ストレス自覚と体型が血圧に及ぼす影響—5年間の追跡結果より

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目的：慢性の心理的ストレスは血圧と正あるいは負の関連をすると報告されている。本研究はこの関連性に注目し、さらに肥満度（(body mass index) BMI）によって修飾されるかを検討した。

方法：1997 年と 2002 年のストレスに関する質問に欠損がなく、同時に心血管系の病気に罹ったことがなく、降圧薬を服用していない男性職員 1,673 名について分析した。女性職員については人数が少なかったため、今回の分析対象からは外した。ストレスについては両年とも「日ごろストレスが多いと思われますか」の問いに、「1. かなり多い、2. やや多い、3. ふつう、4. 少ない」から回答を選ばせ、両年とも 1. または 2. のいずれかを選んだ者を慢性ストレスが多い、3. または 4. のいずれかを選んだ者を慢性ストレスが少ないと判定した。両年で回答が 1. と 2. のいずれかと 3. と 4. のいずれかを交互に選んだ者はストレス中程度と判定した。両年共に BMI が 25 kg/m² 以上の方を肥満型、未満の方をヤセ型と判定し、両年でBMI 値のレベルが入れ替わった場合は体型変化型と判定した。血圧値は 1997 年と 2002 年の健診測定値を平均した値を用いた。慢性ストレスおよび BMI は各々3 つのレベル群を形成するので、両者を組み合わせた合計 9 つの群を用いて、血圧に対するストレスおよび体型の関連性の比較をした。なお、血圧、体型、およびストレス自覚に関連すると考えられる年齢、運動、飲酒、喫煙、塩味の好みについても調べ、群間でこれらの違いが生ずる影響を数学的に補正して検討した。

結果：拡張期血圧（図に示した）と収縮期血圧は同じ結果を示した。対象者を慢性ストレスのレベルで 3 群に分けたときの血圧値には群間で有意な差は認められなかった（図の B の部分）。一方、体型で 3 群に分けた場合、ヤセ型、変化型、肥満型の順に血圧値が有意に高くな
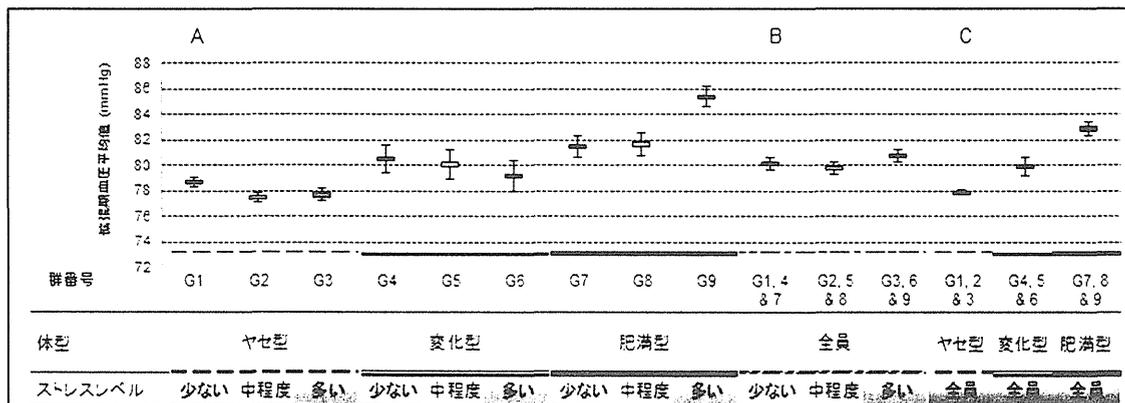
ることが示された(図の C の部分)。次に、慢性ストレスの 3 つのレベル群別に体型と血圧との関連性を見ると、慢性ストレスが少ない群（図の A の部分で G1、G4、G7）、変化した群（同じく G2、G5、G8）、多い群（同じく G3、G6、G9）に共通して、ヤセ型、変化型、肥満型の順に、血圧が有意に上昇した。すなわち、肥満と高い血圧との関連性はストレスレベルによらず認められた。次に体型の 3 つのレベル群別に慢性ストレスと血圧の関連性を見ました（図の A の部分）。慢性ストレスが多くなるにつれて肥満型では高い血圧を示したのに対し（G7、G8、G9 の部分）、ヤセ型では逆に低い血圧を示す傾向が認められた（G1、G2、G3 の部分）。

結論：ストレスと血圧との関連は BMI により修飾されることが示唆された。

肝臓の脂肪量とインスリン抵抗性との関連

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目的：肝臓の脂肪量と homeostasis model assessment-insulin resistance (HOMA-IR)を用いて評価したインスリン抵抗性との関連を日本人集団で検討する。

方法：愛知職域コホートより年齢が 37-69 歳の 53 名のボランティアを対象者にした。3 テスラの Magnetic Resonance Spectroscopy (MRS) 検査により肝臓の脂肪量を推定した。また空腹時採血により血中インスリン、グルコース、中性脂肪、HDL コレステロール、肝臓酵素(AST、ALT、ガンマ GTP) の濃度を測定した。体脂肪率は生体インピーダンス (bioelectrical impedance) 法により測定した。HOMA-IR と肝臓の脂肪量は対数変換後、年齢、性別、肥満度、体脂肪率、腹囲を補正した偏相関係数を算出した。

結果：肝臓脂肪量は肥満度、体脂肪率、腹囲と独立して HOMA-IR と正の関連を示した（偏相関係数 r=0.44 p=0.002）。一方、肥満度、体脂肪率、腹囲それぞれと HOMA-IR との正の関連は肝臓脂肪量でほとんど説明された（表）。

表：　肥満度、体脂肪率、腹囲と log-HOMA-IR との相関係数

	相関係数	P値	性別、年齢を調整 偏相関係数	P値	性別、年齢、log-肝臓脂肪量を調整 偏相関係数	P値
肥満度	0.42	0.002	0.45	0.001	0.18	0.20
体脂肪率	0.39	0.004	0.54	<0.001	0.29	0.039
腹囲	0.49	<0.001	0.50	<0.001	0.20	0.20

結論：肝臓脂肪量は肥満度、体脂肪率、腹囲と独立して HOMA-IR と正の関連を示した。

Ⅳ．研究成果の刊行に関する一覧表

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
1	Satoh M, Ohkubo T, Asayama K, Murakami Y, Sakurai M, Nakagawa H, Iso H, Okayama A, Miura K, Imai Y, Ueshima H, Okamura T; Evidence for Cardiovascular Prevention From Observational Cohorts in Japan (EPOCH–JAPAN) Research Group.	Combined Effect of Blood Pressure and Total Cholesterol Levels on Long-Term Risks of Subtypes of Cardiovascular Death: Evidence for Cardiovascular Prevention From Observational Cohorts in Japan.	Hypertension.	65(3)	517-24	2015
2	Asayama K, Satoh M, Murakami Y, Ohkubo T, Nagasawa SY, Tsuji I, Nakayama T,Okayama A, Miura K, Imai Y, Ueshima H, Okamura T; Evidence for Cardiovascular Prevention From Observational Cohorts in Japan (EPOCH-JAPAN) Research Group.	Cardiovascular risk with and without antihypertensive drug treatment in the Japanese general population: participant-level meta-analysis.	Hypertension.	63(6)	1189-97	2014
3	Sugiyama D, Higashiyama A, Wakabayashi I, Kubota Y, Adachi Y, Hayashibe A, Kawamura K, Kuwabara K, Nishimura K, Kadota A, Nishida Y, Hirata T, Imano H, Miyamatsu N, Miyamoto Y, Sawamura T, Okamura T.	The relationship between lectin-like oxidized low-density lipoprotein receptor-1 ligands containing apolipoprotein B and cardio-ankle vascular index in healthy community inhabitants: The KOBE study.	J Atheroscler Thromb.		In press	2014
4	Kubota Y, Higashiyama A, Imano H, Sugiyama D, Kawamura K, Kadota A, Nishimura K, Miyamatsu N, Miyamoto Y, Okamura T.	Serum polyunsaturated fatty acid composition and serum high-sensitivity C-reactive protein levels in healthy Japanese residents: the KOBE study.	J Nutr Health Aging.		In press	2015
5	Hitara T, Higashiyama A, Kubota Y, Nishimura K, Sugiyama D, Kadota A, Imano H, Nishikawa T, Miyamatsu N, Miyamoto Y, Okamura T.	HOMA-IR values are associated with glycemic control in Japanese subjects without diabetes or obesity: the KOBE Study.	J Epidemiol.		In press	2015
6	Xu D, Murakoshi N, Sairenchi T, Irie F, Igarashi M, Nogami A, Tomizawa T, Yamaguchi I, Yamagishi K, Iso H, Ota H, Aonuma K.	Anemia and Reduced Kidney Function as Risk Factors for New Onset of Atrial Fibrillation (from the Ibaraki Prefectural Health Study).	Am J Cardiol.	115(3)	328-33	2015
7	Murakoshi N, Xu D, Sairenchi T, Igarashi M, Irie F, Tomizawa T, Tada H, Sekiguchi Y, Yamagishi K, Iso H, Yamaguchi I, Ota H, Aonuma K.	Prognostic impact of supraventricular premature complexes in community-based health checkups: The Ibaraki Prefectural Health Study.	Eur Heart J.	36(3)	170-78	2015
8	Fujihara K, Sugawara A, Heianza Y, Sairenchi T, Irie F, Iso H, Doi M, Shimano H, Watanabe H, Sone H, Ota H.	Utility of the triglyceride level for predicting incident diabetes mellitus according to the fasting status and body mass index category: the Ibaraki	J Atheroscler Thromb.	21(11)	1152-69	2014

		Prefectural Health Study.				
9	Tsujimoto T, Sairenchi T, Iso H, Irie F, Yamagishi K, Watanabe H, Tanaka K, Muto T, Ota H.	The dose-response relationship between body mass index and the risk of incident stage ≥3 chronic kidney disease in a general japanese population: the Ibaraki prefectural health study (IPHS).	J Epidemiol.	24(6)	444-51	2014
10	Tsukinoki R, Okamura T, Watanabe M, Kokubo Y, Higashiyama A, Nishimura K, Takegami M, Murakami Y, Okayama A, Miyamoto Y.	Blood pressure, low-density lipoprotein cholesterol, and incidences of coronary artery disease and ischemic stroke in Japanese: the Suita study.	Am J Hypertens.	27(11)	1362-69	2014
11	Nishimura K, Okamura T, Watanabe M, Nakai M, Takegami M, Higashiyama A, Kokubo Y, Okayama A, Miyamoto Y.	Predicting coronary heart disease using risk factor categories for a Japanese urban population, and comparison with the framingham risk score: the suita study.	J Atheroscler Thromb.	21(8)	784-98	2014
12	Gotoh S, Hata J, Ninomiya T, Hirakawa Y, Nagata M, Mukai N, Fukuhara M, Ikeda F, Shikata K, Kamouchi M, Kitazono T, Kiyohara Y.	Trends in the incidence and survival of intracerebral hemorrhage by its location in a Japanese community.	Circ J.	78	403-409	2014
13	Imamura T, Doi Y, Ninomiya T, Hata J, Nagata M, Ikeda F, Mukai N, Hirakawa Y, Yoshida D, Fukuhara M, Kitazono T, Kiyohara Y.	Non-high-density lipoprotein cholesterol and the development of coronary heart disease and stroke subtypes in a general Japanese population: the Hisayama Study.	Atherosclerosis.	233	343-48	2014
14	Kojima I, Ninomiya T, Hata J, Fukuhara M, Hirakawa Y, Mukai N, Yoshida D, Kitazono T, Kiyohara Y.	A low ankle brachial index is associated with an increased risk of cardiovascular disease: the Hisayama Study.	J Atheroscler Thromb.	21	966-73	2014
15	Kishimoto H, Hata J, Ninomiya T, Nemeth H, Hirakawa Y, Yoshida D, Kumagai S, Kitazono T, Kiyohara Y.	Midlife and late-life handgrip strength and risk of cause-specific death in a general Japanese population: the Hisayama Study.	J Epidemiol Community Health.	68	663-68	2014
16	Mukai N, Doi Y, Ninomiya T, Hirakawa Y, Nagata M, Yoshida D, Hata J, Fukuhara M, Nakamura U, Kitazono T, Kiyohara Y.	Trends in the prevalence of type 2 diabetes and prediabetes in community-dwelling Japanese subjects: the Hisayama Study.	J Diabetes Investig.	5	162-69	2014
17	Mukai N, Yasuda M, Ninomiya T, Hata J, Hirakawa Y, Ikeda F, Fukuhara M, Hotta T, Koga M, Nakamura U, Kang D, Kitazono T, Kiyohara Y.	Thresholds of various glycemic measures for diagnosing diabetes based on prevalence of retinopathy in community-dwelling Japanese subjects: the Hisayama Study.	Cardiovasc Diabetol.	13(45)	http://www.cardiab.com/content/13/1/45	2014
18	Izumaru K, Ninomiya T, Nagata M, Usui T, Yoshida D, Yonemoto K, Fukuhara M, Tsuruya K, Kitazono T, Kiyohara Y.	Serum 1, 25-dihydroxyvitamin D and the development of kidney dysfunction in a Japanese community: the Hisayama Study.	Circ J.	78	732-37	2014
19	立川佳美、Cologne JB、山田美智子、大石和佳、飛田あゆみ、古川恭治、	親の放射線被ばくと多因子疾患有病率との関連：被爆二世健康診断調査（第2報）	広島医学	67(4)	375-78	2014

	高橋規郎、中村典、小笹晃太郎、赤星正純、藤原佐枝子、Shore RE.					
20	斎藤重幸	高血圧	最新肥満症学日本臨床増刊号	72	583-85	2014
21	斎藤重幸	JNC8 ガイドライン	血圧	21	496-97	2014
22	斎藤重幸	肥満症・メタボリックシンドローム、高血圧発症・進展の関わり	臨床高血圧学日本臨床	72	269-72	2014
23	斎藤重幸	日本高血圧学会高血圧治療ガイドライン（JSH）の変遷	循環器内科	14	385-91	2014
24	斎藤重幸	糖尿病合併高血圧の降圧目標をめぐって	血圧	21	926-31	2014
25	斎藤重幸	高血圧	Mod Physician.	35	213-15	2015
26	Yoshida Y, Akasaka H, Saitoh, S, Shimamoto K, Miura T.	Comparative effects of telmisartan and valsartan as add-on agents for hypertensive patients with morning blood pressure insufficiency controlled by amlodipine monotherapy.	Hypertens Res.	37	225-31	2014
27	Furuhashi M, Moniwa N, Mita T, Fuseya T, Ishimura S, Ohno K, Shibata S, Tanaka M, Watanabe Y, Akasaka H, Ohnishi H, Yoshida H, Takizawa H, Saitoh S, Ura N, Shimamoto K, Miura T.	Urinary angiotensin- converting enzyme 2 in hypertensive patients may be increased by Olmesartan, an angiotensin II Receptor Blocker.	Am J Hypertens.	28(1)	15-21	2015
28	Ihira H, Furuna T, Mizumoto A, Makino K, Saitoh S, Ohnishi H, Shimada H, Makizako H.	Subjective physical and cognitive age among community-dwelling older peoples aged 75 years and Older: differences with chronological age and its associated factors.	Aging Ment Health.		In press	2014
29	Fuseya T, Furuhashi M, Yuda S, Muranaka A, Kawamukai M, MitaT, Ishimura S, Watanabe Y, HoshinaK, Tanaka M, Ohno K, Akasaka H, OhnishiH, YoshidaH, Saitoh S, Shimamoto K, Miura T.	Elevation of circulating fatty acid-binding protein 4 is independently associated with left ventricular diastolic dysfunction in a general population.	Cardiovasc Diabetol.	13(126)	http://www.cardiab.com/content/13/1/126	2014
30	Miki T, Tobisaw T, Sato T, Tanno M, Yano T, Akasaka H, Kuno A, Ogasawara M, MuraseH, Saitoh S, MiuraT.	Does glycemic control reverse dispersion of ventricular repolarization in type 2 diabetes?	Cardiovasc Diabetol.	13(125)	http://www.cardiab.com/content/13/1/125	2014
31	Wang C, Yatsuya H, Tamakoshi K, Iso H, Tamakoshi A.	Milk drinking and mortality: findings from the Japan collaborative cohort study.	J Epidemiol.	25(1)	66-73	2015
32	Kumagai Y, Chou WT, Tomata Y, Sugawara Y, Kakizaki M, Nishino Y, Tsuji I.	Dietary Patterns and colorectal cancer risk in Japan: the Ohsaki Cohort Study.	Cancer Causes Control.	25(6)	727-36	2014

33	Matsumoto A, Satoh M, Kikuya M, Ohkubo T, Hirano M, Inoue R, Hashimoto T, Hara A, Hirose T, Obara T, Metoki H, Asayama K, Hosokawa A, Totsune K, Hoshi H, Hosokawa T, Sato H, Imai Y.	Day-to-Day variability in home blood pressure is associated with cognitive decline: the Ohasama study.	Hypertension.	63(6)	1333-38	2014
34	Imai E, Tsubota-Utsugi M, Kikuya M, Satoh M, Inoue R, Hosaka M, Metoki H, Fukushima N, Kurimoto A, Hirose T, Asayama K, Imai Y, Ohkubo T.	Animal protein intake is associated with higher-level functional capacity in elderly adults: the Ohasama study.	J Am Geriatr Soc.	62(3)	426-34	2014
35	Satoh M, Hosaka M, Asayama K, Kikuya M, Inoue R, Metoki H, Utsugi MT, Hara A, Hirose T, Obara T, Mori T, Totsune K, Hoshi H, Mano N, Imai Y, Ohkubo T.	Aldosterone-to-renin ratio and nocturnal blood pressure decline assessed by self-measurement of blood pressure at home: the Ohasama Study.	Clin Exp Hypertens.	36(2)	108-14	2014
36	Tsubota-Utsugi M, Satoh M, Hosaka M, Inoue R, Asayama K, Hirose T, Metoki H, Kikuya M, Imai Y, Ohkubo T.	Personality traits as predictors of decline in higher-level functional capacity over a 7-year follow-up in older adults: the Ohasama Study.	Tohoku J Exp Med.	234(3)	197-207	2014
37	Satoh M, Matsumoto A, Hara A, Iwamori S, Obara T, Kikuya M, Metoki H, Hosaka M, Asayama K, Takahashi N, Sato H, Mano N, Imai Y, Ohkubo T.	A survey of self-medication practices and related factors in the general population: the Ohasama study.	Yakugaku Zasshi.	134(12)	1347-55	2014
38	Sakurai M, Nakamura K, Miura K, Takamura T, Yoshita K, Nagasawa SY, Morikawa Y, Ishizaki M, Kido T, Naruse Y, Suwazono Y, Sasaki S, Nakagawa H.	Sugar-sweetened beverage and diet soda consumption and the 7-year risk for type 2 diabetes mellitus in middle-aged Japanese men.	Eur J Nutr.	53(1)	251-58	2014
39	Sakurai M, Nakamura K, Miura K, Yoshita K, Takamura T, Nagasawa SY, Morikawa Y, Ishizaki M, Kido T, Naruse Y, Nakashima M, Nogawa N, Suwazono Y, Nakagawa H.	Association between serum thyroid stimulating hormone within the normal range and indices of obesity in Japanese men and women.	Intern Med.	53	669-74	2014
40	Yoneyama S, Sakurai M, Nakamura K, Morikawa Y, Miura K, Nakashima M, Yoshita K, Ishizaki M, Kido T, Naruse Y, Nogawa K, Suwazono Y, Sasaki S, Nakagawa H.	Associations between rice, noodle, and bread intake and sleep quality in Japanese men and women.	PLoS One.	9(8)	e105198	2014
41	Morikawa Y, Nakamura K, Sakurai M, Nagasawa SY, Ishizaki M, Nakashima M, Kido T, Naruse Y, Nakagawa H.	The effect of age on the relationships between work-related factors and heavy drinking.	J Occup Health.	56	141-49	2014
42	Nakamura K, Sakurai M, Miura K, Morikawa Y, Nagasawa SY, Ishizaki M, Kido T, Naruse Y,	HOMA-IR and the risk of hyperuricemia: A prospective study in non-diabetic Japanese men.	Diabetes Res Clin Pract.	106	154-60	2014

	Nakashima M, Nogawa K, Suwazono Y, Nakagawa H.					
43	Nakamura K, Sakurai M, Miura K, Morikawa Y, Nagasawa SY, Ishizaki M, Kido T, Naruse Y, Nogawa K, Nakashikma M, Suwazono Y, Nakagawa H.	Overall sleep status and high sensitivity C-reactive protein: a prospective study in a Japanese population.	J Sleep Res.	23(6)	717-27	2014
44	Makita S, Onoda T, Ohsawa M, Tanno K, Tanaka F, Omama S, Yoshida Y, Ishibashi Y, Itai K, Sakata K, Ohta M, Kuribayashi T, Ogasawara K, Ogawa A, Okayama A, Nakamura M.	Bradycardia is associated with future cardiovascular diseases and death in men from the general population.	Atherosclerosis.	236	116-20	2014
45	Koeda Y, Tanaka F, Segawa T, Ohta M, Ohsawa M, Tanno K, Makita S, Ishibashi Y, Omama S, Onoda T, Nakamura M.	Usefulness of risk grading system using albuminuria for predicting cardiovascular events and all-cause death in chronic kidney disease: a population-based prospective cohort study in Japan.	Int J Cardiol.	175	576-77	2014
46	Makita S, Tanaka F, Onoda T, Ohsawa M, Tanno K, Omama S, Yoshida Y, Ishibashi Y, Segawa T, Takahashi T, Satoh K, Itai K, Sakata K, Ohta M, Kuribayashi T, Ogasawara K, Ogawa A, Okayama A, Nakamura M.	Elevated blood pressure at the first measurement predicts cardiovascular disease independently from the subsequent second reading in men, but not in women.	Clin Exp Hypertens.	37	39-44	2015
47	Ando A, Tanno K, Ohsawa M, Onoda T, Sakata K, Tanaka F, Makita S, Nakamura M, Omama S, Ogasawara K, Ishibashi Y, Kuribayashi T, Koyama T, Itai K, Ogawa A, Okayama A.	Associations of number of teeth with risks for all-cause mortality and cause-specific mortality in middle-aged and elderly men in the northern part of Japan: the Iwate-KENCO study.	Community Dent Oral Epidemiol.	42	358-65	2014
48	Iso H, Imano H, Yamagishi K, Ohira T, Cui R, Noda H, Sato S, Kiyama M, Okada T, Hitsumoto S, Tanigawa T, Kitamura A; CIRCS Investigators.	Fasting and non-fasting triglycerides and risk of ischemic cardiovascular disease in Japanese men and women: the Circulatory Risk in Communities Study (CIRCS).	Atherosclerosis.	237	361-68	2014
49	Chei CL, Yamagishi K, Ikeda A, Noda H, Maruyama M, Cui , Imano H, Kiyama M, Kitamura A, Asada T, Iso H; CIRCS Investigators.	C-reactive protein levels and risk of disabling dementia with and without stroke in Japanese: the Circulatory Risk in Communities Study (CIRCS).	Atherosclerosis.	236	438-43	2014
50	Cui R, Yamagishi K, Imano H, Ohira T, Tanigawa T, Hitsumoto S, Kiyama M, Okada T, Kitamura A, Iso H; CIRCS investigators.	Relationship between the ankle-brachial index and the risk of coronary heart disease and stroke: the circulatory risk in communities study.	J Atheroscler Thromb.	21	1283-89	2014
51	Ishikawa J, Ishikawa S, Kario K.	Relationships between the QTc interval and cardiovascular, stroke, or sudden cardiac mortality in the general Japanese population.	J Cardiol.		In press	2014

52	Ishikawa J, Ishikawa S, Kario K.	Levels of cornell voltage and cornell product for predicting cardiovascular and stroke mortality and morbidity in the general Japanese population.	Circ J.	78	465-75	2014
53	Kakehi E, Kotani K, Ishikawa S, Gotoh T, Kayaba K, Nakamura Y, Kajii E.	Relationship between screening plasma glucose concentrations and cancer- and all-cause mortality: the Jichi Medical School (JMS) cohort study.	Journal of Public Health.	22	505-11	2014
54	Yamasaki K, Kayaba K, Ishikawa S.	Soy and Soy Products Intake, All-Cause Mortality, and Cause-Specific Mortality in Japan: The Jichi Medical School Cohort Study.	Asia Pac J Public Health.		In press	2014
55	Uemura M, Yatsuya H, Hilawe EH, Li Y, Wang C, Chiang C, Otsuka R, Toyoshima, Tamakoshi K, Aoyama A.	Breakfast Skipping is Positively Associated with Incidence of Type 2 Diabetes Mellitus - Evidence from Aichi Workers' Cohort Study.	J Epidemiol.	25(5)	In press	2015
56	Hilawe EH, Yatsuya H, Li Y, Uemura M, Wang C, Chiang C, Toyoshima H, Tamakoshi K, Zhang Y, Kawazoe N, Aoyama A.	Smoking and Diabetes: Is the Association Mediated by Adiponectin, Leptin, or C-reactive Protein?	J Epidemiol.	25(2)	99-109	2015
57	Toyoshima H, Otsuka R, Hashimoto S, Tamakoshi K, Yatsuya H.	Body mass index-modified relationship of chronic mental stress with resting blood pressure during 5 years in Japanese middle-aged male workers.	Circ J.	78(6)	1379-86	2014
58	Yatsuya H, Nihashi T, Li Y, Hotta Y, Matsushita K, Muramatsu T, Otsuka R, Matsunaga M, Yamashita K, Wang C, Uemura M, Harada A, Fukatsu H, Toyoshima H, Aoyama A, Tamakoshi K.	Independent association of liver fat accumulation with insulin resistance.	Obes Res Clin Pract.	8(4)	E350-55	2014

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
斎藤重幸	血管疾患	日本高血圧学会編	高血圧専門医ガイドブック	診断と治療社	東京	2014	144-47
斎藤重幸	糖尿病	日本循環器病予防学会編	第7版循環器病予防ハンドブック	保健同人社	東京	2014	273-89
斎藤重幸	疫学からみた高齢者高血圧治療の意義	楽木宏美	高齢者高血圧の治療と管理－JSH2014改訂をふまえて	先端医学社	東京	2014	32-38

Ⅴ．研究成果の刊行物・別刷

Combined Effect of Blood Pressure and Total Cholesterol Levels on Long-Term Risks of Subtypes of Cardiovascular Death
Evidence for Cardiovascular Prevention From Observational Cohorts in Japan

Michihiro Satoh, Takayoshi Ohkubo, Kei Asayama, Yoshitaka Murakami, Masaru Sakurai, Hideaki Nakagawa, Hiroyasu Iso, Akira Okayama, Katsuyuki Miura, Yutaka Imai, Hirotsugu Ueshima, Tomonori Okamura, on behalf of the Evidence for Cardiovascular Prevention From Observational Cohorts in Japan (EPOCH–JAPAN) Research Group*

Abstract—No large-scale, longitudinal studies have examined the combined effects of blood pressure (BP) and total cholesterol levels on long-term risks for subtypes of cardiovascular death in an Asian population. To investigate these relationships, a meta-analysis of individual participant data, which included 73 916 Japanese subjects (age, 57.7 years; men, 41.1%) from 11 cohorts, was conducted. During a mean follow-up of 15.0 years, deaths from coronary heart disease, ischemic stroke, and intraparenchymal hemorrhage occurred in 770, 724, and 345 cases, respectively. Cohort-stratified Cox proportional hazard models were used. After stratifying the participants by 4 systolic BP ×4 total cholesterol categories, the group with systolic BP ≥160 mm Hg with total cholesterol ≥5.7 mmol/L had the greatest risk for coronary heart disease death (adjusted hazard ratio, 4.39; $P<0.0001$ versus group with systolic BP <120 mm Hg and total cholesterol <4.7 mmol/L). The adjusted hazard ratios of systolic BP (per 20 mm Hg) increased with increases in total cholesterol categories (hazard ratio, 1.52; $P<0.0001$ in group with total cholesterol ≥5.7 mmol/L). Similarly, the adjusted hazard ratios of total cholesterol increased with increases in systolic BP categories (*P* for interaction ≤0.04). Systolic BP was positively associated with ischemic stroke and intraparenchymal hemorrhage death, and total cholesterol was inversely associated with intraparenchymal hemorrhage, but no significant interactions between BP and total cholesterol were observed for stroke. High BP and high total cholesterol can synergistically increase the risk for coronary heart disease death but not for stroke in the Asian population. (*Hypertension*. 2015;65:517-524. DOI: 10.1161/HYPERTENSIONAHA.114.04639.)
● Online Data Supplement

Key Words: Asia ■ coronary disease ■ epidemiology ■ hypercholesterolemia ■ hypertension ■ meta-analysis ■ stroke

Previous cohort studies in Western countries demonstrated that high total cholesterol levels strengthened the association between high blood pressure (BP) and the risk for death from coronary heart disease (CHD).[1-3] However, the research group of the Asia Pacific Cohort Studies Collaboration (APCSC) reported that the positive associations of BP with the risk for CHD was weaker in the group with higher cholesterol levels than in those with lower cholesterol levels.[4] Because the APCSC study was based on a population including not only whites from Australia and New Zealand but also

Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.114.04639

循環器

日本人のCHD死リスク上昇には高血圧とTC高値が相乗的に作用

アジア人において長期の脳心血管死リスクに対する血圧と総コレステロール（TC）の複合的影響を，死因となった疾患の種類別に検討した大規模な縦断的研究は存在しない。日本学術振興会特別研究員（所属：東北大学病院薬剤部）の佐藤倫広氏らは，EPOCH-JAPAN研究[*1]における日本人7万人超のデータのメタ解析により，冠動脈疾患（CHD）と脳卒中のそれぞれでこうした影響を検討。高血圧とTC高値の併存はCHD死リスクを有意に上昇させたが，脳卒中死に対しては複合的影響は認められなかったとHypertension（2015年1月19日オンライン版）に報告した。

SBP/TC最高群ではHR 4.4

TC高値と高血圧の併存が欧米人においてCHD死リスクを高めることは，複数のコホート研究で示されている。一方，アジアおよびオセアニアのコホート研究を統合した研究APCSCでは，血圧高値とCHDの関連は低TC群で明瞭であると報告されている。ただし，APCSCには白人も含まれており，純粋にアジア人における知見とはいえない。国内の研究としては，吹田研究によりCHDリスク上昇に対するTC高値と高血圧の複合的影響が示されているが，小規模かつイベント発生数が少ないことから結果の解釈は限定的である。

また，欧米人と比べ，脳卒中がアジア人で多いことは周知であり，高血圧が虚血性脳卒中および脳実質内出血の強力な危険因子であることについては複数の報告があるが，血圧とTCの複合的影響についての研究は不十分である。

EPOCH-JAPANは厚生労働省の研究班（研究代表者：滋賀医科大学名誉教授／同大学アジア疫学研究センター特任教授・上島弘嗣氏）として発足した共同研究で，わが国を代表する14のコホート研究における約19万人の長期追跡データを統合することにより日本人の総死亡・循環器疾患死亡に関連する要因の分析を進めている。現在の班長は，慶應義塾大学公衆衛生学教授の岡村智教氏が務めている。今回は，同研究の11のコホートから日本人7万3,916人（平均年齢57.7歳，男性41.1%）のデータを抽出してメタ解析を行った。

平均15.0年の追跡期間中にCHD，虚血性脳卒中，脳実質内出血による死亡がそれぞれ770件，724件，345件発生した。コホートにより層別化したCox比例ハザードモデルを用い，対象を収縮期血圧（SBP）の4分類（120mmHg未満，120〜139mmHg，140〜159mmHg，160mmHg以上）とTCの4分類（180mg/dL未満，180〜199mg/dL，200〜219mg/dL，220mg/dL以上）の組み合わせにより層別化した解析の結果，CHD死のリスクは，SBP 160mmHg以上かつTC 220mg/dL以上の群で最も高かった〔SBP 120mmHg未満かつTC 180mg/dL未満の群に対する調整後のハザード比（HR）[*2] 4.39，95%CI 2.68〜7.18，P＜0.0001，図〕。

SBPが20mmHg上昇するごとの調整後のCHDリスクは，TCの上昇とともに増大した（TC 220mg/dL以上の群におけるHR 1.52，95%CI 1.36〜1.71，P＜0.0001）（交互作用のP≦0.04）。同様に，TC上昇に伴うCHDリスクは，SBPが高くなるほど増大した（交互作用のP≦0.04）。

今回の知見は，アジア人において高血圧とTC高値が相乗的に作用してCHD死のリスクを高める可能性を示唆している。佐藤氏らは「これは，CHD発症には脂質蓄積と高血圧による血管の傷害が併存する必要があると説く傷害反応説または炎症説を部分的に支持する結果である」と述べている。

脳卒中死では相乗作用認められず

一方，脳卒中死に関しては，SBPと虚血性脳卒中死および脳実質内出血死の間に正の関連（それぞれSBP 20mmHg上昇ごとのHR 1.20，95%CI 1.12〜1.28，HR 1.43，95%CI 1.30〜1.58，P＜0.05）が，TCと脳実質内出血死との間に負の関連が認められた（TC 37.0mg/dL上昇ごとのHR 0.75，95%CI 0.67〜0.85，P＜0.05）が，血圧とTCとの間に有意な交互作用は認められなかった（交互作用のP≧0.09）。

佐藤氏らは「低TCと脳実質内出血死の関連は，日本のコホート研究の結果と一致する。しかし，低TCは，低収入，低栄養状態，過度のアルコール摂取などをしばしば反映するため，これらが交絡因子として影響している可能性がある。"発症"をアウトカムとした大規模な検討が待たれる」と指摘している。

[*1] EPOCH-JAPAN：Evidence for Cardiovascular Prevention From Observational Cohorts in Japan
[*2] 性，年齢，BMI，過去および現在の喫煙，過去および現在の飲酒で調整

〈図〉SBPとTCの組み合わせによる死亡リスク

A CHD死　B 虚血性脳卒中死　C 脳実質内出血死　D 全CVD死
*P＜0.05，†P＜0.0001
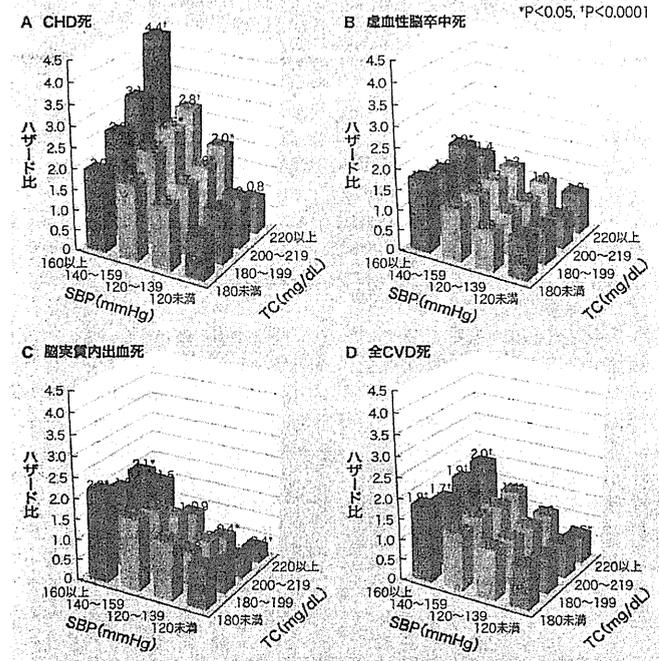
（Hypertension 2015年1月19日オンライン版）

糖尿病／医療機器

スマホで家族と血糖データをリアルタイムに共有

米食品医薬品局（FDA）は1月23日，糖尿病患者とその家族ら第三者がスマートフォン（スマホ）などで持続血糖モニター（CGM）のデータを共有できるアプリ"Dexcom SHARE[TM]"を承認したと発表。携帯端末にインストールすれば，患者本人に加え最大で5人までがCGMのデータをリアルタイムで共有できる。

これまでにも類似のデバイスはオープンソースで入手可能だったが，規制上の要件が遵守されていなかった。Dexcom SHARE[TM]はCGMデータを遠隔地でもリアルタイムにモニタリングするための，公的に認可された初のソリューションとなる。

Dexcom社は，同アプリ使用のメリットとして「遠方の学校に就学した小児患者や，遠方に住む高齢患者の血糖コントロールを家族も把握できる」と説明。血糖値の急激な変化を知らせるアラーム機能や注意喚起機能もあるため，即時の対応が可能になるとしている。ただし，同アプリによる血糖管理は実際のCGMあるいは通常の家庭における血糖測定の代わりにはならないこと，またCGMは皮下の組織間質液中の糖濃度であるため，インスリンの用量など治療内容に関する判断はCGMではなく血糖値をベースに行うべきことなどが，留意点として挙げられている。

Cardiovascular Risk With and Without Antihypertensive Drug Treatment in the Japanese General Population
Participant-Level Meta-Analysis

Kei Asayama, Michihiro Satoh, Yoshitaka Murakami, Takayoshi Ohkubo, Sin-ya Nagasawa,
Ichiro Tsuji, Takeo Nakayama, Akira Okayama, Katsuyuki Miura, Yutaka Imai,
Hirotsugu Ueshima, Tomonori Okamura; on behalf of the Evidence for Cardiovascular Prevention
From Observational Cohorts in Japan (EPOCH-JAPAN) Research Group*

Abstract—To evaluate the cardiovascular mortality risk in association with blood pressure level among people with and without antihypertensive treatment, we performed the participant-level meta-analysis that included 39 705 Japanese from 6 cohorts (58.4% women; mean age, 60.1 years; 20.4% treated). Multivariable-adjusted Cox models were used to analyze the risk of cardiovascular mortality and its subtypes among 6 blood pressure levels according to recent guidelines, optimal to Grade 3 hypertension, and the usage of antihypertensive medication at baseline. During median 10.0 years of follow-up, there were 2032 cardiovascular deaths (5.1 per 1000 person-years), of which 410 deaths were coronary heart disease, 371 were heart failure, and 903 deaths were stroke. Treated participants had significantly higher risk for cardiovascular mortality (hazard ratios, 1.50; 95% confidence intervals, 1.36–1.66), coronary heart disease (hazard ratios, 1.53; confidence intervals, 1.23–1.90), heart failure (hazard ratios, 1.39; confidence intervals, 1.09–1.76), and stroke (hazard ratios, 1.48; confidence intervals, 1.28–1.72) compared with untreated people. Among untreated participants, the risks increased linearly with an increment of blood pressure category ($P \leq 0.011$). The risk increments per blood pressure category were higher in young participants (<60 years; 22% to 79%) than those in old people ($\geq$60 years; 7% to 15%) with significant interaction for total cardiovascular, heart failure, and stroke mortality ($P \leq 0.026$). Among treated participants, the significant linear association was also observed for cardiovascular mortality ($P=0.0003$), whereas no stepwise increase in stroke death was observed ($P=0.19$). The risks of cardiovascular mortality were $\approx$1.5-fold high in participants under antihypertensive medication. More attention should be paid to the residual cardiovascular risks in treated patients. (*Hypertension*. 2014;63:1189-1197.) ● Online Data Supplement

Key Words: cardiovascular diseases ■ hypertension ■ meta-analysis

B lood pressure–lowering treatment reduces cardiovascular risk.[1,2] However, individuals treated with antihypertensive medication had primarily worse prognosis for cardiovascular diseases than untreated hypertensive or normotensive population.[3-5] Although the strong positive relationship between blood pressure level and cardiovascular disease risks were observed among general population,[5-8] there is little argument as to the risk increase with elevation of blood pressure among treated participants. For instance, association between blood pressure level and stroke in treated participants was weak,[7] not observed,[4,5] or observed only based on self-measured home blood pressure.[9] Furthermore, to our knowledge, no previous study compared the risk of different types of cardiovascular diseases, for example, coronary heart disease, heart failure,

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Original Article

The Relationship between Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1 Ligands Containing Apolipoprotein B and the Cardio-Ankle Vascular Index in Healthy Community Inhabitants: The KOBE Study

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Aims: Lectin-like oxidized low-density lipoprotein (LDL) receptor-1 ligands containing apolipoprotein B (LAB) and lectin-like oxidized LDL receptor-1 (LOX-1) are known as LOX-1-related modified LDL indicators. These indicators play an important role in the early phase atherosclerosis, but the relationship between these indicators and subclinical atherosclerosis, as represented by the cardio-ankle vascular index (CAVI), has not been assessed. We herein investigated the association of LOX-1-related modified LDL indicators and the CAVI in healthy, Japanese urban community inhabitants who were considered to be at low risk for cardiovascular disease (CVD).
Methods: The participants were 515 healthy Japanese (310 men and 205 women) without a history of CVD, cancer or the use of medication for hypertension, diabetes or dyslipidaemia. To estimate the association between LOX-1-related modified LDL indicators (LAB, soluble form of LOX-1 (sLOX-1)) and the CAVI, we performed multivariable linear regression analyses with possible confounders such as the serum LDL cholesterol level.
Results: The plasma LAB showed a positive association with the CAVI in men (standardized coefficient: 0.11, *p*=0.04). This relationship was not observed in women. On the other hand, no clear association was observed between the CAVI and the plasma sLOX-1 level in either sex.
Conclusions: The plasma LAB levels may represent a useful marker for detecting potential atherosclerosis in healthy individuals considered to be at low risk for atherosclerosis and CVD. Further studies are needed to confirm the present findings.

J Atheroscler Thromb, 2014; 21:000-000.

Key words: Lectin-like oxidized low-density lipoprotein receptor-1, LOX-1 ligand containing ApoB, Cardio-ankle vascular index, Community-based study

Introduction

Endothelial dysfunction is currently considered to be an early phase in the development of atheroscle-rosis; the oxidative modification of low-density lipo-protein (LDL) is considered to play a key role in endothelial dysfunction[1]. Lectin-like oxidative LDL receptor-1 (LOX-1) is the receptor for oxidative and/

Anemia and Reduced Kidney Function as Risk Factors for New Onset of Atrial Fibrillation (from the Ibaraki Prefectural Health Study).

Xu D, Murakoshi N, Sairenchi T, Irie F, Igarashi M, Nogami A, Tomizawa T, Yamaguchi I, Yamagishi K, Iso H, Ota H, Aonuma K.

Abstract

Chronic kidney disease (CKD) is a potential independent risk factor for atrial fibrillation (AF). It remains unclear whether anemia is synergistically associated with increased risk of AF onset in subjects with CKD. We evaluated the association of kidney function, hemoglobin (Hb), and their combination with new-onset AF in a population-based cohort study. We conducted a 15-year prospective cohort study of 132,250 Japanese subjects aged 40 to 79 years who participated in annual health checkups from 1993. Kaplan-Meier survival analysis was used to compare freedom from new-onset AF between groups classified by estimated glomerular filtration rate grade, Hb grade, and their combination. Cox proportional hazard model analysis was used to estimate hazard ratios (HRs) for new-onset AF. During a 13.8-year mean follow-up period, 1,232 (0.93%) subjects with new-onset AF were identified. Lower estimated glomerular filtration rate and lower Hb grades were significantly associated with a higher incidence of new-onset AF. Multivariate HRs and 95% confidence intervals (CIs) of new-onset AF were 1.38 (1.21 to 1.56) for mild CKD group, 2.56 (2.09 to 3.13) for CKD group, and 1.50 (1.24 to 1.83) for anemia group. Borderline Hb level was not significantly associated with increased risk for new-onset AF (HR 1.07, CI 0.91 to 1.25, p = 0.4284). In the model with interaction term between CKD and anemia, the risk was significantly higher (p = 0.0343 for the interaction) than that predicted by each factor independently. In conclusion, decreased kidney function and lower Hb level are associated with increased risk for new-onset AF, especially when both are present.

Prognostic impact of supraventricular premature complexes in community-based health checkups: The Ibaraki Prefectural Health Study.

Murakoshi N, Xu D, Sairenchi T, Igarashi M, Irie F, Tomizawa T, Tada H, Sekiguchi Y, Yamagishi K, Iso H, Yamaguchi I, Ota H, Aonuma K.

Abstract

AIMS: The long-term prognosis of subjects with supraventricular premature complexes (SVPCs) remains unclear in the general population. The aim of this study was to examine the prognostic significance of SVPCs in community-based health checkups.

METHODS AND RESULTS: We assessed 63 197 individuals (mean age, 58.8 ± 9.9 years; 67.6% women) who participated in annual community-based health checkups in 1993 and were followed until 2008. The primary endpoint was stroke death, cardiovascular death (CVD), or all-cause death during a 14-year mean follow-up, and the secondary endpoint was first atrial fibrillation (AF) event in subjects without self-reported heart diseases or AF at baseline. Compared with subjects without SVPCs, the multivariate-adjusted hazard ratios (HRs) [95% confidence interval (CI)] of stroke death, CVD, and all-cause death in subjects with SVPCs were 1.24 (0.98-1.56) for men and 1.63 (1.30-2.05) for women, 1.22 (1.04-1.44) for men and 1.48 (1.25-1.74) for women, and 1.08 (0.99-1.18) for men and 1.21 (1.09-1.34) for women, respectively. Atrial fibrillation occurred in 386 subjects during the follow-up (1.05/1000 person-years). The presence of SVPCs at baseline was the significant predictor of AF onset [HRs (95% CI): 4.87 (3.61-6.57) for men and 3.87 (2.69-5.57) for women]. Propensity score matched analyses also revealed the presence of SVPCs was significantly associated with increased risks of AF incidence and CVD even after adjusting the potential confounders.

CONCLUSION: The presence of SVPCs in 12-lead electrocardiograms was a strong predictor of AF development, and associated with increased risk of CVD in general population.

Original Article

Utility of the Triglyceride Level for Predicting Incident Diabetes Mellitus According to the Fasting Status and Body Mass Index Category: The Ibaraki Prefectural Health Study

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Aim: The levels of lipids, especially triglycerides (TG), and obesity are associated with diabetes mellitus (DM). Although typically measured in fasting individuals, non-fasting lipid measurements play an important role in predicting future DM. This study compared the predictive efficacy of lipid variables according to the fasting status and body mass index (BMI) category.
Methods: Data were collected for 39,196 nondiabetic men and 87,980 nondiabetic women 40-79 years of age who underwent health checkups in Ibaraki-Prefecture, Japan in 1993 and were followed through 2007. The hazard ratios (HRs) for DM in relation to sex, the fasting status and BMI were estimated using a Cox proportional hazards model.
Results: A total of 8,867 participants, 4,012 men and 4,855 women, developed DM during a mean follow-up of 5.5 years. TG was found to be an independent predictor of incident DM in both fasting and non-fasting men and non-fasting women. The multivariable-adjusted HR for DM according to the TG quartile (Q) 4 vs. Q1 was 1.18 (95% confidence interval (CI): 1.05, 1.34) in the non-fasting men with a normal BMI (18.5-24.9). This trend was also observed in the non-fasting women with a normal BMI. That is, the multivariable-adjusted HRs for DM for TG Q2, Q3 and Q4 compared with Q1 were 1.07 (95% CI: 0.94, 1.23), 1.17 (95%CI: 1.03, 1.34) and 1.48 (95%CI: 1.30, 1.69), respectively.
Conclusions: The fasting and non-fasting TG levels in men and non-fasting TG levels in women are predictive of future DM among those with a normal BMI. Clinicians must pay attention to those individuals at high risk for DM.

J Atheroscler Thromb, 2014; 21:1152-1169.

Key words: Triglycerides, Diabetes prediction, Fasting status

Introduction

The prevalence of diabetes mellitus (DM) has been increasing due to the increase in obesity, and DM is an important cause of mortality and morbidity worldwide[1]. Identifying patients at risk for DM is

challenging, as DM contributes to the development of atherosclerosis in the early stage[2]. Impaired insulin secretion and resistance result in the development of DM.

The lipid levels are a major, modifiable risk factor for atherosclerosis and cardiovascular disease, including acute coronary syndrome and myocardial infarction[3-5]. Among these parameters, triglycerides (TG), which are particularly influenced by insulin resistance[6], represent an independent risk factor for DM[7-15]. Lipotoxicity, which results from the accumulation of lipids in the skeletal muscle, liver and pancreas, plays an important role in the onset of insulin resistance and β-cell damage[16, 17].

Although current guidelines recommend measuring the lipid levels in a fasting state, recent studies suggest that non-fasting lipid profiles may be useful in the clinical setting[18]. The non-fasting TG levels are associated with an increased risk of cardiovascular disease[4, 5]. However, the association between the non-fasting TG levels and the incidence of DM is unclear.

Asian populations tended to develop DM and metabolic syndrome at lower body mass index (BMI) values than other populations, such as Caucasians[19]. Impaired insulin secretion, as well as the accumulation of visceral fat, a decrease in skeletal muscle mass and an increase in animal fat intake, may be related to the development of these diseases[20, 21]. However, the association between TG and the incidence of DM in non-obese Japanese subjects is unclear.

Aim

This study aimed to evaluate the mechanistic links between TG and individual lipid variables and the incidence of DM using fasting and non-fasting lipid profiles in a large prospective cohort study of the Japanese general population. Moreover, the utility of TG for predicting the incidence of DM in the non-fasting state among non-obese subjects was examined.

Methods

The subjects included 194,333 Japanese (63,865 men and 130,468 women) community residents 40-79 years of age who underwent health checkups in 1993 conducted by local governments under the Japan Health Laws. We excluded 2,345 adults (545 men and 1,800 women) due to incomplete data and 10,214 adults (4,933 men and 5,281 women) with a fasting blood glucose concentration of 7.0 mmol/L or greater, a non-fasting blood glucose concentration of 11.1 mmol/L or greater and/or the use of diabetic medica-

tions at baseline. Moreover, we excluded 19,191 men and 35,407 women who did not participate in the 1994 survey, thereby ensuring that subjects were followed up for at least one year. A total of 39,196 men and 87,980 women were followed up annually until the diagnosis of DM or the end of 2007. A fasting state was defined as not having had a meal for at least eight hours based on a self-reported questionnaire. The protocol for this cohort study was approved by the Ibaraki Epidemiology Study Union Ethics Review Committee.

Baseline Examinations

Individuals who did not undergo checkups during the follow-up period were censored on the date of their latest checkup. At baseline in 1993, both height and weight were measured. BMI was calculated as weight in kilograms divided by the square of height in meters. The participants were classified according to a BMI less than 18.5, 18.5-24.9 and 25.0 or greater based on the BMI classification of the Japan Society for the Study of Obesity. The blood glucose concentration was measured according to the glucose oxidase electrode method with a GA1140 device (Kyoto Daiichi Kagaku, Kyoto, Japan) from 1994 to 1996 inclusive and the hexokinase/glucose-6-phosphate dehydrogenase method with a H7170 device (Hitachi, Tokyo, Japan) from 1997 to 2006 inclusive. The measurements were obtained in a single laboratory of the Ibaraki Health Service Association. The serum total cholesterol (TC) and serum TG values were measured according to an enzymatic method with an RX-30 device (Nihon Denshi, Tokyo, Japan). The high-density lipoprotein cholesterol (HDLC) levels were measured in the same laboratory according to the phosphotungstic acid magnesium method with an MTP-32 device (Corona Electric, Ibaraki, Japan). The laboratory participated in external standardization and successfully met the criteria for precision accuracy for the measurement of blood samples issued by the Japan Medical Association, Japanese Association of Medical Technologists and Japan Society of Health Evaluation and Promotion. The serum LDL-cholesterol (LDLC) levels were calculated using the Friedewald equation when the plasma TG concentration did not exceed 4.5 mmol/L. The non-HDLC level was calculated by subtracting HDLC from TC, and the TC/HDLC, non-HDLC/HDLC, LDLC/HDLC and TG/HDLC values were calculated by dividing TC, non-HDLC, LDLC or TG by HDLC, respectively. An interview was conducted to ascertain the patient's smoking status (never smoked; ex-smoker; current smoker, <20 cigarettes per day; and current smoker, ≥20 cigarettes

Table 1. Characteristics of the study participants

	Men					
	Fasting			Non-fasting		
	Non-DM	DM	p value	Non-DM	DM	p value
n	6171	572		29013	3440	
Age (y)	59.3 ± 10.1	60.3 ± 9.1	0.01	61.8 ± 9.8	62.5 ± 8.5	<0.01
BMI (kg/m²)	23.1 ± 2.8	24.0 ± 2.9	<0.01	23.2 ± 2.9	23.5 ± 3.2	<0.01
SBP (mmHg)	134 ± 17	138 ± 18	<0.01	137 ± 17	140 ± 17	<0.01
DBP (mmHg)	81 ± 11	82 ± 11	0.02	81 ± 11	82 ± 10	<0.01
Hypertension treatment (%)	1077 (17)	150 (26)	<0.01	6177 (21)	982 (29)	<0.01
Never smoker (%)	1439 (23)	135 (24)	0.05	6735 (23)	688 (20)	<0.01
ex-smoker (%)	1818 (29)	183 (32)	–	8660 (30)	1037 (30)	–
20 cigarettes per day ≥ (%)	907 (15)	98 (17)	–	4615 (16)	592 (17)	–
≥20 cigarettes per day (%)	2007 (33)	156 (27)	–	9003 (31)	1123 (33)	–
Never drinker (%)	2012 (33)	174 (30)	0.03	10309 (36)	1131 (33)	<0.01
Sometimes (%)	838 (14)	59 (10)	–	3710 (13)	418 (12)	–
66 g/day ≥ (%)	2906 (47)	290 (51)	–	13374 (46)	1670 (49)	–
≥66 g/day (%)	415 (7)	49 (9)	–	1620 (6)	221 (6)	–
TC (mmol/L)	5.2 ± 0.9	5.2 ± 0.9	0.79	4.9 ± 0.9	5.0 ± 0.9	<0.01
HDLC (mmol/L)	1.4 ± 0.4	1.4 ± 0.4	<0.01	1.3 ± 0.4	1.4 ± 0.4	0.31
TG (mmol/L)	1.2 (0.9-1.7)	1.3 (1.0-1.9)	<0.01	1.4 (1.0-2.0)	1.5 (1.0-2.3)	<0.01
Non-HDLC (mmol/L)	3.8 ± 0.9	3.8 ± 0.9	0.15	3.6 ± 0.9	3.6 ± 0.9	<0.01
LDLC (mmol/L)	3.1 ± 0.8	3.1 ± 0.9	0.19	–	–	
TC/HDLC	3.9 ± 1.2	4.1 ± 1.3	<0.01	3.9 ± 1.2	4.0 ± 1.3	<0.01
Non-HDL/HDLC	2.9 ± 1.2	3.1 ± 1.3	<0.01	2.9 ± 1.2	3.0 ± 1.3	<0.01
LDLC/HDLC	2.4 ± 0.9	2.4 ± 0.9	0.47	–	–	
TG/HDLC	1.2 ± 1.0	1.4 ± 1.4	<0.01	1.4 ± 1.2	1.6 ± 1.5	<0.01
Dyslipidemia treatment (%)	91 (1)	11 (2)	0.40	405 (1)	66 (2)	0.02
PG (mmol/L)	5.5 ± 0.6	6.0 ± 0.6	<0.01	6.1 ± 1.3	7.1 ± 1.7	<0.01

per day) and level of alcohol intake (never, sometimes, < 66 g/day and ≥ 66 g/day).

Endpoint Determination

We diagnosed incident DM at the time of a fasting plasma glucose level ≥ 7.0 mmol/L, a non-fasting plasma glucose level of ≥ 11.1 mmol/L and/or the start of treatment for DM.

Statistical Analysis

Due to the differences in distribution for several baseline variables, the hazard ratios (HRs) for DM according to the quartiles of each lipid measurement, sex and fasting status were calculated using a multivariable Cox proportional hazards regression model. HRs for DM according to BMI (< 18.5, 18.5-24.9 and ≥ 25.0 kg/m²) based on sex and fasting status were also calculated using a multivariable Cox proportional hazards regression model. Covariates included age, BMI, antihypertensive medication use, antihyperlipid-

emic medication use, systolic blood pressure level, smoking status and alcohol intake, in accordance with previous studies. In order to evaluate whether the predictive ability improved by adding TG to the model consisting of conventional risk factors, such as age, BMI, antihypertensive medication use, antihyperlipidemic medication use, systolic blood pressure level, smoking status and alcohol intake, we compared the discriminative ability by calculating the area under the receiver operating characteristic (ROC) curve and tested for statistical significance using the DeLong method[22]. All statistical analyses were conducted using the SAS, version 9.1 software program (SAS Institute, Cary, NC). Statistical significance was defined as $p < 0.05$.

Results

Of the 127,176 adults (39,196 men and 87,980 women), 8,867 (4,012 men and 4,855 women) devel-