NA	
Calcium channel blocker	0.109	0.029	NA	
HbA1c	NA		−0.138	0.009
CV-RR	NA		0.148	0.005
Gender (male versus female)	NA		0.130	0.015
Angiotensin receptor blocker	NA		0.114	0.030
Insulin	NA		0.109	0.035

ba-PWV brachial-ankle pulse wave velocity, *CV-RR* Coefficient of variation of RR intervals, *eGFR* estimated glomerular filtration rate, *SBP* systolic blood pressure, *UAE* urinary albumin excretion, *VFA* visceral fat area

of visceral adiposity. Previous studies assessed the interaction of adiposity with the association between hypertension and CVD using BMI or WC [7, 8, 48]. Thus, to the best our knowledge, this study is the first to investigate the interaction of visceral adiposity directly measured and blood pressure both with arterial stiffness and albuminuria. This study has a couple of limitations that should be mentioned. First, it has recently been reported that absolute loss of visceral fat mass may play a major role in resolution of diabetes following bariatric surgery, regardless of the amount of weight loss [49], suggesting the importance of prospectively evaluating the change in visceral adiposity to investigate the association between cardio-metabolic risks including blood pressure and organ damage such as arterial stiffening and albuminuria; however, it is impossible to infer causality because of its cross-sectional design. Second, population in this study was ethnically and socially homogeneous, because this study was hospital-based; therefore, generalization of our findings might be limited. Third, we were unable to obtain information on renin-angiotensin-aldosterone system and sympathetic activity. Fourth, we were unable to obtain any information on diet including vitamin A which may reduce visceral fat [50]. Finally, it is to be elucidated whether the association of blood pressure with arterial stiffness and albuminuria could be mediated by visceral adiposity in populations other than diabetic patients.

Conclusion

The effect of increased blood pressure on arterial stiffness is almost similar in type 2 diabetic patients with both low and high visceral adiposity, while its association with albuminuria is stronger in the latter.

Abbreviations

ALT: Alanine Aminotransferase; ARB: angiotensin receptor blocker; AST: Asparatate Aminotransferase; baPWV: brachial-ankle pulse wave velocity; CCB: calcium channel blocker; CI: confidence interval; CRP: C-reactive protein; CVD: cardiovascular disease; CV-RR: coefficient of variation of R–R intervals; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; PDR: proliferative diabetic retinopathy; SFA: subcutaneous fat area; UAE: urinary albumin excretion; VFA: visceral fat area.

Authors' contributions

All authors have made substantial contributions to this study. RB designed the study, researched data, and wrote and edited the manuscript. RB, IM, TY, and YO contributed to intellectual discussion and reviewed and edited the manuscript. MN, YS, MA, TT, MM, YN, NO, HI and KH researched data. As the corresponding author and guarantor of this manuscript, RB is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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Original Article

Association of Total Energy Intake with 29-Year Mortality in the Japanese: NIPPON DATA80

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Aim: **In animals, dietary energy restriction is reported to increase longevity, whereas in humans, all cohort studies from Western countries have not shown an association between the low energy intake and longevity. We examined the association between total energy intake and longevity in Japan where dietary pattern is different from that in the West.**
Methods: **A total of 7,704 Japanese aged 30–69 years were followed from 1980 to 2009. Participants were divided into the quintiles of total energy (kcal/day) based on data collected from the National Nutrition Survey. Hazard ratios and 95% confidence intervals (CIs) were derived through the use of Cox proportional hazards models to compare the risk of death across and between the quintiles.**
Results: **There was a significant association between increased energy intake and all-cause mortality risk in only men (*P* for linear trend=0.008). In cause-specific analysis, compared with the lowest quintile, there was rise in coronary heart disease (CHD) mortality among men (HR; 2.63, 95%CI; 0.95–7.28, *P* for linear trend 0.016) and women (HR; 2.91, 95%CI; 1.02–8.29, *P* for linear trend 0.032) and cancer mortality among men (HR; 1.50, 95%CI; 0.999–2.24, *P* for linear trend 0.038) in the top quintile.**
Conclusion: **We observed significant associations of high energy intake with all-cause and cancer mortality among men and with CHD mortality among men and women. Further studies are needed to confirm the benefits of caloric restriction.**

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Key words: Energy intake, Mortality, Cardiovascular diseases, Cohort study, Japanese

Introduction

In animal studies (including primates), dietary energy restrictions have been shown to reduce mortality and incidence of chronic diseases, including cancer, hypertension, and diabetes[1-6]. Furthermore, caloric

restriction is an activator of sirtuin, which contributes to an increased lifespan[7]. As a result, it might be expected that a lower energy intake in humans could also be associated with an increase in longevity.

However, studies on humans remain inconclusive. Previous cohort studies showed U shaped or no association between total energy intake and all-cause mortality[8-10]. Meanwhile, some studies showed an inverse and inconsistent association with cardiovascular disease (CVD)[8, 11-14]. One reason for this inconsistency might be the difference in study periods because three of the five studies were conducted before the 1980s.

All previous studies are from Western countries. However, populations living in Asia have markedly different dietary patterns from those in the West[15-17]. The intake of salt, plant, and marine origin food is higher and that of animal food is lower in Japan than that in Western countries[15-17]. With the paucity of data from Asia and large differences in dietary patterns, the association between total energy intake and mortality in Asians remains unknown.

Aim

The purpose of this study was to examine the association between total energy intake and long-term mortality based on population-based samples that were collected in Japan in 1980 from the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged (NIPPON DATA80) among middle-aged and elderly Japanese.

Methods

Study Cohort

Detailed description of the NIPPON DATA80 appears elsewhere[18-23]. Briefly, participants were those enrolled in the 3rd National Survey on Circulatory Disorders of Japan in 1980 through the National Nutrition Survey in Japan (NNSJ)[24]. In the survey, 300 census tracts throughout Japan were randomly selected. The overall population aged ≥30 years in participating districts were invited to participate in the study (n=13,771). The baseline survey included medical examinations, blood pressure measurements, blood tests, and a self-administered questionnaire about lifestyle. The Institutional Review Board of Shiga University of Medical Science approved the study protocol. The survey response rate was 76.6%. There were 10,546 participants (men: 4,639, women: 5,907).

We excluded 909 participants without a residential address because an address was needed for linkage to vital statistics records, and 200 were lost to follow-up. Additional exclusions were made because of missing information on total energy intake (n=85) and body mass index (BMI, n=2). Ninety-two participants were excluded because of extreme total energy intake levels [<0.5th percentile (1,184 kcal/day for men and 970 kcal/day for women) and >99.5th percentile [3,992 kcal/day for men and 3,264 kcal/day for women)][25]. Those with a history of stroke (n=107), myocardial infarction (n=43), diabetes (n=275), and kidney disease (n=337) were excluded because of the potential for confounding between dietary intake and fatal event. Additionally, we limited enrollment to participants aged <70 years because total energy intake is known to be low in the elderly people. For example, NNSJ conducted in 2012 has shown that the total energy intake of Japanese people aged 30–39 years, 40–49 years, 50–59 years, 60–69 years, and ≥70 years was 1,871 kcal, 1,891 kcal, 1,937 kcal, 1,923 kcal, and 1,720 kcal, respectively[26]. By this exclusion (n=792), we aimed to minimize confounding on the relationship between energy intake and mortality by age. As a result, 7704 participants (3373 men and 4331 women) were included in the study analysis.

Nutritional Survey

Detailed methods of NNSJ and estimation of individual intake of nutrients and food groups are described elsewhere[18, 21, 22, 27, 28]. A food intake survey was conducted using the weighing record method for 3 consecutive days in each household by trained interviewers. Participants were asked to weigh and record all food and beverages consumed by all household members for the 3-day period. The surveys were completed and confirmed by the interviewers through home visits that occurred at least once per day. Dietary records were coded using Standard Tables for Foods in Japan, 3rd edition from the NNSJ in 1980[27]. The total intake of nutrient and food groups was calculated for each household. For this report, each nutrient and food group intake for an individual household member were estimated by dividing each total household nutrient and food group intake data of NNSJ in 1980,

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Table 1. Baseline characteristics by quintiles of total energy intake in 7,704 participants aged 30-69 years

	Total energy intake (kcal/day)					*P* valuc
	Q1	Q2	Q3	Q4	Q5	
Men						
No. of participants	674	675	674	675	675	
Mean age (years) (SD)	49.3 (11.6)	47.6 (11.2)	46.5 (10.6)	45.7 (10.1)	46.3 (9.7)	<0.001
Mean energy intake (kcal) (SD)	1,852.3 (189.4)	2,207.5 (69.5)	2,424.4 (61.2)	2,660.3 (75.8)	3,098.7 (250.4)	<0.001
Mean weight (kg) (SD)	58.3 (9.3)	59.2 (8.4)	59.9 (8.7)	61.1 (8.6)	61.5 (8.9)	<0.001
Mean BMI (kg/m^2) (SD)	22.3 (3.0)	22.5 (2.7)	22.5 (2.8)	22.8 (2.7)	23.0 (2.8)	<0.001
Smoking status (%)						
Never smoker	16.5	16.9	17.2	19.6	19.9	0.314
Past smoker	16.9	18.0	17.4	15.3	19.0	
Current smoker ≤ 20	42.2	37.0	39.5	38.7	34.8	
Current smoker > 20	24.4	28.1	25.9	26.4	26.4	
Alcohol drinking (%)						
Never drinker	22.3	20.6	20.1	15.6	16.2	0.004
Past drinker	5.8	4.0	4.3	4.0	3.3	
Current drinker	72.0	75.4	75.6	80.4	80.6	
Type of work (%)						
White collar	35.9	38.5	41.1	40.6	35.3	0.089
Blue collar	64.1	61.5	58.9	59.4	64.7	
Work position						
Management	12.2	15.5	15.3	15.1	13.7	0.466
Professional	34.3	34.4	33.4	36.1	32.3	
Other	53.5	50.2	51.3	48.8	54.0	
Fish intake (g/day)	101.7 (51.0)	117.1 (55.0)	126.3 (57.9)	138.1 (66.8)	155.5 (78.5)	<0.001
Meat intake (g/day)	54.5 (31.5)	64.6 (34.0)	73.2 (36.6)	82.0 (43.9)	92.8 (47.1)	<0.001
Vegetable intake (g/day)	99.7 (20.2)	116.5 (18.7)	128.8 (19.4)	140.4 (20.5)	162.2 (28.0)	<0.001
Fruit intake (g/day)	10.0 (7.4)	12.0 (8.0)	13.9 (8.6)	15.0 (8.8)	17.7 (10.8)	<0.001
Carbohydrate intake (g/day)	277.9 (42.5)	331.9 (33.0)	360.1 (36.0)	393.0 (38.5)	456.8 (61.6)	<0.001
Fat intake (g/day)	40.0 (10.8)	47.7 (11.2)	54.4 (12.9)	60.2 (14.6)	71.6 (20.1)	<0.001
Protein intake (g/day)	71.4 (11.5)	82.9 (11.1)	90.6 (11.3)	99.6 (12.9)	113.7 (17.9)	<0.001
Sodium (g/day)	4.9 (1.7)	5.4 (1.8)	5.9 (1.8)	6.5 (2.1)	7.5 (2.4)	<0.001
SBP (mmHg) (SD)	138.2 (20.9)	136.4 (20.8)	135.2 (19.0)	136.1 (19.3)	137.1 (18.8)	0.059
Antihypertensive drug use (%)	8.6	8.1	5.8	6.2	7.1	0.217
Glucose (mg/dL) (SD)	129.6 (29.2)	125.7 (25.6)	127.0 (25.9)	127.0 (33.9)	127.9 (32.0)	0.176
Total cholesterol (mg/dL) (SD)	187.5 (32.4)	186.8 (32.0)	183.2 (31.2)	186.8 (33.7)	187.0 (33.2)	0.100

proportionally using average intakes by age and sex calculated for NNSJ in 1995[29]. The average intakes in NNSJ in 1995 were calculated by a combination method using household-based food weighing records and an approximation of proportions by which family members shared each dish or food in the household. Familial resemblance in nutrient intake has been reported[30-32], and the validation of this method was ascertained in a previous study[28]. For each person, the means of estimated individual nutrients from 3-day records were used in the analyses.

We divided the participants into quintiles for each sex according to their energy intake: Q1 (men; <2,085.4 kcal/day, women; <1,656.7 kcal/day), Q2 (men; ≥2,085.4 kcal/day, <2,322.8 kcal/day, women; ≥1,656.7 kcal/day, <1,851.3 kcal/day), Q3 (men; ≥2,322.8 kcal/day, <2,534.9 kcal/day, women; ≥1,851.3 kcal/day, <2,027.3 kcal/day), Q4 (men; ≥2,534.9 kcal/day, <2,801.2 kcal/day, women; ≥2,027.3 kcal/day, <2,239.4 kcal/day), and Q5 (men; ≥2,801.2 kcal/day, women; ≥2,239.4 kcal/day).

Follow Up

Follow-up in the NIPPON DATA80 has been

(Cont Table 1)

	Total energy intake (kcal/day)					*P* value
	Q1	Q2	Q3	Q4	Q5	
Women						
No. of participants	863	869	866	865	868	
Mean age (years) (SD)	49.9 (11.6)	47.8 (11.8)	46.4 (10.7)	46.5 (10.3)	46.8 (9.6)	<0.001
Mean energy intake (kcal) (SD)	1,483.4 (147.3)	1,757.0 (56.8)	1,938.1 (50.7)	2,123.8 (59.3)	2,487.6 (212.7)	<0.001
Mean weight (kg) (SD)	51.4 (8.4)	51.3 (8.2)	51.9 (7.9)	52.9 (8.0)	52.6 (7.9)	<0.001
Mean BMI (kg/m^2) (SD)	22.9 (3.5)	22.7 (3.4)	22.8 (3.3)	23.0 (3.3)	23.0 (3.1)	0.309
Smoking status (%)						
Never smoker	84.1	89.5	90.7	91.6	92.2	<.0001
Past smoker	2.7	2.0	1.0	1.9	1.5	
Current smoker ≤ 20	12.1	8.0	7.7	6.0	5.9	
Current smoker > 20	1.2	0.6	0.6	0.6	0.5	
Alcohol drinking (%)						
Never drinker	78.1	79.1	76.8	76.9	79.9	0.466
Past drinker	1.7	1.3	1.0	2.1	1.4	
Current drinker	20.2	19.7	22.2	21.0	18.7	
Type of work (%)						
White collar	23.0	25.7	25.0	25.8	23.2	0.498
Blue collar	77.0	74.3	75.0	74.2	76.8	
Work position						
Management	1.3	1.0	1.3	0.6	0.9	0.426
Professional	11.1	13.1	14.1	12.5	11.8	
Other	87.7	85.9	84.7	86.9	87.3	
Fish intake (g/day)	77.7 (38.3)	89.8 (42.1)	94.4 (43.9)	106.0 (48.1)	117.3 (56.5)	<0.001
Meat intake (g/day)	40.9 (24.7)	48.0 (25.4)	56.3 (28.5)	60.6 (32.8)	71.5 (37.8)	<0.001
Vegetable intake (g/day)	79.0 (16.3)	91.1 (15.4)	99.3 (15.3)	109.1 (16.8)	128.5 (24.5)	<0.001
Fruit intake (g/day)	13.9 (9.9)	16.0 (10.2)	18.3 (11.0)	20.4 (11.8)	25.8 (15.8)	<0.001
Carbohydrate intake (g/day)	232.4 (33.6)	274.9 (27.8)	298.1 (31.2)	326.6 (34.0)	382.0 (51.3)	<0.001
Fat intake (g/day)	34.5 (9.7)	41.2 (10.2)	47.7 (11.5)	52.3 (13.0)	62.5 (17.7)	<0.001
Protein intake (g/day)	58.9 (9.2)	68.1 (9.2)	74.0 (9.0)	81.6 (10.0)	93.5 (14.8)	<0.001
Sodium (g/day)	4.2 (1.3)	4.7 (1.5)	5.0 (1.5)	5.6 (1.8)	6.4 (2.0)	<0.001
SBP (mmHg) (SD)	134.4 (21.9)	131.4 (19.6)	131.4 (20.6)	131.4 (21.0)	130.9 (17.8)	0.002
Antihypertensive drug use (%)	11.7	9.7	9.4	8.6	6.7	0.008
Glucose (mg/dL) (SD)	126.8 (25.3)	126.1 (23.3)	127.0 (25.4)	125.3 (23.2)	127.4 (32.4)	0.482
Total cholesterol (mg/dL) (SD)	192.1 (36.4)	188.3 (33.5)	188.3 (33.4)	190.5 (33.4)	189.0 (33.9)	0.100

Q1: <2,099.7 kcal (men), <1,669.9 kcal (women), Q2: ≥2,099.7 kcal, <2,337.5 kcal (men), ≥1,669.9 kcal, <1865.6 kcal (women), Q3: ≥2,337.5 kcal, <2,555.0 kcal (men), ≥1865.6 kcal, <2,039.8 kcal (women), Q4: ≥2,555.0 kcal, <2,816.6 kcal (men), ≥2,039.8 kcal, <2253.0 kcal (women), Q5: ≥2,816.6 kcal (men), ≥2253.0 kcal (women).
P values were calculated by chi-squared test (categorical variables), or ANOVA (continuous variables).
SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure.

ongoing since 1994 at 5-year intervals to ascertain the vital status and the cause of death by reviewing the National Vital Statistics data until 2009. Mortality end points included death from all-cause and death due to cancer and CVD. Deaths were coded according to the International Classification of Diseases and Related Health Problems, the Ninth Revision (ICD-9) until the end of 1994 and the Tenth Revision (ICD-10) from 1995[33, 34]. Deaths from cancer included ICD-9 codes 140–239 and ICD-10 codes C00–D48. Deaths from CVD included ICD-9 codes 393–459 and ICD-10 codes I00–I99. Deaths from coronary heart disease (CHD) included ICD-9 codes 410–414 and ICD-10 codes I20–I25. Deaths from heart failure included ICD-9 codes 428 and ICD-10 codes I50. Deaths from stroke included ICD-9 codes 430–

Table 2. The association between total energy intake and all-cause mortality in 7,704 participants aged 30-69 years

	Total energy intake (kcal/day)					*P* for linear trend
	Q1	Q2	Q3	Q4	Q5	
No. of participants	1,537	1,544	1,540	1,540	1,543	
No. of death	569	493	416	404	407	
Crude model						
Mortality rate (/1,000 person-years)	14.7	12.3	10.3	9.9	9.9	
HRs	1.00 (reference)	0.83 (0.73-0.93)	0.68 (0.60-0.77)	0.65 (0.57-0.74)	0.66 (0.58-0.74)	<0.001
Age-sex adjusted model						
Mortality rate (/1,000 person-years)	17.5	16.9	16.0	16.0	16.4	
HRs	1.00 (reference)	0.97 (0.86-1.10)	0.92 (0.81-1.05)	0.93 (0.82-1.06)	0.96 (0.84-1.09)	0.327
Model 1	1.00 (reference)	1.00 (0.89-1.13)	0.97 (0.85-1.10)	0.97 (0.85-1.10)	1.02 (0.90-1.16)	0.987
Model 2	1.00 (reference)	1.02 (0.90-1.15)	0.97 (0.85-1.10)	0.98 (0.86-1.12)	1.02 (0.90-1.16)	0.991
Model 3	1.00 (reference)	1.08 (0.95-1.23)	1.07 (0.92-1.24)	1.10 (0.93-1.30)	1.17 (0.97-1.41)	0.146

P for linear trend values were calculated as a categorical variable.
Age-sex adjusted model was adjusted for sex and age (continuous).
Model 1 was adjusted for sex, age (continuous), cigarette smoking (never smoker, past smoker, current smoker ≤20 cigarettes/day, and current smoker >20 cigarettes/day), alcohol drinking (never, past, and current drinker), type of work (white, and blue collar), and work position (management, professional, and other).
Model 2 was adjusted for variables in Model 1 plus body mass index (<18.5 kg/m^2, 18.5-24.9 kg/m^2, 25.0-29.9 kg/m^2, and ≥30.0 kg/m^2), systolic blood pressure (continuous), blood glucose (continuous), total cholesterol (continuous), and the use of antihypertensive medications (yes and no).
Model 3 was adjusted for variables in Model 2 plus fish intake (quartile category), meat intake (quartile category), vegetable intake (quartile category), fruit intake (quartile category), and sodium (quartile category).

438 and ICD-10 codes I60−I69. Deaths from cerebral infarction included ICD-9 codes 433, 434, 437.8a, and 437.8b, and ICD-10 codes I63 and I69.3. Deaths from cerebral hemorrhage included ICD-9 codes 431−432 and ICD-10 codes I61 and I69.1.

Statistical Analysis

Crude and age- and sex-adjusted mortality in person-years of follow-up for each event were estimated across the quintiles based on the standard analysis of covariance methods[35]. We used Cox proportional hazards regression analysis to calculate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for a mortality outcome with the quintiles having the lowest quintile (Q1) serving as a reference. Tests for trend were based on modeling total energy intake in its quintile categories. Statistical analyses were conducted using SAS software (version 9.2, Cary, NC, USA).

We considered the following variables to be potential confounding factors: sex, age (continuous), cigarette smoking (never smoker, past smoker, current smoker ≤20 cigarettes per day, and current smoker >20 cigarettes per day), alcohol drinking (never, past, and current drinker), type of work (white or blue collar), and work position (management, professional, and other) in Model 1. Additional covariates included BMI (<18.5 kg/m^2, 18.5−24.9 kg/m^2, 25.0−29.9 kg/m^2, and ≥30.0 kg/m^2), systolic blood pressure (continuous), blood glucose (continuous), total cholesterol (continuous), and use of antihypertensive medications (yes and no) in Model 2. Model 3 was also adjusted for sex-specific quartiles of fish intake (g/day), meat intake (g/day), vegetable intake (g/day), fruit intake (g/day), and sodium intake (g/day). An increase in total energy intake is associated with an increase in the absolute intake of these foods or nutrients. Therefore, intake greater than that amount increases with an increase in total energy intake. However, previous studies did not consider this effect in the analysis[8-14].

As a source of potential confounding and interaction, analyses were repeated after stratifying by age (<50 years, or ≥50 years), smoking status (ever smoker, past and current smoker, or never smoker), alcohol drinking status (ever drinker, past and current drinker, or never drinker), and BMI (normal weight: 18.5−24.9 kg/m^2 or overweight and obesity: ≥25.0 kg/m^2) in men and women[36]. We could not stratify by BMI <18.5 kg/m^2 because of small number of participants (men: 174, women: 280). As surrogates for physical activity and socioeconomic status (SES), participants were further stratified by type of work (white and blue collar) and work position (management or profes-