D．考察

中年期の血液検査結果と高齢期の要介護認定との関連についての研究はこれまでに報告おらず関連については未だ確立していない。

1994 年に実施した「大崎国保コホート研究」、および宮城県大崎市の 65 歳以上の住民を対象に 2006 年に実施した「大崎市民コホート 2006 研究」の双方に回答した者を５年間追跡調査し、中年期の血液検査結果と要介護認定との関連を検討した。総コレステロール、HDL コレステロール、中性脂肪、GOT、GPT、γGTP、随時血糖のいずれにおいても血液検査結果と要介護認定との有意な関連は認められなかった。

本研究においては、中年期の血液検査結果から高齢期の要介護認定を予測することは困難であると考えられた。今回検討した検査項目がコレステロール、随時血糖、肝酵素値であり、生活習慣の変化等で比較的変動しやすい項目であり測定から要介護認定をうけるまでの期間が 10 年間以上の時間があるため、要介護認定の予測が困難であった可能性がある。

本研究の長所としては中年期の血液検査結果と高齢期の要介護認定との関連を検討した初めての研究である。また、対象集団が 4,819 人（随時血糖のみ 3,744 人）と規模が大きいことおよび追跡期間が長期間であることである。

本研究の限界としては、血液検査を受診したものが限定的であり受診したものが健康的な生活をより意識していた集団である可能性が除外できないこと、2006 年時点で要介護認定を既にうけていたものを除外しており、高齢期早期に要介護を受けたものと血液検査結果についての関連が不明であること、血液検査が単回の測定であるため測定後の変動が不明であることが挙げられる。

E．結論

中年期の血液検査結果と高齢期の要介護認定との間に関連は認められなかった。

F．健康危険情報

なし

G．研究発表

1．論文発表

なし

2．学会発表

なし

H．知的財産権の出願・登録状況

なし

厚生労働科学研究費補助金（循環器疾患・糖尿病等生活習慣病対策総合研究事業）
分担研究報告書

生活習慣の変化と要介護認定リスクに関する研究

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研究要旨

本研究の目的は、中年期から高齢期の喫煙・飲酒・Body Mass Index（BMI）の変化と要介護状態発生との関連を前向きコホート研究により検証することである。

1994年に実施した「大崎国保コホート研究」、および宮城県大崎市の65歳以上の住民を対象に実施した「大崎市民コホート2006研究」の双方に回答した者12,676名のうち、要介護認定の情報提供に非同意の者、2006年12月15日までに要介護認定を受けていた者と死亡または転出により異動した者、1994年調査と2006年調査で回答に不備がある者を除外した6,066名（喫煙）、6,024名（飲酒）、6,654名（BMI）を4年間追跡した。

結果、喫煙者で要介護認定リスクが有意に上昇した。男性では、禁煙者および喫煙者で有意に要介護認定リスクが上昇した。

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A．研究目的

先行研究より、喫煙・飲酒・Body Mass Index（BMI）といった生活習慣と、全死亡・循環器疾患死亡との関連が示されている。

喫煙により、脳卒中の罹患リスクや、慢性閉塞性肺炎の罹患リスクが上昇することで、その後の日常活動動作に支障をきたすリスクが上昇するという報告もある。同様に、飲酒により、循環器疾患や認知症の罹患リスクの上昇が報告されており、このような疾病罹患によりその後の日常活動動作に支障をきたすリスクが高まると考えられる。また、BMIは循環器疾患罹患およびがん罹患との関連が報告され、要介護認定リスクとの関連が報告されているだけではなく、青年期から中年期にかけてのBMIの変化が、その後の全死亡および循環器疾患死亡リスクと関連することが示されている。

しかしながら、これら喫煙・飲酒・BMIという生活習慣の変化が、要介護認定にどのように関連するか調査した研究はほとんどない。

本研究は、中年期から高齢期にかけてのこれらの生活習慣の変化と要介護状態発生との関連を前向きコホート研究により検証することを目的とし、1994年に実施した「大崎国保コホート研究」、および宮城県大崎市の65歳以上の住民を対象に2006年に実施した「大崎市民コホート2006研究」の双方に回答した者を対象とし、生活習慣の変化と要介護認定との関連を検討した。

B．研究方法

1）対象者と調査・追跡方法

「大崎国保コホート研究」は、宮城県の大崎保健所管内1市13町に居住する40歳から79歳の国民健康保険加入者全員54,996人を対象として1994年9月から12月に生活習慣などに関する自記式アンケート調査を行った。

対象者 54,966 人に対し、有効回答者数は 52,029 人（95%）であった。

「大崎市民コホート 2006 研究」の調査対象は、宮城県大崎市（上記の１市 13 町のうち、１市６町が 2006 年３月 31 日に合併）の 65 歳以上の住民全員である。2006 年 12 月に、性、年齢、身長、体重などの基本的情報、病歴、身体活動能力、嗜好や食習慣などの健康に関する自記式質問紙調査を実施した。

本研究の対象者は、1994 年に実施した「大崎国保コホート研究」、および宮城県大崎市の 65 歳以上の住民を対象に 2006 年に実施した「大崎市民コホート 2006 研究」の双方に回答した者 12,676 名であった。

要介護認定の区分および認定年月日に関する情報は、大崎市と東北大学大学院医学系研究科社会医学講座公衆衛生学分野との調査実施協定に基づき、文書による同意が得られた者を対象として、本分野に提供された。本研究ではベースライン調査後から５年以内に新規に要介護認定（要支援・要介護の全区分）を受けた場合を、「要介護認定発生」と定義した。なお、死亡または転出の情報は、住民基本台帳の除票により確認した。

２）本研究における解析対象者

1994 年に実施した「大崎国保コホート研究」、および宮城県大崎市の 65 歳以上の住民を対象に実施した「大崎市民コホート 2006 研究」の双方に回答した者 12,676 名のうち、要介護認定の情報提供に非同意の者、2006 年 12 月 15 日までに要介護認定を受けていた者と死亡または転出により異動した者を除外した 8,093 名から、1994 年調査と 2006 年調査にそれぞれの生活習慣の設問への回答に不備がある者を除外した者を解析した。喫煙状況については、6,066 名、飲酒状況については 6,024 名、BMI については 6,654 名をそれぞれ解析対象とした。

３）分析方法

「大崎国保コホート研究」（1994 年）と「大崎市民コホート 2006 研究」（2006 年）における喫煙・飲酒・BMI の回答をそれぞれカテゴリ化し、それぞれの生活習慣の変化について喫煙および飲酒については４カテゴリ、BMI については５カテゴリに分類した。その分類については下記に示す。

喫煙については 1994 年調査時、2006 年調査時ともに「非喫煙」または「過去喫煙」であった者を「非喫煙」、1994 年調査時「過去喫煙」または「非喫煙」かつ、2006 年調査時「現在喫煙」だった者を「喫煙開始・再開」、1994 年調査時「現在喫煙」かつ 2006 年調査時「過去喫煙」だった者を「禁煙」、1994 年調査時「現在喫煙」かつ 2006 年調査時「現在喫煙」だった者を「喫煙」として４カテゴリに分類し、「非喫煙」群を基準とした際の他の群のハザード比と 95%信頼区間を Cox 比例ハザードモデルにより算出した。

飲酒については、1994 年調査時および 2006 年調査時に「非飲酒」または「過去飲酒」だった者を「非飲酒」、1994 年調査時「過去飲酒」または「非飲酒」かつ、2006 年調査時「現在飲酒」だった者を「飲酒開始・再開」、1994 年調査時「現在飲酒」かつ 2006 年調査時「過去飲酒」だった者を「飲酒中断」、1994 年調査時「現在飲酒」かつ 2006 年調査時「現在飲酒」だった者を「飲酒」として４カテゴリに分類し、「非飲酒」群を基準とした際の他の群のハザード比と 95%信頼区間を Cox 比例ハザードモデルにより算出した。

BMI については、1994 年、2006 年調査時の BMI を、それぞれ「やせ（BMI18.5 未満）」、「普通体重（BMI18.5 以上 25.0 未満）」、「肥満（BMI25.0 以上）」とし、1994 年調査時および 2006 年調査時にカテゴリが変化しなかった者をそれぞれ「普通」「やせ」「肥満」とし、1994 年調査時－2006 年調査時のカテゴリが「やせ－普通」「普通－肥満」「やせ－肥満」であった群を「体重増加」、「肥満－普通」「普通－やせ」「肥満－やせ」であった群を「体重

減少」とし、「普通」群を基準とした際の他の群のハザード比と95%信頼区間をCox比例ハザードモデルにより算出した。

主要エンドポイントは、5年間の新規要介護認定の発生とした。調整項目は2006年「大崎市民コホート2006研究」に回答された性別、年齢、既往歴（脳卒中、心筋梗塞、がん、高血圧、関節炎、骨粗鬆症、転倒・骨折）、最終学歴、喫煙（飲酒・BMIの解析時のみ）、飲酒（喫煙・BMIの解析時のみ）、BMI（喫煙・飲酒の解析時のみ）、体の痛み、身体機能の制限とした。身体機能の制限については、基本チェックリストにより運動機能に関する5項目の質問のうち、3項目以上に「はい」と回答した者は身体機能の制限があると定義した。

すべての解析は、統計ソフトSAS Version 9.2（SAS Inc, Cary, NC）を用いた。

4）倫理面への配慮

本調査研究は、東北大学大学院医学系研究科倫理審査委員会の承認を得た。また対象者に対しては、調査目的を書面にて説明した上で、要介護認定に関する情報提供について書面による同意を得ており、倫理面の問題は存在しない。

C．研究結果

1）基本特性

対象者の基本特性を表1－1・表1－2・表1－3に示す。

非喫煙者は、男性、歩行時間30分未満の者が少なく、非飲酒者、短大卒以上、骨粗鬆症既往者、転倒・骨折既往者が多い傾向にあった。禁煙者には、男性、体に痛みのない者が多く、非飲酒者が少ない傾向にあった。

表1－1 喫煙習慣の変化別対象者の基本特性

	非喫煙[a]	喫煙開始・再開[b]	禁煙[c]	喫煙[d]
対象者	4,396	44	776	850
平均年齢(SD)	75.0 (5.7)	73.9 (6.3)	75.0 (5.3)	73.7 (5.4)
男性(%)	36.9	63.6	93.3	92.0
非飲酒者(%)	60.2	34.1	24.1	18.2
短大卒以上(%)	26.5	11.4	16.6	15.1
痛みなし・あまり痛みなし(%)	66.4	50.0	72.8	73.5
肥満者(%)	26.5	27.3	24.1	16.5
歩行30分未満(%)	27.3	36.4	28.1	31.5
身体機能制限なし(%)	73.6	75.0	79.1	80.9
脳卒中(%)	3.0	2.3	4.1	3.3
高血圧(%)	45.8	43.2	39.4	39.1
心筋梗塞(%)	5.0	2.3	8.6	4.0
関節炎(%)	18.6	25.0	11.5	9.9
骨粗鬆症(%)	12.5	6.8	3.4	2.6
がん(%)	8.8	6.8	13.5	8.2
転倒骨折(%)	17.9	18.2	13.0	11.7

[a]1994年調査時、2006年調査時ともに「非喫煙」または「過去喫煙」

[b]1994年調査時「過去喫煙」または「非喫煙」かつ、2006年調査時「現在喫煙」

[c]1994年調査時「現在喫煙」かつ2006年調査時「過去喫煙」

[d]1994年調査時「現在喫煙」かつ2006年調査時「現在喫煙」

表1－2 飲酒習慣の変化別対象者の基本特性

	非飲酒[a]	飲酒開始・再開[b]	飲酒中断[c]	飲酒[d]
対象者	3,065	152	543	2264
平均年齢(SD)	75.2 (5.8)	76.5 (6.3)	75.8 (5.4)	74.1 (5.5)
男性(%)	25.1	45.4	79.7	83.7
非喫煙(%)	75.8	57.2	26.3	30.5
短大卒以上(%)	27.7	17.8	17.3	19.9
痛みなし・あまり痛みなし(%)	65.9	64.5	68.3	72.0
肥満者(%)	25.6	22.4	17.9	25.4
歩行30分未満(%)	26.0	23.7	24.7	33.2
身体機能制限なし(%)	70.4	75.7	73.9	83.9
脳卒中(%)	2.8	4.0	5.5	3.1
高血圧(%)	43.2	40.8	44.2	45.5
心筋梗塞(%)	5.3	9.2	7.9	4.7
関節炎(%)	19.7	14.5	13.8	12.9
骨粗鬆症(%)	15.1	12.5	4.2	3.9
がん(%)	8.1	8.6	15.5	8.8
転倒骨折(%)	18.3	21.7	14.7	14.1

[a]1994年調査時および2006年調査時に「非飲酒」または「過去飲酒」

[b]1994年調査時「過去飲酒」または「非飲酒」かつ、2006年調査時「現在飲酒」

[c]1994年調査時「現在飲酒」かつ2006年調査時「過去飲酒」

[d]1994年調査時「現在飲酒」かつ2006年調査時「現在飲酒」

表1－3 BMIの変化別対象者の基本特性

	普通体重	やせ	肥満	体重増加	体重減少
対象者	3,651	89	1,383	694	837
平均年齢(SD)	74.7 (5.6)	75.7 (6.2)	73.9 (5.3)	73.9 (5.5)	75.9 (5.6)
男性(%)	47.1	33.7	37.6	44.2	42.9
非喫煙(%)	49.9	51.7	56.6	52.2	55.8
非飲酒者(%)	45.1	59.6	48.0	47.1	48.5
短大卒以上(%)	25.6	40.5	23.7	22.6	24.5
痛みなし・あまり痛みなし(%)	70.2	59.6	63.4	66.4	64.8
歩行30分未満(%)	29.2	27.0	25.9	26.5	26.1
身体機能制限なし(%)	80.2	74.2	69.3	72.9	72.3
脳卒中(%)	2.6	3.4	3.3	3.2	3.0
高血圧(%)	39.2	21.4	58.8	46.0	42.1
心筋梗塞(%)	4.5	5.6	5.3	6.1	5.9
関節炎(%)	14.9	15.7	21.6	19.9	14.9
骨粗鬆症(%)	10.8	15.7	11.0	10.1	12.7
がん(%)	8.4	15.7	5.9	7.1	15.2
転倒骨折(%)	16.7	23.6	15.3	16.4	16.9

喫煙者は、平均年齢が若く、男性、体に痛みのない者が多く、肥満者、骨粗鬆症既往者、転倒・骨折既往者が少ない傾向があった。

非飲酒者は男性、身体機能に制限がない者、脳卒中既往者、心筋梗塞既往者、がん既往者が少なく、非喫煙者、短大卒以上、肥満者が多い傾向があった。飲酒者は、1日の歩行時間が30分未満の者、骨粗しょう症既往者、転倒・骨折既往、骨粗鬆症、男性、あまり痛みのない者が多い傾向があった。

普通体重群では、非飲酒者、高血圧既往者が少なく、男性、歩行時間が1日30分未満の者、身体機能に制限がない者が多い傾向があった。体重減少群では、関節炎既往者が少な

く、がん既往者が多い傾向があった。

2）喫煙習慣の変化と要介護認定との関連（表2－1）

5年間の追跡調査の結果、解析対象者6,066名のうち、新規要介護認定の発生者は577例であった。非喫煙群を基準とした際の、喫煙開始・再開、禁煙、喫煙それぞれの群の多変量補正ハザード比（95%信頼区間）はそれぞれ、1.22（0.45-3.30）、1.29（0.99-1.69）、1.39（1.06-1.82）となり、喫煙の群でハザード比が有意に高い傾向にあった。男女別の解析では、男性の禁煙群および喫煙群、女性の喫煙開始・再開群でハザード比が有意に高くなった。

3）飲酒習慣の変化と要介護認定との関連（表2－2）

5年間の追跡調査の結果、解析対象者6,024名のうち、新規要介護認定の発生者は583名であった。

非飲酒群を基準とした際の、飲酒開始・再開、飲酒中断、飲酒の群のハザード比（95%信頼区間）はそれぞれ、0.80（0.50-1.31）、1.17（0.87-1.58）、1.05（0.84-1.31）であった。

4）BMIの変化と要介護認定との関連（表2-3）

5年間の追跡調査の結果、解析対象者6,654名のうち、新規要介護認定の発生者は583名であった。

普通体重群を基準とした際の、やせ、肥満、体重増加、体重減少群のハザード比（95%信頼区間）はそれぞれ、1.15（0.63-2.11）、0.85（0.67-1.07）、0.92（0.69-1.22）、1.20（0.96-1.51）であった。男女別解析の結果では、男性のやせ群でリスク増加傾向が、男女共に体重減少群でリスク増加傾向がそれぞれ示されたが、いずれも有意ではなかった。

表2－1　喫煙習慣の変化と要介護認定リスク

	非喫煙[a]	喫煙開始・再開[b]	禁煙[c]	喫煙[d]
全体				
イベント数	419	4	77	77
性・年齢補正	1.00 (reference)	1.26 (0.47-3.39)	1.42 (1.08-1.85)	**1.48 (1.13-1.94)**
多変量補正[e]	1.00 (reference)	1.22 (0.45-3.30)	1.29 (0.99-1.69)	**1.39 (1.06-1.82)**
男性				
イベント数	126	1	74	69
年齢補正	1.00 (reference)	0.44 (0.06-3.14)	**1.53 (1.15-2.05)**	**1.50 (1.12-2.03)**
多変量補正[f]	1.00 (reference)	0.41 (0.06-2.97)	**1.40 (1.04-1.87)**	**1.42 (1.05-1.92)**
女性				
イベント数	293	3	3	8
年齢補正	1.00 (reference)	**3.77 (1.21-11.81)**	0.53 (0.17-1.65)	1.40 (0.69-2.82)
多変量補正[f]	1.00 (reference)	**4.05 (1.27-12.97)**	0.49 (0.16-1.54)	1.32 (0.64-2.72)

[a]1994年調査時、2006年調査時ともに「非喫煙」または「過去喫煙」

[b]1994年調査時「過去喫煙」または「非喫煙」かつ、2006年調査時「現在喫煙」

[c]1994年調査時「現在喫煙」かつ2006年調査時「過去喫煙」

[d]1994年調査時「現在喫煙」かつ2006年調査時「現在喫煙」

[e]性、年齢、既往歴（脳卒中、心筋梗塞、がん、高血圧、関節炎、骨粗鬆症、転倒・骨折）、最終学歴、飲酒、BMI、体の痛み、身体機能の制限

[f]年齢、既往歴（脳卒中、心筋梗塞、がん、高血圧、関節炎、骨粗鬆症、転倒・骨折）、最終学歴、飲酒、BMI、体の痛み、身体機能の制限

表２－２　飲酒習慣の変化と要介護認定リスク

	非飲酒[a]	飲酒開始・再開[b]	飲酒中断[c]	常に飲酒[d]
全体				
イベント数	328	18	63	174
性・年齢補正	1.00 (reference)	0.93 (0.58–1.50)	1.27 (0.95–1.70)	1.01 (0.81–1.25)
多変量補正[e]	1.00 (reference)	0.80 (0.50–1.31)	1.17 (0.87–1.58)	1.05 (0.84–1.31)
男性				
イベント数	81	5	51	134
年齢補正	1.00 (reference)	0.57 (0.23–1.42)	1.18 (0.83–1.68)	0.86 (0.65–1.13)
多変量補正[f]	1.00 (reference)	0.58 (0.24–1.44)	1.07 (0.75–1.53)	0.90 (0.68–1.20)
女性				
イベント数	247	13	12	40
年齢補正	1.00 (reference)	1.16 (0.66–2.03)	1.18 (0.66–2.10)	1.20 (0.86–1.68)
多変量補正[f]	1.00 (reference)	0.97 (0.53–1.75)	1.19 (0.66–2.16)	1.28 (0.91–1.82)

[a]1994年調査時および2006年調査時に「非飲酒」または「過去飲酒」

[b]1994年調査時「過去飲酒」または「非飲酒」かつ、2006年調査時「現在飲酒」

[c]1994年調査時「現在飲酒」かつ2006年調査時「過去飲酒」

[d]1994年調査時「現在飲酒」かつ2006年調査時「現在飲酒」

[e]性、年齢、既往歴（脳卒中、心筋梗塞、がん、高血圧、関節炎、骨粗鬆症、転倒・骨折）、最終学歴、喫煙、BMI、体の痛み、身体機能の制限

[f]年齢、既往歴（脳卒中、心筋梗塞、がん、高血圧、関節炎、骨粗鬆症、転倒・骨折）、最終学歴、喫煙、BMI、体の痛み、身体機能の制限

表２－３　BMI の変化と要介護認定リスク

	普通体重	やせ	肥満	体重増加	体重減少
全体					
イベント数	286	42	18	63	174
性・年齢補正	1.00 (reference)	1.17 (0.64–2.14)	0.96 (0.77–1.20)	1.00 (0.75–1.34)	**1.29 (1.04–1.61)**
多変量補正	1.00 (reference)	1.15 (0.63–2.11)	0.85 (0.67–1.07)	0.92 (0.69–1.22)	1.20 (0.96–1.51)
男性					
イベント数	49	32	5	51	134
年齢補正	1.00 (reference)	1.81 (0.74–4.41)	0.93 (0.63–1.36)	0.83 (0.51–1.36)	1.24 (0.85–1.79)
多変量補正	1.00 (reference)	1.62 (0.65–4.02)	0.87 (0.59–1.29)	0.72 (0.44–1.18)	1.23 (0.84–1.79)
女性					
イベント数	237	10	13	12	40
年齢補正	1.00 (reference)	0.89 (0.39–2.00)	0.97 (0.74–1.28)	1.10 (0.77–1.57)	1.29 (0.98–1.71)
多変量補正	1.00 (reference)	0.89 (0.39–2.03)	0.85 (0.64–1.12)	1.04 (0.73–1.49)	1.19 (0.90–1.58)

[a]性、年齢、既往歴（脳卒中、心筋梗塞、がん、高血圧、関節炎、骨粗鬆症、転倒・骨折）、最終学歴、喫煙、飲酒、体の痛み、身体機能の制限

[b]年齢、既往歴（脳卒中、心筋梗塞、がん、高血圧、関節炎、骨粗鬆症、転倒・骨折）、最終学歴、喫煙、飲酒、体の痛み、身体機能の制限

D．考　察

1994 年に実施した「大崎国保コホート研究」、および宮城県大崎市の 65 歳以上の住民を対象に 2006 年に実施した「大崎市民コホート 2006 研究」の双方に回答した者を５年間追跡調査し、生活習慣の変化と要介護認定との関連を検討した結果、喫煙者において有意に要介護認定リスクが高まり、特に男性の禁煙者、喫煙者でもリスクが高くなった。また、体重減少者、男性のやせの者でリスクの上昇傾向が見られたがいずれも有意ではなかった。

中年期に喫煙していた者ののうち、その後も喫煙を継続していたもので要介護認定リスクが有意に高まり、男性において中年期の喫煙者が禁煙をしても、その後の要介護認定リスクは高いままであることから、禁煙するか否かに関わらず、中年期の喫煙習慣そのものがその後の要介護認定リスクを高めることが考えられる。これは、中年期の喫煙習慣により、脳血管疾患のリスクが高まり、要介護認定リスクが高まるためではないかと考えられる。また、やせは脳卒中のリスクを高めることがすでに報告されており、やせの状態が継続すること、体重が減少することで脳卒中のリスクが高まり、要介護認定リスクも高まることが考えられる。

本研究の特徴は、1994 年および 2006 年に独立して調査を行っており、思い出しバイアスの可能性が低いことである。さらに、生活習慣について関連する要因（既往歴・体の痛み・運動機能の制限）がある者はこれらの生活習慣が変化しやすい傾向があるため、生活習慣の変化と要介護認定リスクとの間の重要な交絡要因であると考えられる。しかし、これらの因子を調整した場合でも、同様の関連が認められたことから、これらの要因からも独立した関連であることが示唆された。

更に、がん・脳卒中・心筋梗塞の既往は、これらの生活習慣を変化させ、要介護認定リスクにも影響を及ぼす。そのため、がん・脳卒中・心筋梗塞の既往者を除外した解析も行ったが、同様の結果が示された。

E．結　論

前向きコホート研究により、喫煙者で有意に要介護認定リスクの上昇が示された。また、男性の禁煙者、喫煙者、女性の喫煙開始・再開者において有意に要介護認定リスクの上昇が示された。これらの結果により、男性では中年期の不健康な生活習慣そのものが、その後の生活習慣の変化に関わらず、高齢期の要介護認定リスクを高める可能性があることが示された。

F．健康危険情報

なし

G．研究発表

なし

H．知的財産権の出願・登録状況

なし

Ⅳ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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1. Chou WT, Kakizaki M, Tomata Y, Nagai M, Sugawara Y, Kuriyama S, Tsuji I.
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Impact of Weight Change Since Age 20 and Cardiovascular Disease Mortality Risk

– The Ohsaki Cohort Study –

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Background: It is unclear whether weight change since young adulthood affects the risk of mortality due to cardiovascular disease (CVD). The aim of this study was to investigate weight change since age 20 in relation to the risk of CVD mortality.

Methods and Results: A total of 41,364 eligible Japanese men and women aged 40–79 years participated in the Ohsaki Cohort Study baseline survey in 1994. Hazard ratios (HRs) and 95% confidence intervals (CIs) for CVD mortality were calculated according to weight change since age 20 (loss ≥10.0 kg; loss 5.0–9.9 kg; stable [±4.9 kg]; gain 5.0–9.9 kg; gain ≥10.0 kg). During 13.3 years of follow-up, 1,756 participants died of CVD. The association between weight change and CVD mortality was L-shaped in men and U-shaped in women; the multivariate HR (95% CI) for men with weight loss ≥10.0 kg was 1.52 (1.25–1.85), and that for women with weight loss ≥10.0 kg and weight gain ≥10.0 kg was 1.62 (1.25–2.11) and 1.36 (1.09–1.69), respectively. Cross-classification analysis based on body mass index (BMI) at age 20 and weight change tended to be U-shaped, except for men whose BMI had been <25 kg/m^2 at age 20, in which case it was L-shaped.

Conclusions: Weight loss since young adulthood is associated with excess risk of mortality due to CVD in men, while a U-shaped relationship was observed for women.

Key Words: Body mass index; Cardiovascular disease mortality; Japan; Weight change; Young adulthood

Obesity is an established risk factor for cardiovascular disease (CVD) morbidity[1–3] and mortality.[4–6] In addition to a high body mass index (BMI), weight gain also adversely affects CVD risk factors.[7–10] The effect of weight change on CVD mortality has been assessed in several studies, but the results have varied. Some studies have reported weight gain associated with CVD mortality,[11,12] or that there was a U-shaped association,[13–15] whereas others have shown that only weight loss was associated with CVD mortality.[16–20]

Editorial p???

These differences in results could have been due to differences in the age composition of the study participants, the life stage at which weight change occurred, the duration of the weight change, or the length of follow-up among the studies.[21] The elevated mortality risk associated with recent weight loss due to antecedent disease, especially in studies of older people or those with short follow-up periods may easily lead to biased results. Monitoring long-term weight change, which represents the transition of weight trajectories during the course of life, may help to clarify the mixed results for CVD mortality among older subjects.[22] Both being persistently obese since early adulthood and having an increase in BMI category from normal to obese were associated with higher all-cause mortality in the Ohsaki Cohort Study.[23] An inverse relationship in men and L-shaped association in women between weight change and all-cause and CVD mortality, however, were observed in another study among middle-aged Japanese individuals.[19]

Additionally, a previous study has suggested that the metabolic and health consequences of weight change may differ between men and women.[24] Furthermore, sex differences in major cardiovascular risk factors have been noted as a substantial reason for the sex difference in CVD risk.[25] Previous studies of the association between weight change and subsequent CVD morbidity or mortality, however, were based mainly

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on men or on composite results,[7–10,12–16] whereas sex-specific studies have been few and their results inconsistent.[17–20]

To our knowledge, no prospective study has reported the relationship between weight change since early adulthood and specific causes of CVD mortality including ischemic heart disease (IHD) and stroke. The objective of the present study was to investigate weight change since age 20 in relation to the risks of total CVD mortality and mortality due to type of CVD, using data obtained from a large prospective population-based cohort study in Japan.

Methods

Subjects

The present data were derived from the Ohsaki Cohort Study, the study design of which has been described in detail previously.[26–29] The subjects were all National Health Insurance (NHI) beneficiaries, aged 40–79 years, living in the catchment area of the Ohsaki Public Health Center, Miyagi Prefecture, north-east Japan. The Ohsaki Public Health Center is a local government agency that provides preventive health services to the residents of 14 municipalities in Miyagi Prefecture. The NHI is a community-based health insurance system for farmers, the self-employed, pensioners, and their dependants. The study area is a typical rural area and the main industry is agriculture. Thirty-nine percent of men were farmers, 28% were self-employed, and 28% were retired. Among women, 31% were housewives, 25% were farmers, and 15% were self-employed.[27]

We conducted a baseline survey of various lifestyle habits during the period from October through December 1994. Trained survey personnel visited the subjects and informed them of the survey objectives, the fact that subjects were treated anonymously at the data analysis stage, and their freedom to decline. The subjects were asked to complete the questionnaires by themselves and return them to the same personnel member within 1 week. Return of the self-administered questionnaires signed by the participants was considered to imply their consent to participate in the study. In order to protect the subjects' privacy, their personal names were deleted from all NHI Claims History files, Withdrawal History files, and our baseline data files in the subsequent follow-up record linkage. The study protocol was approved by the Ethics Committee of Tohoku University School of Medicine.

Among the 54,996 eligible individuals, 52,029 (95%) responded to the questionnaires. Participants who withdrew from the NHI before 1 January 1995, the time when the prospective collection of data on NHI withdrawals began, were excluded (n=776). Thus, the study cohort consisted of the remaining 51,253 participants. For the present analysis, participants with histories of myocardial infarction or stroke (n=2,510) or cancer (n=1,638) were excluded. After further excluding participants for whom data were missing, or who had extreme values for current height, current weight or weight at age 20 (n=5,741), we included 41,364 subjects (men, n=20,112; women, n=21,252) in the analysis.

Classification of Exposure

The self-administered questionnaire included questions on current height at baseline (in cm), current weight at baseline and recalled weight at age 20 (in kg). For the present analysis, weight change (in kg) was defined as the difference between current weight and recalled weight. The participants were categorized into 5 groups according to weight change since age 20: weight loss ≥10.0 kg; weight loss 5.0–9.9 kg; stable weight (±4.9 kg change); weight gain 5.0–9.9 kg; and weight gain ≥10.0 kg. BMI at baseline and at age 20 was also calculated as current weight and recalled weight at age 20 divided by the square of current height (kg/m^2), respectively.

The self-reported current height and weight data were highly correlated with measured data (correlation coefficient: 0.96 for weight and 0.93 for height) in a subsample who received health examinations in 1995 (n=14,883), the year after the baseline survey.[28]

Follow-up

The primary endpoints for the present analysis were CVD mortality, including IHD and stroke mortality, occurring between 1 January 1995 and 31 March 2008. All participants were followed up for mortality and emigration by reviewing the NHI withdrawal history files. When a participant withdrew from the NHI system because of death, emigration or employment, the date of and reason for withdrawal were coded in the NHI withdrawal history files. Because subsequent information on participants who withdrew from the NHI because of emigration or employment was unavailable, their follow-ups were discontinued. As of 31 March 2008, the follow-up rate in the Ohsaki NHI Cohort Study was 85.2% (80.7% among non-deceased subjects).

For all the decedents, we investigated the causes of death by reviewing the death certificates filed at Ohsaki Public Health Center with permission from the Ministry of Health, Labour, and Welfare, Japan. Causes of death were encoded by trained physicians in accordance with the International Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), for total CVD (group I), IHD (I20–25), total stroke (I60–69), ischemic stroke (I63), and hemorrhagic stroke (I61).

Statistical Analysis

The person-years of follow-up were calculated from 1 January 1995 to the date of death, withdrawal from the NHI, or 31 March 2008, whichever occurred first. Cox proportional hazards regression analysis was used to investigate the sex-specific hazard ratios (HRs) and 95% confidence intervals (CIs) between weight change since age 20 and CVD mortality.

The following variables were considered as potential confounders: age (in years), current height (in cm), body weight at age 20 (in kg), educational levels (junior high school or less, high school and college or higher), baseline job status (employed and not employed), smoking status at age 20 (yes/no), smoking status at baseline (never smoked, smoked in the past, currently smoking <20 cigarettes/day and currently smoking ≥20 cigarettes/day), alcohol consumption (never drank, drank in the past, currently drinking <45.6 g ethanol/day and current drinking ≥45.6 g ethanol/day), time spent walking (≥1 h/day and <1 h/day). For women, menopausal status (yes/no), oral contraceptive use (yes/no) and hormone replacement therapy (yes/no) were also considered as confounders.

To assess whether the risk of CVD death associated with weight change differed between subjects who were underweight, normal weight and overweight, we cross-classified the participants into groups according to their BMI at age 20 (<22.5 kg/m^2, underweight; 22.5–24.9 kg/m^2, normal weight; and ≥25.0 kg/m^2, overweight), treating BMI 22.5–24.9 kg/m^2 at age 20 with subsequent stable weight as the reference group. Furthermore, we repeated the analysis after exclusion of deaths in the first 3 years of follow-up. Other stratified analyses were conducted according to the age at study entry (40–59 years vs. 60–79 years) and smoking status at baseline (never-smokers

Table 1. Subject Characteristics vs. Weight Change Since Age 20

	Weight change since age 20					P-value
	Loss		Stable	Gain		
	≥10.0 kg	5.0–9.9 kg	±4.9 kg	5.0–9.9 kg	≥10.0 kg	
Men (n=20,112)						
No. subjects	1,609	3,117	7,578	3,880	3,928	
Age (years)	66.9±8.3	63.9±9.0	58.2±10.4	56.2±10.2	55.4±9.9	<0.0001
BMI at age 20 (kg/m²)	26.1±4.1	24.2±2.4	22.5±2.1	21.7±2.0	21.1±2.1	<0.0001
BMI at baseline (kg/m²)	20.9±2.7	21.8±2.3	22.4±2.1	24.2±2.0	26.3±2.4	<0.0001
Hypertension	28.3	24.3	20.2	22.6	26.7	<0.0001
Diabetes mellitus	12.7	8.7	5.1	7.0	7.0	<0.0001
Education until age 15	72.5	72.1	60.6	54.9	52.8	<0.0001
Unemployed at baseline	32.8	22.9	16.3	15.7	13.7	<0.0001
Smoker at age 20	35.4	37.3	41.3	42.3	42.3	<0.0001
Current smoker	62.5	60.3	59.3	51.7	49.3	<0.0001
Current drinker	63.0	69.7	75.4	75.0	76.7	<0.0001
Walking <1 h/day	52.6	48.1	47.4	55.0	55.3	<0.0001
Women (n=21,252)						
No. subjects	1,192	2,822	7,417	4,865	4,956	
Age (years)	67.0±9.1	63.7±9.7	59.2±10.0	58.5±9.5	58.7±9.3	<0.0001
BMI at age 20 (kg/m²)	26.5±3.9	24.4±2.7	22.4±2.5	21.5±2.2	20.7±2.3	<0.0001
BMI at baseline (kg/m²)	20.7±2.8	21.6±2.6	22.5±2.4	24.4±2.3	26.9±2.7	<0.0001
Hypertension	26.9	26.1	22.4	26.5	36.1	<0.0001
Diabetes mellitus	8.0	6.2	4.5	4.3	5.7	<0.0001
Education until age 15	68.7	62.0	52.8	53.7	56.3	<0.0001
Unemployed at baseline	61.4	57.2	46.2	48.5	51.6	<0.0001
Smoker at age 20	1.5	1.4	1.4	1.3	1.8	<0.0001
Current smoker	14.1	8.8	8.5	7.2	9.7	<0.0001
Current drinker	18.8	20.6	23.0	24.6	26.5	<0.0001
Walking <1 h/day	58.1	56.4	55.0	57.2	60.4	<0.0001

Data given as mean±SD or %. BMI, body mass index.

vs. former smokers and current smokers in men; never-smokers vs. ever-smokers in women, because the number of former smokers was too few). The statistical evidence for the difference in effect between these subgroup participants was assessed by computing log-likelihood ratio tests of the interaction. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

The mean BMI at age 20 was 22.5±2.8 kg/m² and at study entry it was 23.5±3.0 kg/m². The mean change in body weight from age 20 to study entry was a gain of 2.0±8.8 kg in men and a gain of 3.3±8.4 kg in women.

The sex-specific baseline characteristics of participants according to the weight change categories are summarized in **Table 1**. The participants who had lost ≥10.0 kg in weight were older, and were more likely to have hypertension and diabetes, to have been educated until age 15, to have been unemployed at baseline, and to be current smokers. In contrast, the participants who had gained ≥10.0 kg in weight were more likely to be smokers at age 20, current drinkers, and to walk <1 h a day. The proportions of current smokers and current drinkers among women, however, were much lower than among men.

During the 13.3 years of follow-up (451,081 person-years), we documented 1,756 CVD deaths (1,017 men and 739 women), including 408 IHD deaths (253 men and 155 women) and 790 stroke deaths (436 men and 354 women). **Table 2** lists the multivariate-adjusted HRs for CVD mortality according to the weight change categories. There was an L-shaped association in men and a U-shaped association in women between weight change and CVD mortality (P=0.006 for interaction with sex). In men, the multivariate-adjusted HR relative to the stable weight group was 1.52 (95% CI: 1.25–1.85) for the weight loss ≥10.0 kg group, and no significant risks were observed in the other weight change groups. In women, the multivariate-adjusted HR relative to the stable weight group was 1.62 (95% CI: 1.25–2.11) for the weight loss ≥10.0 kg group and 1.36 (95% CI: 1.09–1.69) for the weight gain ≥10.0 kg group.

The risk of IHD and stroke mortality had trends similar to overall CVD mortality. In men, the weight loss ≥10.0 kg group had a significantly higher risk of death due to all forms of stroke (HR, 1.38; 95% CI: 1.01–1.89) and ischemic stroke (HR, 1.54; 95% CI: 1.00–2.37). A noticeably lower risk of IHD mortality was observed among men with weight gain ≥10.0 kg (HR, 0.59; 95% CI: 0.37–0.94). In women, the relationship tended to be U-shaped for IHD and for stroke mortality. These excess risks for all CVD and IHD mortality related to weight loss were persistently observed even after exclusion of early deaths in the first 3 years of follow-up.

Table 3 lists the multivariate-adjusted HRs for CVD mortality according to BMI at age 20 and weight change categories, treating subjects with a BMI 22.5–24.9 kg/m² at age 20 and subsequent stable weight (±4.9 kg change) as the reference

Table 2. CVD Mortality vs. Weight Change Since Age 20

	Weight change since age 20				
	Loss		Stable	Gain	
	≥10.0 kg	5.0–9.9 kg	±4.9 kg	5.0–9.9 kg	≥10.0 kg
Men (n=20,112)					
Person-years	14,652	31,798	83,070	43,485	44,506
All CVD					
No. deaths	189	211	345	139	133
HR1 (95% CI)	1.52 (1.25–1.85)‡	1.04 (0.87–1.24)	1 (Reference)	0.95 (0.78–1.16)	0.99 (0.80–1.21)
HR2 (95% CI)	1.36 (1.08–1.70)†	0.99 (0.81–1.20)	1 (Reference)	0.97 (0.78–1.21)	0.96 (0.76–1.20)
IHD					
No. deaths	45	49	97	39	23
HR1 (95% CI)	1.41 (0.95–2.10)	0.92 (0.64–1.31)	1 (Reference)	0.92 (0.63–1.35)	0.59 (0.37–0.94)*
HR2 (95% CI)	1.27 (0.80–1.99)	0.79 (0.52–1.18)	1 (Reference)	0.86 (0.57–1.31)	0.54 (0.32–0.92)*
All strokes					
No. deaths	74	83	148	68	63
HR1 (95% CI)	1.38 (1.01–1.89)*	0.96 (0.73–1.26)	1 (Reference)	1.08 (0.81–1.45)	1.08 (0.80–1.47)
HR2 (95% CI)	1.24 (0.86–1.78)	0.96 (0.70–1.30)	1 (Reference)	1.19 (0.87–1.63)	1.03 (0.73–1.45)
Ischemic stroke					
No. deaths	43	38	65	35	30
HR1 (95% CI)	1.54 (1.00–2.37)*	0.90 (0.60–1.36)	1 (Reference)	1.34 (0.88–2.04)	1.25 (0.80–1.96)
HR2 (95% CI)	1.24 (0.74–2.06)	0.85 (0.54–1.35)	1 (Reference)	1.56 (1.00–2.41)*	1.16 (0.70–1.91)
Hemorrhagic stroke					
No. deaths	15	20	49	15	17
HR1 (95% CI)	1.16 (0.61–2.21)	0.84 (0.49–1.44)	1 (Reference)	0.66 (0.37–1.18)	0.78 (0.44–1.39)
HR2 (95% CI)	0.91 (0.39–2.10)	0.82 (0.43–1.56)	1 (Reference)	0.66 (0.33–1.32)	0.87 (0.45–1.65)
Women (n=21,252)					
Person-years	12,266	30,175	82,206	53,797	55,126
All CVD					
No. deaths	104	173	195	110	157
HR1 (95% CI)	1.62 (1.25–2.11)‡	1.52 (1.23–1.88)‡	1 (Reference)	0.98 (0.77–1.24)	1.36 (1.09–1.69)†
HR2 (95% CI)	1.48 (1.09–2.00)*	1.54 (1.21–1.95)‡	1 (Reference)	1.08 (0.84–1.41)	1.48 (1.16–1.89)†
IHD					
No. deaths	24	42	35	25	29
HR1 (95% CI)	1.98 (1.11–3.53)*	2.02 (1.27–3.22)†	1 (Reference)	1.24 (0.74–2.08)	1.39 (0.84–2.31)
HR2 (95% CI)	1.92 (1.00–3.71)*	2.01 (1.20–3.39)†	1 (Reference)	1.31 (0.74–2.33)	1.29 (0.72–2.30)
All strokes					
No. deaths	42	83	98	57	74
HR1 (95% CI)	1.39 (0.93–2.07)	1.49 (1.10–2.01)*	1 (Reference)	0.99 (0.71–1.38)	1.24 (0.90–1.69)
HR2 (95% CI)	1.28 (0.80–2.05)	1.71 (1.21–2.41)†	1 (Reference)	1.20 (0.83–1.73)	1.42 (0.99–2.03)
Ischemic stroke					
No. deaths	21	35	39	25	26
HR1 (95% CI)	1.23 (0.68–2.22)	1.30 (0.81–2.08)	1 (Reference)	1.19 (0.72–1.98)	1.21 (0.72–2.02)
HR2 (95% CI)	0.97 (0.49–1.93)	1.41 (0.85–2.35)	1 (Reference)	1.18 (0.67–2.08)	1.41 (0.81–2.44)
Hemorrhagic stroke					
No. deaths	7	29	15	11	20
HR1 (95% CI)	1.00 (0.40–2.50)	1.43 (0.77–2.68)	1 (Reference)	0.71 (0.35–1.46)	1.26 (0.68–2.33)
HR2 (95% CI)	–§	1.83 (0.88–3.81)	1 (Reference)	1.21 (0.55–2.65)	1.70 (0.80–3.58)

*P≤0.05; †P≤0.01; ‡P≤0.001. §No. deaths <3.

HR1 adjusted for age (in years), current height (in cm), body weight at age 20 (in kg), education (junior high school or less, high school, and college or higher), baseline job status (employed and unemployed), smoking status at age 20 (yes/no), smoking status at baseline (never smoked, smoked in the past, currently smoking <20 cigarettes/day and currently smoking ≥20 cigarettes/day), alcohol consumption (never drank, drank in the past, currently drinking <45.6 g ethanol/day and current drinking ≥45.6 g ethanol/day), time spent walking (≥1 h/day and <1 h/day); women plus menopause status (yes/no), oral contraceptive use (yes/no) and hormone replacement therapy (yes/no); HR2, participants excluded from HR1: those who died <3 years after baseline.

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; IHD, ischemic heart disease.

Table 3. CVD Mortality vs. Weight Change Since Age 20 and BMI at Age 20

BMI at age 20	Weight change since age 20				
	Loss		Stable	Gain	
	≥10.0 kg	5.0–9.9 kg	±4.9 kg	5.0–9.9 kg	≥10.0 kg
Men (n=20,112)					
<22.5 kg/m²					
No. deaths	22	47	157	88	100
HR1 (95% CI)	2.02 (1.27–3.20)†	1.17 (0.83–1.65)	1.11 (0.86–1.43)	1.02 (0.76–1.37)	1.05 (0.78–1.41)
HR2 (95% CI)	1.71 (0.98–2.97)	1.13 (0.77–1.66)	1.10 (0.83–1.45)	1.01 (0.73–1.40)	1.03 (0.74–1.43)
22.5–24.9 kg/m²					
No. deaths	68	91	132	39	25
HR1 (95% CI)	1.84 (1.36–2.47)‡	1.11 (0.85–1.45)	1 (Reference)	0.99 (0.69–1.41)	1.05 (0.69–1.62)
HR2 (95% CI)	1.60 (1.13–2.26)†	1.02 (0.75–1.38)	1 (Reference)	1.05 (0.71–1.55)	0.97 (0.60–1.59)
≥25.0 kg/m²					
No. deaths	99	73	56	12	8
HR1 (95% CI)	1.50 (1.10–2.04)†	1.14 (0.84–1.54)	1.32 (0.95–1.83)	1.48 (0.81–2.69)	1.83 (0.89–3.77)
HR2 (95% CI)	1.53 (1.08–2.16)*	1.24 (0.88–1.73)	1.49 (1.05–2.13)*	1.67 (0.89–3.14)	1.43 (0.58–3.54)
Women (n=21,252)					
<22.5 kg/m²					
No. deaths	16	39	101	67	115
HR1 (95% CI)	4.32 (2.45–7.62)‡	2.18 (1.42–3.34)‡	1.49 (1.04–2.12)*	1.25 (0.85–1.83)	1.70 (1.18–2.45)†
HR2 (95% CI)	4.04 (2.06–7.92)‡	2.29 (1.42–3.72)‡	1.55 (1.04–2.30)*	1.51 (0.99–2.30)	1.91 (1.28–2.86)†
22.5–24.9 kg/m²					
No. deaths	19	56	54	27	33
HR1 (95% CI)	1.68 (0.99–2.85)	1.84 (1.26–2.68)†	1 (Reference)	1.12 (0.70–1.77)	2.08 (1.35–3.21)‡
HR2 (95% CI)	1.40 (0.74–2.67)	1.83 (1.20–2.81)†	1 (Reference)	0.97 (0.56–1.68)	2.13 (1.30–3.47)†
≥25.0 kg/m²					
No. deaths	69	78	40	16	9
HR1 (95% CI)	1.86 (1.23–2.81)†	1.86 (1.27–2.71)†	1.33 (0.86–2.05)	1.86 (1.05–3.30)*	1.90 (0.93–3.89)
HR2 (95% CI)	1.84 (1.16–2.93)*	2.01 (1.32–3.05)†	1.40 (0.87–2.25)	2.32 (1.28–4.19)†	2.39 (1.15–4.97)*

*P≤0.05; †P≤0.01; ‡P≤0.001.
HR1 adjusted for age (in years), current height (in cm), body weight at age 20 (in kg), education (junior high school or less, high school, and college or higher), baseline job status (employed and unemployed), smoking status at age 20 (yes/no), smoking status at baseline (never smoked, smoked in the past, currently smoking <20 cigarettes/day and currently smoking ≥20 cigarettes/day), alcohol consumption (never drank, drank in the past, currently drinking <45.6 g ethanol/day and current drinking ≥45.6 g ethanol/day), time spent walking (≥1 h/day and <1 h/day); women plus menopause status (yes/no), oral contraceptive use (yes/no) and hormone replacement therapy (yes/no); HR2, participants excluded from HR1: those who died <3 years after baseline.
Abbreviations as in Tables 1,2.

group. For those whose BMI had been <25 kg/m² at age 20, there was an L shaped association in men and a U-shaped association in women between weight change and CVD mortality. For those whose BMI had been ≥25 kg/m² at age 20, the associations tended to be U-shaped in both men and women; the multivariate HR (95% CI) for men was 1.50 (1.10–2.04) for the weight loss ≥10.0 kg group and 1.83 (0.89–3.77) for the weight gain ≥10.0 kg group, while for women it was 1.86 (1.23–2.81) for the weight loss ≥10.0 kg group and 1.90 (0.93–3.89) for the weight gain ≥10.0 kg group. These excess risks for CVD mortality were persistently observed even after exclusion of early deaths in the first 3 years of follow-up. In summary, the association tended to be U-shaped except for men whose BMI had been <25 kg/m² at age 20.

Table 4 lists the associations between weight change and CVD mortality, after stratification by age at study entry (40–59 years vs. 60–79 years) and smoking status. For the participants aged 60–79 years, the associations remained L-shaped in men and U-shaped in women. The risks of CVD mortality among the weight loss ≥10.0 kg groups were not altered significantly by smoking habit. The multivariate HR (95% CI) for men was 1.67 (0.92–3.03) among never-smokers, 1.60 (1.10–2.33) among former smokers, and 1.52 (1.16–2.00) among current smokers; the interaction was not statistically significant (P=0.15).

Discussion

In this large population-based prospective study of Japanese men and women, we observed that the associations between weight change and CVD mortality differed by gender. Weight loss since age 20 was associated with significantly higher risk of CVD mortality in both men and women. Weight gain ≥10.0 kg was a predictor of CVD mortality in women, but not in men. In cross-classification analysis based on BMI at age 20 and weight change, the association tended to be U-shaped, except for men whose BMI had been <25 kg/m² at age 20. This excess risk among the participants who had lost weight persisted after we excluded deaths within 3 years of follow-up.

Previous studies have recognized different association between weight change and CVD mortality according to the life stage at which weight change occurred, being L-shaped in studies examining middle-aged men,[16,17,19,20] and U-shaped in studies examining elderly populations.[14,15] Higher CVD mor-

Table 4. CVD Mortality vs. Weight Change Since Age 20, Age and Baseline Smoking Status

	Weight change since age 20				
	Loss		Stable	Gain	
	≥10.0 kg	5.0–9.9 kg	±4.9 kg	5.0–9.9 kg	≥10.0 kg
Men (n=20,112)					
Age					
40–59					
No. deaths	10	20	55	28	41
HR (95% CI)	1.85 (0.86–3.97)	1.37 (0.80–2.34)	1 (Reference)	0.93 (0.59–1.48)	1.26 (0.83–1.91)
60–79					
No. deaths	179	191	290	111	92
HR (95% CI)	1.46 (1.19–1.80)‡	1.00 (0.83–1.20)	1 (Reference)	0.97 (0.78–1.22)	0.92 (0.72–1.17)
Baseline smoking status					
Never					
No. deaths	20	22	45	16	25
HR (95% CI)	1.67 (0.92–3.03)	0.83 (0.49–1.41)	1 (Reference)	0.88 (0.49–1.58)	1.29 (0.78–2.14)
Former					
No. deaths	52	58	92	38	37
HR (95% CI)	1.60 (1.10–2.33)*	1.06 (0.76–1.49)	1 (Reference)	0.82 (0.56–1.21)	0.77 (0.52–1.15)
Current					
No. deaths	101	118	187	75	67
HR (95% CI)	1.52 (1.16–2.00)†	1.09 (0.86–1.38)	1 (Reference)	1.04 (0.79–1.36)	1.08 (0.81–1.45)
Women (n=21,252)					
Age					
40–59					
No. deaths	3	13	19	17	19
HR (95% CI)	1.86 (0.50–6.85)	2.49 (1.19–5.22)*	1 (Reference)	1.28 (0.66–2.48)	1.16 (0.60–2.24)
60–79					
No. deaths	101	160	176	93	138
HR (95% CI)	1.53 (1.17–2.01)†	1.44 (1.15–1.79)†	1 (Reference)	0.95 (0.74–1.23)	1.40 (1.11–1.76)†
Baseline smoking status					
Never					
No. deaths	63	116	139	78	119
HR (95% CI)	1.50 (1.08–2.08)*	1.48 (1.14–1.90)†	1 (Reference)	1.00 (0.75–1.32)	1.50 (1.17–1.94)†
Ever					
No. deaths	18	16	20	11	9
HR (95% CI)	1.83 (0.87–3.84)	1.31 (0.65–2.61)	1 (Reference)	1.01 (0.48–2.12)	0.59 (0.26–1.33)

*P≤0.05; †P≤0.01; ‡P≤0.001.
HR adjusted for age (in years), current height (in cm), body weight at age 20 (in kg), education (junior high school or less, high school, and college or higher), baseline job status (employed and unemployed), smoking status at age 20 (yes/no), smoking status at baseline (never smoked, smoked in the past, currently smoking <20 cigarettes/day and currently smoking ≥20 cigarettes/day), alcohol consumption (never drank, drank in the past, currently drinking <45.6 g ethanol/day and current drinking ≥45.6 g ethanol/day), time spent walking (≥1 h/day and <1 h/day); women plus menopause status (yes/no), oral contraceptive use (yes/no) and hormone replacement therapy (yes/no).
Abbreviations as in Table 2.

tality associated with weight loss might be a direct consequence of ill health[14,16,17] or be confounded by smoking and changes in smoking habits since age 20. In the present study, the higher risk in subjects who had lost weight was persistently observed in the subgroup without self-reported histories of hypertension and diabetes mellitus at baseline (data not shown), or after exclusion of early deaths in the first 3 years of follow-up. Furthermore, the higher risk of CVD mortality was not altered by smoking status at age 20 or at baseline. Therefore, the excess risk of CVD mortality associated with weight loss could not be totally explained by pre-existing disease or smoking status. BMI at study entry, however, was low (men, 20.9 kg/m^2; women, 20.7 kg/m^2) among those participants who had lost weight, while low BMI has been reported as an unfavorable prognostic factor among Japanese patients with congestive heart failure[30] or those who have undergone first coronary revascularization.[31] The higher case-fatality rate among those subjects may be 1 possible reason for the excess risk of CVD mortality associated with weight loss.

In men, the present study yielded mixed results among weight gain groups. The risk of CVD mortality for the weight gain groups tended to be higher than that among the stable weight groups, except for men who were aged >60 years at study entry or whose BMI at age 20 had been <25 kg/m^2. Older men who had gained weight since young adulthood, or those who had not been overweight at age 20, might receive a beneficial effect. In other words, weight gain appeared to be harmful to younger men, or those whose BMI had been ≥25 kg/m^2 at age

20. Furthermore, there was a noticeably lower risk of IHD mortality among men with a weight gain ≥10.0 kg, the majority of whom had a BMI <22.5 kg/m^2 at age 20. A previous study also reported that high BMI in middle age may be the most important weight-related risk factor for IHD mortality in old age,[15] because atherosclerosis begins in the first decade of life, even though its clinical manifestations most often occur in the fifth decade and beyond.[32] According to the National Health and Nutrition Survey conducted by the Ministry of Health, Labour, and Welfare, Japan, the prevalence of being overweight among men aged 20–29 years has increased from 12% to 21% during the last 20 years,[33] indicating that the unfavorable effect of weight gain might impose a substantial public health burden on Japan in the near future.

In this study, we observed that the associations between weight change and CVD mortality differed by gender (P=0.006 for interaction with sex), in that weight gain was associated with a higher mortality in women but not in men. Few studies have examined sex-specific effects on the association between weight change and CVD mortality.[17,19,20] In Norway, Drøyvold et al reported that both men and women who lost weight had a higher CVD mortality than those who were weight-stable,[17] whereas Wilsgaard et al showed that weight loss was associated with excess mortality only in men.[20] A previous study has suggested that weight change is associated with more relative changes in fat-free mass in men than in women,[24] and body fat percentage has been reported as highly indicative of CVD risk factors in another study.[34] In other words, weight gain in women is associated with a higher degree of fat mass gain than is the case in men, possibly leading to unfavorable metabolic and health consequences. In Japanese women, Saito et al reported that there was no significant association between weight change since age 20 and CVD mortality,[19] although we observed a U-shaped relationship for women in the present study. The difference may be explained by the age of the subjects, in that most of the present female subjects were >60 years old and thus post-menopausal, lacking the estrogen protection effect.[35]

The present study had several strengths in addition to its prospective nature and high response rate. First, we assessed the effects of several important confounding factors on weight change and CVD mortality: smoking status at age 20 and at baseline; alcohol drinking; and physical activity. Subgroup analysis of smoking status was also conducted to clarify that there was no interaction between smoking and weight loss with CVD mortality. Second, to our knowledge, this is the first reported study to have examined the association of weight change since young adulthood with specific causes of CVD mortality.

Several limitations should also be noted. First, body weight at age 20 was based on recall and could not be validated in the present subjects. The accuracy of long-term recall of previous body weight, however, has been verified in a study involving middle-aged Japanese subjects, and that had indicated high correlation (r=0.85).[36] Regarding the validity of self-reported past body weight in the elderly population, previous studies showed that persons with a higher current BMI tended to underestimate their past weight, whereas those with a lower current BMI tended to overestimate their past weight.[37,38] This potential for overestimation of weight change may have weakened, but not substantially distorted the association between weight change and risk of CVD mortality in the present study. Second, information about weight was available only at 2 time points: age 20 and study entry, and there was no information about whether any weight loss was intentional or unintentional. Because long-term weight change is an indicator of long-term energy balance, while negative energy balance could occur as a result of high expenditure such as a debilitating condition or low calorie intake such as that associated with dieting, the present findings should not be interpreted as evidence against the benefit of intentional weight reduction. Third, the validity of cause of death information based on death certificates, which were encoded by trained physicians, was somewhat limited. Possible misclassification should be noted because cause of death encoded as heart failure (code I50) or cardiac arrest (code I46) may also include death due to other underlying diseases.[39] The association between weight change and the risk of CVD mortality, however, did not alter even when we omitted those deceased subjects.

Conclusion

Weight loss since young adulthood was found to be associated with excess risk of CVD mortality in men, while a U-shaped relationship was observed for women. Men and women whose BMI had been <22.5 kg/m^2 at age 20 and then lost ≥10 kg in weight had the highest risk of CVD mortality. The present results suggest that if lean young people maintain a stable weight, and overweight young people do not gain weight as they age, then the risk of mortality due to CVD may be reduced.

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Original Article

Association between sleep duration, weight gain, and obesity for long period

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ABSTRACT

Background: Although previous studies showed the long-term effects of sleep duration on risk of weight gain, Western tends to gain weight irrespective of sleep duration over a long period. Conversely, it is showed that body mass index (BMI) decreases during a long period in Japanese and thus, the long-term effect of sleep duration on weight gain and obesity is still unclear in Asia.

Methods: We followed up 13,629 participants aged 40–79 years and prospectively collected data from 1995 to 2006. We divided the participants into five groups according to their self-reported sleep duration: ⩽5 h (short sleep), 6 h, 7 h (reference), 8 h, and ⩾9 h (long sleep). The main outcome was ⩾5 kg weight gain or BMI ⩾ 25 kg/m^2 (obesity). We used logistic regression analyses to derive odds ratios (ORs) and 95% confidence intervals (CIs), adjusted for several confounding factors.

Results: We observed no association between sleep duration and risk of ⩾5 kg weight gain and obesity. After stratification by BMI, long sleepers had a significantly increased risk of ⩾5 kg weight gain (OR: 1.36, 95%CI: 1.09–1.70) in obese participants.

Conclusions: Among community-dwelling Japanese, only obese long sleepers have a significantly increased long-term risk of ⩾5 kg weight gain.

1. Introduction

Obesity is increasing worldwide and its associated health problems are now widely recognized. According to the World Health Organization, Asia has a low prevalence of obesity in comparison to other areas of the world [1]. They recommended that obesity should be defined lower in Asia than Western [2]. In Japan, the prevalence of obesity is only 3%, and severe obesity almost never exists [3]. However, the percentage age of body fat is higher in Asian than in Western with the same body mass index (BMI) [4]. Meanwhile, according to the Organisation for Economic Co-operation and Development, Koreans have the shortest mean sleep duration in the world, followed by the Japanese [5].

The associations between sleep duration, weight gain, and/or obesity have been examined previously in seven meta-analyses and a systematic review [6–12]. However, almost all of the populations studied were Western, with longer mean sleep durations and higher prevalence of obesity than Asian populations. In Asia, three prospective studies, all from Japan, have examined the association between sleep duration and obesity [13–15]. However, the study participants were recruited from among people who were undergoing health checkups. The effect of sleep duration on weight gain and obesity has not yet been examined in an Asian population or recruited from the general community.

In addition, some previous studies have examined the long-term effects of sleep duration on weight gain and obesity from data accumulated over periods of at least 10 years [16,17]. Even though these studies showed that short sleepers were at risk of weight gain and obesity, Patel et al. showed that their study participants gained weight irrespective of sleep duration over a 16 year period [16]. In contrast, Matsushita et al. showed that mean BMI tended to decrease during a 10 year follow-up period in Japanese participants aged ⩾50 years [18]. Thus, the long-term association between sleep duration, weight gain, and obesity might differ between Western and Japanese populations, and the long-term effect of sleep duration on weight gain and obesity is still unclear in Asia.

In the present study, therefore, we examined the long-term association between sleep duration, weight gain, and obesity in Japanese subjects recruited from the general community based on data accumulated over 12 years.

2. Methods

2.1. Study cohort

Between October and December 1994, we distributed a self-administered questionnaire survey of various lifestyle habits to all National Health Insurance (NHI) beneficiaries aged 40–79 years

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who lived in the catchment area of Ohsaki Public Health Center, Miyagi Prefecture, northeastern Japan [19]. Among 54,996 eligible individuals, 52,029 (95%) responded. We followed-up with the participants from January 1, 1995 through December 31, 2008 and recorded any mortality or migration by reviewing the NHI withdrawal history files. On December 1, 2006, we distributed another questionnaire to all community-dwelling individuals aged over 40 years in Ohsaki City [20]. Among the 77,325 eligible individuals, 40,027 individuals who participated in the survey in 1994, were included without death or lost to follow-up until December 1, 2006. By combining the data for these two surveys, we were able to use the questionnaire responses for 16,982 participants (response rate 42.4%).

For the present analysis, we excluded 3116 participants who did not provide information about body weight and height, and 237 participants who did not provide information about sleep duration. As a result, a final total of 13,629 participants were included.

The study protocol was approved by the Ethics Committee of Tohoku University School of Medicine. We considered the return of self-administered questionnaires signed by the participants to imply their consent to participate in the study.

2.2. Sleep duration

The self-administered questionnaire included question on sleep duration. Sleep duration was assessed through each participant's response to the question, "How many hours on average do you sleep per day ?" The participants entered the mean integer number representing the hours of sleep taken per day during the previous year. We divided the participants into five groups according to their sleep duration: ⩽5 h (short sleep), 6 h, 7 h (reference), 8 h, and ⩾9 h (long sleep).

2.3. Outcome measures

The main outcome measure was ⩾5 kg weight gain calculated as weight (kg) in the NHI Cohort Study minus self-reported weight (kg) recorded in the Ohsaki Cohort 2006 Study. We also assessed BMI ⩾ 25.0 kg/m^2 (obesity) calculated as weight (kg) divided by the square of height (m^2). These self-reported heights, weights, and BMI in the questionnaire were considered to be sufficiently valid [21]. The Pearson's correlation coefficient (r) between the self-reported values and measured values were $r = 0.96$ ($p < 0.01$) for weight, $r = 0.93$ ($p < 0.01$) for height, and $r = 0.88$ ($p < 0.01$) for BMI.

2.4. Statistical analysis

We used logistic regression analyses to derive odds ratios (ORs) and 95% confidence intervals (CIs) for ⩾5 kg weight gain and obesity according to each sleep duration category and to adjust for potentially confounding factors, using the SAS version 9.2 statistical software package. The 7 h sleep duration category was selected as the reference. All p values were two-tailed and differences at $p < 0.05$ were accepted as statistically significant.

We considered the following variables to be potential confounding factors: sex (men or women), age (continuous), BMI (<18.5, 18.5–24.9, 25.0–29.9, or ⩾30.0 kg/m^2), education (junior high school or less, high school, or college/university or higher), smoking status (never smoker, past smoker, current smoker consuming 1–19 cigarettes per day, or current smoker consuming at least 20 cigarettes per day), alcohol drinking (never drinker, past drinker, or current drinker), time spent walking per day (less than 1 h, or 1 h or longer), sports and physical exercise time per week (less than 1 h, 1–2 h, 3–4 h, or 5 h or longer), job status (employed, or no occupation or housewife), marital status (married or unmarried), menopausal status (premenopausal or postmenopausal), coffee consumption (never or occasionally, 1–2 cups/day, 3–4 cups/day, ⩾5 cups/day), and self-rated health (good or not good). We further adjusted for energy consumption (kcal/day) in the multivariate models 2.

In addition, we repeated analyses after excluding participants who had functional limitation, poor self-rated health, or history of disease. Physical function status was assessed using the 6 item measure of the Medical Outcomes Study (MOS) Short-form General Health Survey [22]. Participants were excluded if they stated on the MOS questionnaire that they were unable to perform moderate or vigorous activities ($n = 3576$), walk one block ($n = 25$), or perform self-care activities such as eating, dressing, bathing, or using the toilet ($n = 2$). We excluded participants who reported severe bodily pain ($n = 246$), poor self-rated health ($n = 896$), or history of cancer ($n = 160$), myocardial infarction ($n = 100$), or stroke ($n = 45$). The remaining 8579 participants were apparently healthy and their sleep duration was not affected these physical conditions.

3. Results

3.1. Baseline characteristics in terms of sleep duration categories

Table 1 shows the baseline characteristics of the study participants according to the categories of sleep duration.

The mean age was highest in the long sleep category. The proportions of women decreased linearly as the sleep duration category increased. Even though the mean weight was the lowest in the short sleep category, the mean BMI showed no significant difference. The mean weight change increased linearly as the sleep duration category increased. The proportion of participants who were employed was lowest in the short sleep category, whereas the proportions of participants who were current drinkers and consumed ⩾3 cups/day of coffee were lowest in the long sleep category. The proportions of participants who walked ⩾1 h/day and did ⩾3 h/week sports and physical exercise were highest in the long sleep category. Mean energy consumption was lowest in the short sleep category.

3.2. Weight gain and obesity by sleep duration category

Table 2 shows the numbers of participants who had ⩾5 kg weight gain and obesity and the ORs of ⩾5 kg weight gain and obesity with 95% CIs according to the sleep duration categories.

We observed no association between sleep duration, ⩾5 kg weight gain, and obesity. The multivariate OR1 for ⩾5 kg weight gain was 0.93 (95%CIs; 0.73–1.19) in short sleeper and 1.05 (0.91–1.20) in long sleepers (p for trend = 0.3087). Similarly, the multivariate OR1 for obesity was 1.08 (0.77–1.52) in short sleeper and 1.06 (0.86–1.30) in long sleeper (p for trend = 0.3712). After further adjustments of multivariate ORs1 for energy consumption, the multivariate ORs2 showed associations similar to those for ORs1 (⩾5 kg weight gain; p for trend = 0.3097, obesity; p for trend = 0.3655). In addition, after stratification by BMI, the present study also demonstrated a null association between sleep duration and ⩾5 kg weight gain in normal weight participants (p for trend = 0.6236). However, among obese participants, long sleepers had a significantly increased risk of ⩾5 kg weight gain (OR: 1.36, 95%CI: 1.09–1.70).

Table 3 shows the numbers of healthy participants who had ⩾5 kg weight and obesity and ORs with 95% CIs according to the sleep duration categories. We also observed no association between sleep duration, ⩾5 kg weight gain, and obesity in participants who had no physical limitations or history of disease. The multivariate OR1 for ⩾5 kg weight gain was 0.88 (0.61–1.26) in

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