厚生労働科学研究費補助金

地球規模保健課題推進研究事業

東アジアにおける生活習慣病予防モデルの開発-ベトナムにおける予防介入支援

（ H23-地球規模-若手-002 ）

平成24年度　総括研究報告書

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研究要旨

近年、糖尿病のような生活習慣に関連する疾患が、経済的発展による生活習慣の劇的な変容にともない、先進国のみならず発展途上国においても社会的重要課題の一つとなってきている。世界保健機構（WHO）の2002 年々次報告では、世界的にみた健康増進施策上の重要課題として‘心血管病’を挙げ、さらに、今後 30 年の間に、特にアジアの発展途上国において糖尿病患者の数が劇的に増加することに警告を発している。これらの国々では健診システムが整備されておらず、生活習慣病が悪化している状態の人のほとんどは無自覚で放置されている。早期に確実に生活習慣病を診断し、進展を防ぐシステムを構築し、効果を検証することが急務である。当該国の１つであるベトナムにおいて、日本の特定健診の仕組みを参考に地域の実情に則した健診システムを開発し、健診で生活習慣病と診断された人に対し、指導を行う群と行わない群に無作為割りつけを行い、指導効果を比較し、アジアにおける生活習慣病対策の基本パッケージを作成する必要がある。

日本発の保健指導システムを発展途上国へ導入し、WHO 西太平洋事務局と協力しながら地域行動計画の全国レベルの普及とネットワーク構築について検討を行い、アジア全土の生活習慣病対策の仕組みを構築し、普及することを目的とし、本研究を行う。このことにより、日本発の特定健診・特定保健指導を基にした生活習慣病対策が根付き、アジアの健康作りに貢献することができる。

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A. 研究目的

健診を実施していないアジアの発展途上国の１つであるベトナム国内に日本発の健診、保健指導を導入することで、住

民の健康状態の向上がみられるかを検討する。さらに、医療経済学的観点からも検証し、WHO 西太平洋事務局と協力しながら地域行動計画の全国レベルの普及とネットワーク構築について検討を行い、生活習慣病対策の仕組みをアジア全土に広めることを目的とする。

B. 方法

1.研究実施体制の整備

国内で、専門家や特定保健指導のプログラムを作成した人と協力して今回の臨床研究計画を立案した。今回の研究に関し、研究実施方法、検体の取り扱い、お互いの責任範囲などを明示した研究契約書による契約締結を行った。

2.保健指導スタッフの教育

ベトナムの調査スタッフおよび介入スタッフの研修および教育を行った。

3.生活習慣病予防プログラムのベトナム版の作成

現地の事情に合わせた費用対効果の高い介入プログラム（ベトナム版）を作成した。

（倫理面への配慮）

本研究の実施計画は「疫学研究に関する倫理指針」に則って作成し、研究実施前に、研究代表者及び海外共同研究者は研究計画書をそれぞれが所属する機関の倫理委員会に諮り、承認を得る。また調査・介入にあたっては、その内容をわかりやすく示した図入りのパンフレットを用いて、自由意志に基づく参加であることや個人情報の保護対策を含め調査員が対象者に説明した後に、本人から署名入りの同意書を得た上で実施する。調査票は個人情報管理者の監督下に匿名化（連結可能）した上で、鍵のかかる部屋及びロッカーに保管する。結果の公表に際しては個人が特定できない形式で行う。

C. 研究結果

1) アジアにおけるメタボリックシンドロームのリスク重積検出のウエストカットオフ値の性・年齢・民族別検討

メタボリックシンドロームは、循環器疾患のリスクファクターとされている。ウエスト周囲径は、内臓脂肪蓄積の簡易指標とされ、国際糖尿病連合（IDF）によるメタボリックシンドロームの診断基準では、民族特異的なウエスト周囲径のカットオフ値が必要とされているが、開発途上国ではまだあまり検討されていない。そこで、我々は、年齢、地域、民族別にいくつかのアジアの国々の人を対象として最適なウエスト周囲径のカットオフ値を見出すことを目的として本研究を行った。

トータル 12,877 名（中国：北京 3,957 名、太原 3,034 名、スリランカ：2,984 名、ベトナム：ハノイ 1,205 名、タイビン 1,697 名）を対象とした。IDF のメタボリックシンドロームの診断基準（ウエスト周囲径を除く）のうち、2 つ以上持っている人をメタボリックシンドロームのリスク重積ありと判定し、ROC 曲線を描き、最適なウエスト周囲径カットオフを求めた。

ROC 曲線による感度と特異度の和が最大になるウエスト周囲径は、北京、太原、

スリランカ、ハノイ、タイビンでは男性では、88.1cm、81.5cm、83.3cm、81.9cm、75.3cm、女性では、82.4cm、76.5cm、86.2cm、72.2cm、73.8cm であった。それぞれの地域の、感度 80%でメタボリックシンドロームのリスク重積者を拾い上げることのできるウエスト周囲径は、男性では、84.8cm、78.5cm、81.9cm、75.9cm、70.1cm、女性では、80.1cm、73.4cm、79.0cm、72.4cm、66.4cm であった。さらに年齢別にも解析を試みたところ、同じ地域であっても年齢により大きくウエストカットオフ値が異なることが明らかになった。

アジア人用のウエストカットオフ値は、IDF のメタボリックシンドローム診断基準では現在、統一されている（男性が 90cm、女性が 80cm）。しかしながら、年齢と地域により同じアジア人でも違いがみられ、最適なウエストカットオフ値は、環境要因だけではなく、民族による影響も大きいことが示唆された。

2) 体格指数の変化がメタボリックシンドロームの各要因の変化に及ぼす影響

肥満指数のゴールドスタンダードは内臓脂肪面積とされている。複数回 CT で測定した内臓脂肪面積と他の体格指数の変化がメタボリックシンドロームの各要因の変化に及ぼす影響について検討を行った。

2004 年度と 2007 年度の 2 回、健診で腹部 CT 検査を受診した男性 1,106 名を対象とした。内臓脂肪面積、皮下脂肪面積、ウエスト周囲径は CT により測定した。3 年間の各体格指数の変化と各メタボリックシンドローム要因の変化を相関解析、重回帰分析により解析した。

体重、皮下脂肪面積、ウエスト周囲径の変化の相関は強く、体重変化と内臓脂肪面積の変化の相関は弱かった。内臓脂肪面積の変化は特に中性脂肪、HDL コレステロールの変化と強く関連しており、体重、ウエスト周囲径の変化とは独立に関係していた。

内臓脂肪面積が増加しないような生活習慣が大切であることを明らかにした。

（DiabetesCare2012;35(5):1139-43.
日本肥満学会、京都　2012 年発表）

3) 内臓脂肪面積の変化がメタボリックシンドロームの各要因の発症に及ぼす影響

2004 年度、2007 年度の腹部 CT 受診者のうち、高血圧、高脂血症、糖尿病の現在治療中の人を除外した男性 1,106 人を対象とした。3 年間の内臓脂肪面積の変化量により 7 群に分け、±10 cm^2 以内の群を基準とした。①中性脂肪高値②HDL コレステロール低値③血圧高値④糖代謝異常、および⑤メタボリックシンドローム（①-④のうち 2 項目以上あり）の 3 年後の発症オッズ比を求めた。⑤のオッズ比は 50cm^2 以上内臓脂肪面積が増加した人で有意な上昇がみられた。②、④でも同様の結果が得られた。①は－50cm^2 以下の群でオッズ比が有意に下がり、30cm^2 以上の群で有意に上昇していた。内臓脂肪の増加を抑制することがメタボリックシンドロームの解消につながる可能性が示唆された。（Obesity in press）

4) アディポネクチン・内臓脂肪面積がメタボリックシンドロームのリスク重積に及ぼす影響

男性6,221名、女性775名、合計6,996名を対象とし、アディポネクチン、内臓脂肪面積別にそれぞれ4分位、16群に群分けし、アディポネクチン最高値・内臓脂肪面積最低値群を基準（1.0）とした時のメタボリックシンドロームのリスク重積の調整オッズ比を求めた。アディポネクチン最低値・内臓脂肪面積最高値群が最も高いオッズ比（95%信頼区間）であった（男性：12.7 (9.7-16.6)、女性：13.5 (6.0-30.2)）。さらに、内臓脂肪面積とアディポネクチンは、独立してメタボリックシンドロームに影響を及ぼしていることが明かになった。（Obesity in press）

D.考察

同じアジア人であっても、肥満とメタボリックシンドロームの関係は年齢、民族により異なることが明らかとなり、生活習慣病対策を行っていくにあたり、その点も考慮し、ベトナムの現状に即したプログラムの作成が必要であることがわかった。肥満が生活習慣病に及ぼす影響の強さも民族により異なるかどうかについても検討していく必要がある。

E. 結論

生活習慣病対策のプログラムを作成する際、性・民族差だけではなく、年齢についても考慮していかなければならない。

F. 健康危険情報

なし

G. 研究発表

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2) Y Matsushita, T Nakagawa, S Yamamoto, Y Takahashi, T Yokoyama, T Mizoue, M Noda. Effect of longitudinal changes in visceral fat area on incidence of metabolic risk factors: the Hitachi Health Study. Obesity (in press).

3) Y Matsushita, T Nakagawa, S Yamamoto, Y Takahashi, T Yokoyama, T Mizoue, M Noda. Visceral fat area cutoff for the detection of multiple risk factors of metabolic syndrome in Japanese: the Hitachi Health Study. Obesity. 2012;20: 1744-1749.

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association with CT-scanned abdominal fat areas: the Hitachi Health Study. Int J Obes. 2012; 37: 129-134.

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1) インターネットを介した減量支援の実施状況
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4) 血中アディポネクチン値及び空腹時インスリン値を利用した、糖尿病発症予測 日立健康研究から
山本修一郎, 松下由実, 中川徹, 林剛司, 溝上哲也
（日本肥満学会、京都 2012年）

5) 肺気腫に対するアディポネクチンの防御作用
中田博文, 松下由実, 草野涼, 山本修一郎, 中川徹, 林剛司
（日本肥満学会、京都 2012年）

H. 知的財産権の出願・登録状況

1) 特許取得
なし

2) 実用新案登録
なし

3) その他
なし

研究成果の刊行に関する一覧表

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
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Y Matsushita, T Nakagawa, S Yamamoto, T Kato, T Ouchi, N Kikuchi, Y Takahashi, T Yokoyama, T Mizoue,M Noda	Adiponectin and visceral fat associate with cardiovascular risk factors.	Obesity			In press
Y Matsushita, T Nakagawa, S Yamamoto, Y Takahashi, T Yokoyama, T Mizoue, M Noda.	Effect of longitudinal changes in visceral fat area on incidence of metabolic risk factors: the Hitachi Health Study.	Obesity	-	-	In press
Y Matsushita, T Nakagawa, S Yamamoyo, Y Takahashi, T Yokoyama, T Mizoue and M Noda.	Visceral fat area cutoff for the detection of multiple risk factors of metabolic syndrome in Japanese:TheHitachi Health Study.	Obesity	20	1744-1749	2012

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nature publishing group

Visceral Fat Area Cutoff for the Detection of Multiple Risk Factors of Metabolic Syndrome in Japanese: The Hitachi Health Study

Matsushita Yumi[1], Nakagawa Toru[2], Yamamoto Shuichiro[2], Takahashi Yoshihiko[3], Yokoyama Tetsuji[4], Mizoue Tetsuya[5] and Noda Mitsuhiko[3]

The relationships between metabolic risk factors and abdominal fat distribution determined using computed tomography (CT) are poorly defined in large populations. We investigated the cutoff values of the visceral fat area (VFA) to detect subjects with multiple risk factors of metabolic syndrome (MS) by sex and age groups, and attempted to examine whether sex- and age-specific cutoff values are needed. The subjects of this study were 11,561 Japanese men and women who participated in the Hitachi Health Study, received CT examination, and answered questionnaires on lifestyles between 2004 and 2009. VFA and waist circumference were measured using CT. The VFA cutoff values yielding an 80% sensitivity for the detection of multiple risk factors of MS were typically smaller among men under the age of 40 years (<40 years vs. ≥40 years; 86.4 cm^2 vs. 103.9 cm^2). The area under the receiver operator characteristic curve of VFA for the detection tended to decrease according to age ($P = 0.056$ and $P = 0.020$ for trends in men and women). Age- and sex-specific cutoff values are needed. The sensitivity of the subjects under the age of 40 years is relatively smaller (70.0% for men and 60.0% for women) compare to other age groups when the same cutoff value is used regardless of age (e.g., cutoff value calculated to correspond to 80% sensitivity for subjects of all ages). Therefore, a smaller VFA cutoff point should be used among men under the age of 40 years.

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The prevalence of metabolic syndrome (MS), which is comprised of a cluster of factors such as obesity, high blood pressure, impaired lipid metabolism, and hyperglycemia, has been growing globally. Individuals with MS have a higher risk of cardiovascular disease and a subsequent increase in disease mortality or morbidity (1–3). For the detection of MS, waist circumference (WC) is almost always used as one criterion, and this measure is typically used as a simplified measure of the visceral fat area (VFA (4–7)). Fat tissue is regarded as an endocrine organ, secreting adipocytokines, and other vasoactive substances that can influence the risk of developing traits of MS (8). In a previous study, we analyzed the epidemiological impact of VFA, compared with that of the subcutaneous fat area, WC, and BMI, against the clustering of metabolic risk factors and its components and demonstrated a superior performance of VFA for predicting the clustering of metabolic risk factors compared with other anthropometric indexes (9). Despite it is reported that the anthropometric values are changed by age (10), we had a limitation that the sample size was not enough to analyze by age groups in the previous study.

In this study, we extended the surveillance period and increased the study subjects (n = 11,561; which was approximately double in our previous study (9)). We investigated the cutoff values of the VFA to detect subjects with multiple risk factors of MS by sex and age groups, and attempted to examine whether sex- and age-specific cutoff values are needed for a Japanese population.

METHODS AND PROCEDURES

The employees of a company in Ibaraki Prefecture and their spouses underwent health examinations between 2004 and 2009; all the health examinations were performed after more than 12 h of fasting. Of these participants, we analyzed the data for 11,561 Japanese subjects (9,867 men and 1,694 women) between the ages of 20–76 years who had undergone a computed tomography (CT) examination, answered a questionnaire on lifestyle and health, and did not have a current treatment of serious illness (cancer, cerebrovascular disease, myocardial infarction). The VFA and WC were measured using a CT scanner and calculated using the PC software application (fatPointer; Hitachi Medico, Tokyo,

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Table 1 Areas under the curve of ROC for detecting multiple risk factors of metabolic syndrome

		Anthropometric indexes		Presence/absence for the metabolic risk factors			L_{pos}					L_{neg}			
	Age	Mean	(s.d.)	*n*	Area under the curve	s.e.	Corresponding to 80% sensitivity	Specificity corresponding to 80% sensitivity (%)	Corresponding to maximal sensitivity plus specificity	Sensitivity (%)	Specificity (%)	Corresponding to 80% sensitivity	Corresponding to maximal sensitivity plus specificity	Corresponding to 80% sensitivity	Corresponding to maximal sensitivity plus specificity
Men															
VFA	under 40 years	100.7 cm^2	(49.0)	366/994	0.741	(0.015)	86.4 cm^2	49.2	114.0 cm^2	64.2	72.9	1.58	2.37	0.41	0.49
	40s	118.7 cm^2	(51.8)	1,041/1,727	0.722	(0.010)	103.6 cm^2	52.6	106.6 cm^2	78.2	55.4	1.69	1.75	0.38	0.39
	50s	125.6 cm^2	(53.9)	1,429/1,897	0.697	(0.009)	104.5 cm^2	47.3	124.8 cm^2	67.6	62.6	1.52	1.81	0.42	0.52
	60s	127.2 cm^2	(57.0)	858/1,029	0.678	(0.012)	102.1 cm^2	44.2	120.4 cm^2	68.4	57.6	1.44	1.61	0.45	0.55
	70s	128.7 cm^2	(57.4)	242/284	0.706	(0.022)	109.4 cm^2	50.4	104.8 cm^2	83.1	49.3	1.61	1.64	0.39	0.34
	all ages	120.7 cm^2	(54.2)	3,936/5,931	0.712	(0.005)	102.4 cm^2	50.2	115.6 cm^2	72.1	59.8	1.61	1.79	0.40	0.47
	over 40 years	123.9 cm^2	(54.3)	3,570/4,937	0.702	(0.006)	103.9 cm^2	48.8	121.1 cm^2	68.9	61.3	1.56	1.78	0.41	0.51
WC	Under 40 years	85.9 cm	(10.0)	366/994	0.729	(0.015)	83.4 cm	51.9	85.6 cm	72.1	62.0	1.66	1.90	0.39	0.45
	40s	87.0 cm	(9.2)	1,041/1,727	0.701	(0.010)	83.8 cm	47.1	87.6 cm	64.2	65.0	1.52	1.83	0.42	0.55
	50s	86.4 cm	(8.4)	1,429/1,897	0.680	(0.009)	83.1 cm	43.4	85.5 cm	68.7	58.1	1.42	1.64	0.46	0.54
	60s	85.0 cm	(8.2)	858/1,029	0.666	(0.012)	81.8 cm	43.9	83.2 cm	74.0	52.1	1.43	1.54	0.45	0.50
	70s	85.3 cm	(8.8)	242/284	0.677	(0.023)	82.0 cm	46.5	81.9 cm	80.6	46.1	1.49	1.50	0.44	0.42
	All ages	86.2 cm	(8.9)	3,936/5,931	0.685	(0.005)	82.9 cm	45.4	83.7 cm	77.1	49.8	1.47	1.53	0.44	0.46
	Over 40 years	86.2 cm	(8.7)	3,570/4,937	0.679	(0.006)	82.8 cm	44.1	83.7 cm	77.0	49.0	1.43	1.51	0.45	0.47
BMI	Under 40 years	24.3 kg/m^2	(3.5)	366/994	0.729	(0.015)	23.3 kg/m^2	49.8	25.3 kg/m^2	58.7	78.0	1.60	2.67	0.40	0.53
	40s	24.4 kg/m^2	(3.3)	1,041/1,727	0.691	(0.010)	22.9 kg/m^2	44.8	24.6 kg/m^2	61.2	69.0	1.45	1.97	0.45	0.56
	50s	23.9 kg/m^2	(2.8)	1,429/1,897	0.675	(0.009)	22.6 kg/m^2	43.3	23.8 kg/m^2	66.1	60.3	1.41	1.66	0.46	0.56
	60s	23.6 kg/m^2	(2.6)	858/1,029	0.651	(0.013)	22.4 kg/m^2	41.4	22.8 kg/m^2	75.3	47.6	1.37	1.44	0.48	0.52
	70s	23.5 kg/m^2	(2.6)	242/284	0.661	(0.024)	22.3 kg/m^2	38.7	23.9 kg/m^2	60.7	67.6	1.30	1.88	0.52	0.58
	all ages	24.0 kg/m^2	(3.0)	3,936/5,931	0.673	(0.005)	22.7 kg/m^2	43.1	24.2 kg/m^2	59.5	66.0	1.41	1.75	0.46	0.61
	over 40 years	24.0 kg/m^2	(2.9)	3,570/4,937	0.669	(0.006)	22.6 kg/m^2	42.1	23.8 kg/m^2	65.5	59.5	1.38	1.62	0.48	0.58
Women															
VFA	under 40 years	45.6 cm^2	(33.1)	10/123	0.759	(0.015)	36.5 cm^2	51.2	60.2 cm^2	70.0	80.5	1.64	3.59	0.39	0.37
	40s	61.6 cm^2	(41.6)	40/251	0.823	(0.032)	66.4 cm^2	67.7	63.3 cm^2	85.0	66.1	2.48	2.51	0.30	0.23

Table 1 Continued on next page

Table 1 Continued

		Anthropometric indexes		Presence/absence for the metabolic risk factors							L_{pos}		L_{neg}	
	Age	Mean	(s.d.)	*n*	Area under the curve	s.e.	Corresponding to 80% sensitivity	Specificity corresponding to 80% sensitivity (%)	Corresponding to maximal sensitivity plus specificity	Sensitivity (%)	Specificity (%)	Corresponding to 80% sensitivity	Corresponding to maximal sensitivity plus specificity	Corresponding to 80% sensitivity	Corresponding to maximal sensitivity plus specificity
	50s	79.5 cm^2	(41.6)	146/449	0.746	(0.023)	68.3 cm^2	53.2	67.8 cm^2	82.9	53.0	1.71	1.76	0.37	0.32
	60s	93.7 cm^2	(46.7)	205/381	0.694	(0.023)	75.7 cm^2	43.0	97.7 cm^2	65.9	65.7	1.40	1.92	0.46	0.52
	70s	98.4 cm^2	(48.0)	31/58	0.672	(0.061)	77.3 cm^2	43.1	75.7 cm^2	87.1	43.1	1.42	1.53	0.45	0.30
	all ages	79.7 cm^2	(45.8)	432/1,262	0.754	(0.014)	69.0 cm^2	54.0	67.8 cm^2	82.9	53.5	1.74	1.78	0.37	0.32
	over 40 years	82.6 cm^2	(45.6)	422/1,139	0.743	(0.014)	69.2 cm^2	50.9	97.6 cm^2	60.4	74.5	2.37	1.63	0.53	0.39
WC	under 40 years	78.0 cm	(9.0)	10/123	0.818	(0.058)	78.7 cm	64.2	75.3 cm	100.0	50.4	2.24	2.02	0.31	0.00
	40s	81.1 cm	(10.0)	40/251	0.759	(0.035)	80.7 cm	55.0	79.5 cm	92.5	49.8	1.78	1.84	0.36	0.15
	50s	83.4 cm	(9.3)	146/449	0.688	(0.025)	80.5 cm	45.9	84.7 cm	63.7	65.5	1.47	1.85	0.45	0.55
	60s	84.6 cm	(9.6)	205/381	0.658	(0.024)	79.8 cm	34.6	88.9 cm	46.8	79.5	1.22	2.29	0.58	0.67
	70s	84.6 cm	(8.7)	31/58	0.679	(0.060)	81.8 cm	46.6	89.4 cm	51.6	82.8	1.51	2.99	0.42	0.58
	all ages	83.0 cm	(9.6)	432/1,262	0.701	(0.014)	80.2 cm	45.7	84.1 cm	66.4	63.2	1.47	1.46	0.44	0.40
	over 40 years	83.5 cm	(9.6)	422/1,139	0.689	(0.015)	80.2 cm	43.3	84.1 cm	66.6	61.4	1.41	1.72	0.46	0.54
BMI	under 40 years	21.7 kg/m^2	(3.5)	10/123	0.869	(0.056)	22.1 kg/m^2	69.1	23.0 kg/m^2	80.0	80.5	2.59	4.10	0.29	0.25
	40s	22.7 kg/m^2	(3.6)	40/251	0.774	(0.037)	22.2 kg/m^2	54.6	23.9 kg/m^2	70.0	74.9	1.76	2.79	0.37	0.40
	50s	23.0 kg/m^2	(3.4)	146/449	0.689	(0.025)	21.6 kg/m^2	46.1	23.6 kg/m^2	57.5	70.8	1.49	1.97	0.43	0.60
	60s	23.2 kg/m^2	(3.2)	205/381	0.664	(0.024)	21.7 kg/m^2	40.2	23.8 kg/m^2	54.6	71.1	1.34	1.89	0.50	0.64
	70s	22.8 kg/m^2	(3.2)	31/58	0.715	(0.056)	21.6 kg/m^2	48.3	22.9 kg/m^2	71.0	65.5	1.56	2.06	0.40	0.44
	all ages	22.9 kg/m^2	(3.4)	432/1,262	0.704	(0.014)	21.7 kg/m^2	46.9	23.5 kg/m^2	58.6	71.7	1.51	2.07	0.42	0.58
	over 40 years	23.0 kg/m^2	(3.4)	422/1,139	0.692	(0.015)	21.7 kg/m^2	45.1	23.8 kg/m^2	56.2	72.3	1.46	2.02	0.44	0.61

Multiple risk factors: having two or more risk factors of metabolic syndrome defined by NCEP-ATPIII (2005).

VFA, visceral fat area; WC, waist circumference.

Japan) according to a protocol described elsewhere (11). Briefly, single slice imaging at the umbilical level was performed using a CT machine (Redix turbo; Hitachi Medico, Tokyo, Japan) while the subject was in a supine position. The imaging conditions were 120 kV, 50 mA, and a 5-mm slice thickness. Height, weight, and body fat were measured using an automated scale (BF-220; Tanita, Tokyo, Japan) with the patient wearing a light gown. The BMI was defined as the weight (kg) divided by the square of the height (m). The blood was collected from each subject after more than 12 h of fasting. The plasma glucose was measured using the glucose oxidase enzyme-electrode method (A&T, Tokyo, Japan) Triglyceride and high-density lipoprotein cholesterol levels were measured using the enzymatic colorimetric method (Cholestest TG; Sekisui Medical, Tokyo, Japan), the nonsettling enzymatic method (Choletest NHDL; Sekisui Medical, Tokyo, Japan), respectively. Blood pressure was measured using automated sphygmomanometer (Kentaro ADVANCE BP-203RV III A/B; Colin, Tokyo, Japan). Informed consent was obtained from each examinee regarding the use of his or her data for research purposes. This study was approved by the ethics review committee of the National Center for Global Health and Medicine.

In this study, subjects with two or more of the four risk factors (high blood pressure, high triglyceride, low HDL-cholesterol, and hyperglycemia) defined according to the criteria of the National Cholesterol Education Program's Adult Treatment Panel III guidelines in 2005 (6) except for WC were defined as having the clustering of metabolic risk factors. Subjects currently receiving treatment for hyperlipidemia, hypertension, or diabetes were deemed as having the respective risk factors, regardless of the biochemical values.

Receiver operator characteristic (ROC) analysis was used to develop a cutoff of each anthropometric value associated with the presence of two or more risk factors of MS, with the exception of WC. ROC analysis is a formal method that plots sensitivity against 1-specificity for assessing the trade-offs between sensitivity and specificity at various test cutoff points or thresholds, providing a measure of diagnostic accuracy called area under the curve (AUC). We drew the ROC curves for each anthropometric value, and calculated the corresponding AUC. To test for the equality of the AUCs, an algorithm suggested by DeLong, DeLong, and Clarke-Pearson was applied for each anthropometric value (12). Pairwise comparisons of VFA with WC and BMI were also performed, and the *P* values for multiple tests (two comparisons) were adjusted using the Bonferroni–Holm method. The AUC and the s.e. were calculated for each of the 10-year age groups. The decreasing trend in the AUCs according to age was statistically tested using a weighted regression analysis of AUC on age groups, where $1/\text{s.e.}^2$ was used as the weight and the age group was coded as the median age of the group. Sensitivity was plotted against 1-specificity for each segment of anthropometric value. Likelihood ratios were calculated as for positive results ((L_{pos}) = sensitivity/(1-specificity)), and negative results ((L_{neg}) = (1-sensitivity)/specificity) for each segment of anthropometric value. All analyses were performed using SPSS for Windows version 15.0 (SPSS, Chicago, IL) and Stata 10 (StataLP, College Station, TX).

RESULTS

The mean age was 51.9 ± 10.4 years in men and 55.8 ± 9.8 years in women. The mean VFA was 120.7 ± 54.2 cm^2 in men and 79.7 ± 45.8 cm^2 in women. The mean WC was 86.2 ± 8.9 cm in men and 83.0 ± 9.6 cm in women. The mean BMI was 24.0 ± 3.0 kg/m^2 in men and 22.9 ± 3.4 kg/m^2 in women. The mean body fat percentage was 22.9 ± 5.0% in men and 29.1 ± 6.1% in women. The prevalence of the multiple risk factors of MS was 39.9% in men and 25.5% in women.

We plotted the ROC curve to determine the cutoff values of VFA, BMI, and WC in relation to the detection of multiple risk factors. **Table 1** shows the AUC values for VFA, BMI, and WC. The AUC values were greater in women than in men for all ages. The anthropometric measurement with the largest AUC value was the VFA for both men and women ($P < 0.001$; VFA vs. each anthropometric values). Given that a WC is used for the first screening of subjects as a prerequisite for the detection of multiple risk factors of MS, setting a cutoff level to obtain a high sensitivity of at least 80% may be justified, even if the specificity is reduced to some extent. The VFA, BMI, and WC cutoff values yielding an 80% sensitivity for the detection of multiple risk factors of MS for all ages were 102.4 cm^2, 22.7 kg/m^2, and 82.9 cm in men and 69.0 cm^2, 21.7 kg/m^2, and 80.2 cm in women, respectively. At an 80% sensitivity for all age group, men who had multiple risk factors were 1.61 times more likely to be above the criteria of VFA (102.4 cm^2), and were only 0.40 times more likely to be below it as compared to those who do not have. Both L_{pos} and L_{neg} had a monotonically increasing trend along with VFA. Therefore, we could not identify a cut off that simultaneously satisfied maximized L_{pos} and minimized L_{neg} ratios.

The VFA cutoff values yielding an 80% sensitivity for the detection of clusters of multiple risk factors were typically smaller in subjects under the age of 40 years (<40 years vs. ≥40 years; 86.4 cm^2 vs. 103.9 cm^2 for men and 36.5 cm^2 vs. 69.2 cm^2 for women, respectively). The AUC of the body fat percentage was the smallest of all of anthropometric values (data not shown).

The mean VFA was larger in the higher age groups. The AUC of the ROC curve of VFA for the detection of multiple risk factors of MS tended to decrease according to age ($P = 0.056$ and $P = 0.020$ for trends in men and women, respectively). The cutoff values for maximal sensitivity and specificity differed according to age groups, yielding inconsistent sensitivity and specificities among the groups.

DISCUSSION

In the present study, we proposed VFA cutoff points for the detection of multiple risk factors of MS of 103.9 cm^2 in men and 69.2 cm^2 in women over the age of 40 years, yielding a sensitivity of at least 80% for the prediction of clusters of multiple risk factors in a Japanese population. Among subjects under the age of 40 years, a smaller cutoff point should be used, i.e., 86.4 cm^2 in men. However, among the subjects under the age of 40 years for women, the number of subjects having multiple risk factors of MS was small; thus it may be difficult to detect the cutoff values of VFA.

A few studies have reported appropriate VFA cutoff points for the detection of multiple risk factors of MS (13,14). However, as age-specific cutoff values were not calculated, the present study is the first to examine whether age-specific cutoff values are needed.

Two methods have been reported for determining the cutoff point. One is calculating L_{pos} and L_{neg} and using the cutoff point that yields the highest value of L_{pos} and the lowest value of L_{neg} concurrently. If there is no cutoff point that corresponds to both the highest and lowest values, the cutoff point for highest value of L_{pos} and that for the lowest value of L_{neg} are shown, respectively. According to this method, a previous study indicated that intra-abdominal adipose tissue above 131 cm^2 was related to elevated multiple risk factors of cardiovascular

disease, and intra-abdominal adipose tissue below 71 cm^2 was associated with reduced multiple risk factors of cardiovascular disease in men (15). Similarly, another study showed the upper and lower cutoff points of intra-abdominal adipose tissue as 110 cm^2 and 40 cm^2 in female subjects who have multiple risk factors of cardiovascular disease (16). Another method to determine the cutoff point is calculating the Youden index (sensitivity + specificity −1) and using the maximal value of it (17,18). Incorporating this method, Oka *et al.* showed the optimal cutoff points of VFA for discriminating the subjects with multiple risk factors of MS as 132.6 cm^2 and 91.5 cm^2 for men and women, respectively (14). A separate study showed the cutoff points of it as 103.0 cm^2 and 69.0 cm^2 for men and women, respectively (19). Though there have been several studies before our own, our results show that both L_{pos} and L_{neg} tend to rise with an increase in VFA. Therefore, a cutoff point that simultaneously meets a requirement of both maximized L_{pos} and minimized L_{neg} ratios could not be determined in our study. When attempting to classify individuals based on anthropometric levels, it is always the intent to do so "optimally". However, the event of interest may intrinsically involve constraints that must be considered for ethical or fiscal reasons. These constraints commonly account for the prevalence of the event and the costs of misclassification, both monetary and physiological (20). The maximal value of the Youden index, used in previous studies to calculate the cutoff values, does not take these points into consideration. Our purpose was to screen individuals with multiple risk factors for MS; thus, the cost of false-positive results may not be a serious problem because the interventions, even among "false-positive" individuals, to improve lifestyles would have some benefits and would have a relatively low cost in the Japanese system. In Japan, the prevalence of MS is increasing because of the increasing prevalence of obesity; thus, the Ministry of Health, Labour and Welfare of Japan is making a strong effort to prevent MS. Therefore, for the first screening of subjects as a prerequisite for the diagnosis of MS, we set a cutoff level so as to obtain a relatively high sensitivity (80%) to increase the probability of identifying people with this disease.

The VFA cutoff point for the detection of multiple risk factors of MS yielding a sensitivity of 80% increased with age. This observation can likely be explained by the increase in the mean VFA values in older age groups given the relationship between VFA and having multiple risk factors does not differ among age groups. The cutoff values were typically smaller among subjects under the age of 40 years. If the same cutoff value (e.g., cutoff value corresponding to 80% sensitivity for all ages) is used regardless of age, the sensitivity under the age of 40 years is relatively smaller (70.0% for men and 60.0% for women, respectively) than that in other age groups. Thus, age-specific cutoff values are especially needed for this generation.

Furthermore, the AUC of the ROC curve of VFA for the detection of multiple risk factors of MS tended to decrease with age in both sexes. The effect of VFA on the detection of multiple risk factors of MS is thought to be stronger among young individuals and weaker among elderly individuals. In the elderly, MS may also be caused by risk factors other than VFA (such as age-related hyperglycemia and high blood pressure).

The AUC for women was larger than that for men in all the age groups. This finding can likely be explained by the fact that men tend to have more other risk factors of MS which are not used for the diagnostic criteria of MS (such as a smoking habit, and alcohol drinking habit, stress, hard work, etc (21)); thus, the contribution of VFA to the multiple risk factors of MS may be relatively smaller in men than it is in women.

The present study described the VFA cutoff values yielding a sensitivity of 80% according to age group. Further studies are needed to elucidate the most suitable and easy method of measuring VFA and the most appropriate cutoff point for use in clinical settings.

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DISCLOSURE

The authors declared no conflict of interest.

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ORIGINAL ARTICLE

Short sleep duration in association with CT-scanned abdominal fat areas: the Hitachi Health Study

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OBJECTIVE: To examine the relationship between short sleep duration and body mass index (BMI), waist circumference (WC), visceral fat area (VFA) and subcutaneous fat area (SFA) among a working population in Japan.
DESIGN: Health-center-based, cross-sectional study.
SUBJECTS: The study subjects included 5400 men and 642 women aged 30 to 75 years who underwent an abdominal computed tomography (CT) scanning examination in a comprehensive health checkup.
MEASUREMENTS: Height and weight were measured, and BMI was calculated. WC, VFA and SFA were measured using a CT scanner. Sleep duration was self-reported. Analysis of covariance was used to estimate adjusted means of BMI, WC, VFA and SFA across categories of sleep duration with adjustments for potential confounders. Trend of the association was assessed using multiple linear regression analysis.
RESULTS: In men, the mean values of BMI, WC and SFA decreased with increasing sleep duration after adjustment for age, physical activity, smoking and drinking (*P*-value for trend <0.001). Additional adjustment for physical illnesses did not attenuate the explanatory power of the models (*P*-value for trend <0.001). In addition, the association between sleep duration and SFA did not change after controlling for VFA (*P*-value for trend <0.001). The mean values of SFA for subjects sleeping '<5 h', '5 to <6 h', '6 to <7 h' and '$\geqslant 7$ h' per day were $145.8 \pm 67.4\,cm^2$, $138.7 \pm 61.5\,cm^2$, $134.7 \pm 60.4\,cm^2$ and $132.5 \pm 49.2\,cm^2$, respectively. Sleep duration was not appreciably associated with VFA. In women, no significant association was detected in any models.
CONCLUSION: Shorter sleep duration is associated with higher BMI, WC and SFA in men. Further research is needed to explicate the biological mechanisms behind these relationships and to see whether interventions addressing inadequate sleep could treat or prevent obesity by taking gender differences into consideration.

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Keywords: sleep duration; general obesity; central obesity; abdominal fat area; Japan

INTRODUCTION

In the past few decades, there has been a significant increase in the prevalence of obesity worldwide. The World Health Organization describes obesity as one of the most visible, yet neglected, public health problems, which threatens to overwhelm both more and less developed countries.[1] The observation that obesity prevalence has increased over the past decades at the same time as sleep duration has decreased has drawn attention to the possibility that sleep deprivation may have contributed to the obesity epidemic.[2] The interest may have been further promoted by the recognition that obesity epidemic cannot easily be attributed to the so-called obesogenic environment, which is assumed to lead to overeating and sedentary lifestyle.[3]

In Japan, the prevalence of obesity in men aged 30 to 60 years increased from ~20% in 1986 to >30% in 2006.[4] Meanwhile, the average sleep duration among Japanese has decreased steadily over the past 40 years. The average daily sleep duration in people aged 10 years and older has declined from 493 min (8.2 h) in 1960 to 447 min (7.5 h) in 1995, and further drop was observed in 2005 to 442 min (7.3 h).[5] The small decrease in sleep duration from 1995 to 2005 may suggest that the average sleep in Japanese has reached the minimum requirement for human survival.[6]

Evidence has grown over the past decade supporting the roles of habitual sleep duration as a novel risk factor for obesity in both children and adults[7] and its subsequent health outcomes including all-cause mortality,[8] type 2 diabetes,[9] hypertension[10] and other cardiovascular outcomes.[11] The relationship is typically a U-shaped curve where the lowest risk is found at ~7 to 8 h of sleep per day with the odds rising for shorter and longer sleepers.[12] This pattern suggests that different mechanisms may operate at either end of the distribution of sleep duration.[13] As a result of these findings, both sleep restriction[14] and sleep extension[15] have been suggested for potential health interventions.

Although consistent findings have been observed in children, controversy remains in the relationship between sleep duration and obesity and/or weight gain in adults.[2,16] Such relationships have not been found in several epidemiological studies.[17,18] Furthermore, gender differences have also been reported, with the significant association found in men but not in women[19] or vice versa.[20] The interpretation and conclusion of the findings is

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hampered by fundamental conceptual and methodological issues.[2,16] Few studies, for example, have considered physical and mental health conditions as potential confounders. As shown in a recent German study, the relationship between sleep duration and body mass index (BMI) did not persist after controlling for self-rated physical health and emotional status.[21]

Moreover, the inconsistency might have been caused in part by the different definitions and measurements of obesity. BMI, an indicator of overall obesity, has been frequently used in previous studies to define weight gain and obesity. The importance of central obesity and abdominal fat mass has been known to have a stronger relation to the prevalence of each component of metabolic syndrome (hyperglycemia, diabetes and hypertension) than BMI.[22] Our previous study has indicated a superior performance of visceral fat area (VFA) to predict the clustering of metabolic risk factors compared with BMI, waist circumference (WC) and subcutaneous fat area (SFA) in a Japanese population.[23] It remains unclear, however, whether sleep duration is related to abdominal fat areas after taking potential confounders into account. The objective of this study was therefore to examine the relationship between sleep duration and BMI, WC, VFA and SFA in a large sample of Japanese working population enrolled in the Hitachi Health Study.

MATERIALS AND METHODS

Study procedure and subjects

This cross-sectional study was conducted in 2009 and 2010 during a comprehensive annual health examination conducted at the Hitachi Health Care Center, Ibaraki prefecture, Japan. The procedure of the study has been described elsewhere.[24,25] In brief, participants were asked to fill in a computer-based survey questionnaire on the day of the regular health checkup. In total, 17 606 male employees and their spouses underwent the checkup after having fasted overnight. Of these participants, 6537 subjects received an abdominal computed tomography (CT) scanning examination and were the targets for this study. We excluded subjects with a history of diabetes mellitus ($n = 229$), stroke ($n = 28$), myocardial infarction ($n = 39$), cancer ($n = 38$), psychiatric illnesses ($n = 98$) and insomnia ($n = 59$). We further excluded four subjects who did not provide information regarding sleep duration. Some subjects were overlapped and fell into more than one exclusion criteria. We finally included 6271 subjects in the analyses. We obtained written informed consent from each participant after the nature and possible consequences of the study had been fully explained. The study protocol was reviewed and approved by the Ethics Committee of the National Center for Global Health and Medicine, Tokyo.

Variables and measurements

Anthropometric and blood measurements. WC, VFA and SFA were measured by using a CT scanner, the details of which have been described elsewhere.[25] In brief, single slice imaging was performed at the umbilical level in a supine position (Redix Turbo; Hitachi Medico, Chiyoda-ku, Tokyo). The imaging conditions were 120 kV, 50 mA, with a slice thickness of 5 mm. WC, SFA and VFA were calculated by using the PC software application fatPointer (Hitachi Medico). Body height and weight were measured by using an automated scale (BF-220; TANITA; Itabashi-ku, Tokyo) with the subjects wearing a light gown. BMI was calculated as body weight in kg divided by the square of body height in meter.

Sleep duration. Sleep duration was self-reported. The average sleep duration on weekdays was defined by the response to the question (as translated into English): 'On average, how many hours do you sleep per day?' The response categories included: '<5 h', '5 to <6 h', '6 to <7 h' and '$\geqslant 7$ h'.

Confounding variables. Health-related lifestyles were ascertained by using a questionnaire. Participants entered their responses to the questionnaire directly into a computer using a custom-designed data entry system. Regarding the health conditions of participants , data were obtained from the routine health examination. Physical illness was defined as having been diagnosed with and/or being currently under treatment of at least one of the following diseases: hypertension, diabetes mellitus, hyperlipidemia, hyperuricemia, anemia, gastric ulcer, duodenal ulcer, colon polyp, chronic hepatitis, fatty liver, gallstone, disk hernia, rheumatoid arthritis, epilepsia, thyroid-gland-related diseases, angina, cardiac dysrythmia, tuberculosis, bronchial asthma, kidney diseases and other diseases. Similarly, psychiatric illness was defined as having been diagnosed with and/or being currently under treatment of any psychiatric diseases. Regarding cigarette smoking, the questionnaire inquired whether the participants were nonsmokers, ex-smokers or current smokers. Nonsmokers and ex-smokers were later combined for statistical analyses. For alcohol consumption, participants were asked whether they were nondrinkers or current drinkers. For current drinkers, the frequency of drinking and the amount of alcohol consumed per session was assessed in terms of *go* (one go contains ~ 23 g of ethanol). A yes/no question was used to assess regular physical activity.

Statistical analyses

To explore gender differences, all data analyses were conducted separately in men and women. Characteristics of participants are presented as numbers (percentages) for categorical variables and mean with s.d. for continuous variables. Statistical differences in characteristics and anthropometric measurements and according to sleep duration categories in men and women were assessed using χ^2 test or Fisher's exact test for categorical variables and *t*-test or one-way analysis of variance for continuous variables.

Analysis of covariance was used to estimate adjusted means of BMI, WC, VFA and SFA across categories of sleep duration (<5 h, 5 to <6 h, 6 to <7 h and $\geqslant 7$ h). In model 1, we adjusted for age (continuous), regular physical activity (yes or no), current smoking status (nonsmokers or smoker) and current alcohol drinking (nondrinkers or drinker). Because physical illness has been found to be a potential confounder in the association between sleep duration and obesity,[21] we included it in model 2 in addition to the covariates in model 1. An additional model (model 3) was constructed for VFA and SFA. In addition to the covariates in model 2, SFA was included in the model for VFA, and VFA was included in the model for SFA. Trend of the association was assessed by using multiple linear regression models with ordinal numbers of 0 to 3 assigned to the categories of sleep duration with adjustments for the same covariates included in each model of analysis of covariance. In addition, statistical tests for a gender interaction were performed by including pair-wise interaction terms (that is, BMI × gender, WC × gender, VFA × gender and SFA × gender) in the multiple regression models. Two-sided *P*-values of <0.05 were regarded as statistically significant. We used IBM SPSS Statistics version 19.0 (IBM Corporation, New York, NY, USA) for all the statistical analyses.

RESULTS

The study subjects included 5400 men and 642 women with an age range between 30 to 75 years (mean = 53.3 years ± 10.0 years in men and mean = 58.2 years ± 9.4 years in women). Regarding the average sleep duration, 5.4% of the total study population slept <5 h, 42.6% slept 5 to <6 h, 39.4% slept 6 to <7 h and 12.6% slept $\geqslant 7$ h per day. The proportion of subjects sleeping >6 h per day was significantly higher in men than in women (53.0% vs 47.5%). Men were also significantly more likely to be current cigarette smokers (33.9% vs 3.3%) and current alcohol drinkers (76.4% vs 21.2%). The mean value of BMI, WC and VFA was significantly higher in men (mean = 24.2 ± 3.1 kg m^{-2}, mean = 86.7 ± 8.3 cm and mean = 124.2 ± 53.8 cm^2, respectively) than in women (mean = 23.1 ± 3.3 kg m^{-2}; mean = 83.6 ± 9.5 cm; and mean = 82.8 ± 45.1 cm^2; respectively). However, the mean value of SFA was significantly lower in men (mean = 136.5 ± 57.8 cm^2) than in women (mean = 185.9 ± 75.8 cm^2). Men were

significantly less likely to be living with at least one physical illness compared with women (37.1% vs 47.8%).

Tables 1 and 2 show characteristics of subjects according to sleep duration categories in men and women, respectively. In men, sleep duration increased as age increased. Men with shorter sleep duration were more likely to be current cigarette smokers and to be living with at least one physical illness. However, men with shorter sleep duration were less likely to be current alcohol drinkers, and they were less likely to involve with regular physical activity compared with those with longer sleep duration. In men, mean values of BMI, WC and SFA significantly decreased as sleep duration increased. In women, no significant association was found between characteristics of subjects and sleeping duration.

Table 3 shows the adjusted mean values of anthropometric indexes of subjects according to sleep duration categories in men. After adjustment for age, regular physical activity, cigarette smoking and alcohol drinking in model 1, mean values of BMI, WC and SFA decreased significantly with increasing sleep duration (*P*-values for trend <0.001). Adjustment for physical illnesses (model 2) did not significantly change the explanatory power of the models. For subjects sleeping '<5 h', '5 to <6 h', '6 to <7 h' and '$\geqslant 7$ h' per day, mean values of BMI were $24.8 \pm 3.5\ kg\,m^{-2}$, $24.3 \pm 3.2\ kg\,m^{-2}$, $24.0 \pm 2.7\ kg\,m^{-2}$ and $23.8 \pm 2.6\ kg\,m^{-2}$, respectively (*P*-values for trend <0.001), and mean values of WC were 87.9 ± 9.3 cm, 86.9 ± 8.7 cm, 86.4 ± 7.8 cm and 85.7 ± 7.5 cm, respectively (*P*-values for trend <0.001). The significant inverse association between sleep duration and SFA was also not attenuated after additional adjustment for physical illnesses (model 2) and VFA (model 3). In fully adjusted model, the mean values of SFA for subjects sleeping '<5 h', '5 to <6 h', '6 to <7 h' and '$\geqslant 7$ h' per day were $145.8 \pm 67.4\ cm^2$, $138.7 \pm 61.5\ cm^2$, $134.7 \pm 60.4\ cm^2$ and $132.5 \pm 49.2\ cm^2$, respectively (*P*-values for trend <0.001). Sleep duration was not appreciably associated with VFA in men. As shown in Table 4, sleep duration was not significantly associated with BMI, WC, VFA or SFA in any models in women. Gender interaction tests were all statistically significant for all the outcomes of interest (all *P*-values <0.001).

DISCUSSION

In this cross-sectional study, we investigated the relationship of sleep duration with general obesity and abdominal fat areas. To the best of our knowledge, this is the first study of its kind in which CT scanner was used to measure WC, VFA and SFA. We found that short sleep duration was strongly associated with higher BMI, WC and SFA in men. The association was independent of the effects of potential confounding factors such as physical and psychiatric illnesses. However, sleep duration was not appreciably associated with VFA. Apparent gender differences were observed as significant relationship was not detected between sleep duration and any obesity-related measures in women.

Table 1. Characteristics of subjects according to sleep duration categories in men

Variables	*Average sleep duration (hours per day)*					
	Total	*<5*	*5 to <6*	*6 to <7*	*≥7*	P-*value*
Number of subjects	5400	272	2285	2152	690	
Age (years, mean ± s.d.)	53.3 ± 10.0	49.1 ± 9.4	50.5 ± 9.2	54.5 ± 9.8	60.3 ± 9.6	<0.001
Current smokers (*n*, %)	1829 (33.9)	92 (33.8)	832 (36.4)	721 (33.5)	184 (26.7)	<0.001
Current alcohol drinkers (*n*, %)	4127 (76.4)	191 (70.2)	1735 (75.9)	1656 (77.0)	545 (79.0)	0.03
Regular physical activity (*n*, %)	2419 (44.8)	82 (30.1)	942 (41.2)	1028 (47.8)	379 (54.9)	<0.001
Physical illnesses[a] (*n*, %)	2001 (37.1)	88 (32.4)	743 (32.5)	826 (38.4)	344 (49.9)	<0.001
Body mass index (years, mean ± s.d.)	24.1 ± 3.0	24.9 ± 3.4	24.3 ± 3.2	24.0 ± 2.7	23.7 ± 2.5	<0.001
Waist circumference (cm, mean ± s.d.)	86.6 ± 8.3	88.1 ± 9.2	87.0 ± 8.7	86.3 ± 7.8	85.6 ± 7.4	<0.001
Visceral fat area (cm^2, mean ± s.d.)	124.1 ± 53.7	124.9 ± 54.6	122.2 ± 54.3	124.9 ± 52.6	127.2 ± 54.0	0.16
Subcutaneous fat area (cm^2, mean ± s.d.)	136.7 ± 57.2	152.5 ± 69.4	141.5 ± 61.8	133.4 ± 51.6	124.6 ± 48.5	<0.001

[a]Physical illness was defined as having and/or being currently under treatment for at least one of the following diseases: hypertension, diabetes mellitus, hyperlipidemia, hyperuricemia, anemia, gastric ulcer, duodenal ulcer, colon polyp, chronic hepatitis, fatty liver, gallstone, disk hernia, rheumatoid arthritis, epilepsia, thyroid-gland-related diseases, angina, cardiac dysrythmia, tuberculosis, bronchial asthma, kidney diseases and other diseases.

Table 2. Characteristics of subjects according to sleep duration categories in women

Variables	*Average sleep duration (hours per day)*					
	Total	*<5*	*5 to <6*	*6 to <7*	*≥7*	P-*value*
Number of subjects	642	57	286	230	69	
Age (years, mean ± s.d.)	58.2 ± 9.4	57.5 ± 9.6	57.2 ± 9.2	59.2 ± 9.7	59.6 ± 8.9	0.04
Current smokers (*n*, %)	21 (3.3)	1 (1.8)	12 (4.2)	3 (1.3)	5 (7.2)	0.06
Current alcohol drinkers (*n*, %)	136 (21.2)	11 (19.3)	66 (23.1)	39 (17.0)	20 (29.0)	0.13
Regular physical activity (*n*, %)	295 (46.0)	27 (47.4)	120 (41.9)	118 (51.3)	32 (46.3)	0.20
Physical illnesses[a] (*n*, %)	307 (47.8)	31 (54.4)	126 (44.1)	118 (51.3)	32 (46.4)	0.29
Body mass index (years, mean ± s.d.)	23.1 ± 3.4	23.2 ± 3.0	23.3 ± 3.6	22.9 ± 3.2	23.0 ± 3.5	0.32
Waist circumference (cm, mean ± s.d.)	83.4 ± 9.5	83.2 ± 9.1	83.5 ± 9.8	83.2 ± 9.0	83.8 ± 9.5	0.83
Visceral fat area (cm^2, mean ± s.d.)	82.2 ± 44.7	88.1 ± 46.5	80.4 ± 44.8	82.8 ± 44.6	82.4 ± 42.8	0.98
Subcutaneous fat area (cm^2, mean ± s.d.)	185.9 ± 74.6	182.7 ± 66.7	186.0 ± 75.2	185.3 ± 73.8	190.5 ± 74.6	0.71

[a]Physical illness was defined as having and/or being currently under treatment for at least one of the following diseases: hypertension, diabetes mellitus, hyperlipidemia, hyperuricemia, anemia, gastric ulcer, duodenal ulcer, colon polyp, chronic hepatitis, fatty liver, gallstone, disk hernia, rheumatoid arthritis, epilepsia, thyroid-gland-related diseases, angina, cardiac dysrythmia, tuberculosis, bronchial asthma, kidney diseases and other diseases.

Table 3. Adjusted mean values of anthropometric indexes of subjects according to sleep duration categories in men

Variables	*Average sleep duration (hour per day)*				
	<5	*5 to <6*	*6 to <7*	*⩾7*	*P for trend*[a]
Number	272	2285	2152	690	
Body mass index (kg m^{-2})					
Model 1[b]	24.8 ± 3.5	24.3 ± 3.2	24.0 ± 2.7	23.8 ± 2.6	<0.001
Model 2[c]	24.8 ± 3.5	24.3 ± 3.2	24.0 ± 2.7	23.8 ± 2.6	<0.001
Waist circumference (cm)					
Model 1[b]	87.9 ± 9.3	86.9 ± 8.7	86.4 ± 7.8	85.8 ± 7.5	<0.001
Model 2[c]	87.9 ± 9.3	86.9 ± 8.7	86.4 ± 7.8	85.7 ± 7.5	<0.001
Visceral fat area (cm^2)					
Model 1[b]	127.4 ± 54.6	124.3 ± 54.4	124.0 ± 52.6	122.0 ± 54.0	0.23
Model 2[c]	127.3 ± 54.6	124.4 ± 54.4	124.1 ± 52.6	121.4 ± 53.9	0.16
Model 3[d]	121.1 ± 53.9	123.1 ± 53.8	125.2 ± 52.9	124.7 ± 54.4	0.09
Subcutaneous fat area (cm^2)					
Model 1[b]	147.9 ± 69.5	138.9 ± 61.8	134.7 ± 51.6	131.3 ± 48.6	<0.001
Model 2[c]	147.9 ± 69.5	139.0 ± 61.9	134.7 ± 51.6	130.8 ± 48.5	<0.001
Model 3[e]	145.8 ± 67.4	138.7 ± 61.5	134.7 ± 51.6	132.5 ± 49.2	<0.001

Values are means ± s.d. [a]*P* for trend values were based on linear regression analyses with ordinal numbers 0 to 3 assigned to lowest through highest categories of sleep duration. [b]Adjusted for age (continuous), regular physical activity (yes or no), current cigarette smoking (yes or no) and current alcohol drinking (yes or no). [c]Adjusted for age (continuous), regular physical activity (yes or no), current cigarette smoking (yes or no), current alcohol drinking (yes or no) and physical illnesses (yes or no). [d]Adjusted for age (continuous), regular physical activity (yes or no), current cigarette smoking (yes or no), current alcohol drinking (yes or no), physical illnesses (yes or no) and subcutaneous fat area (continuous). [e]Adjusted for age (continuous), regular physical activity (yes or no), current cigarette smoking (yes or no), current alcohol drinking (yes or no), physical illnesses (yes or no) and visceral fat area (continuous).

Table 4. Adjusted mean values of anthropometric indexes of subjects according to sleep duration categories in women

Variables	*Average sleep duration (hour per day)*				
	<5	*5 to <6*	*6 to <7*	*⩾7*	*P for trend*[a]
Number	57	286	230	69	
Body mass index (kg m^{-2})					
Model 1[b]	23.2 ± 3.0	23.3 ± 3.6	22.9 ± 3.2	23.0 ± 3.5	0.24
Model 2[c]	23.1 ± 2.9	23.3 ± 3.5	22.9 ± 3.2	23.0 ± 3.6	0.28
Waist circumference (cm)					
Model 1[b]	83.3 ± 9.1	83.6 ± 10.0	83.1 ± 9.0	83.5 ± 9.6	0.79
Model 2[c]	83.1 ± 8.9	83.7 ± 10.1	83.0 ± 8.9	83.6 ± 9.7	0.86
Visceral fat area (cm^2)					
Model 1[b]	89.0 ± 46.5	82.0 ± 44.9	81.1 ± 44.7	80.8 ± 42.9	0.34
Model 2[c]	88.3 ± 45.8	82.1 ± 45.1	81.0 ± 44.6	81.2 ± 43.2	0.38
Model 3[d]	89,7 ± 47.3	81.7 ± 44.4	81.6 ± 45.1	79.7 ± 42.2	0.17
Subcutaneous fat area (cm^2)					
Model 1[b]	183.3 ± 66.7	186.9 ± 75.3	184.3 ± 73.8	189.2 ± 82.1	0.88
Model 2[c]	182.0 ± 65.2	187.2 ± 76.4	184.1 ± 73.6	189.9 ± 82.6	0.81
Model 3[e]	174.9 ± 62.3	187.2 ± 76.5	185.4 ± 74.9	191.0 ± 84.2	0.29

Values are means ± s.d. [a]*P* for trend values were based on linear regression analyses with ordinal numbers 0 to 3 assigned to lowest through highest categories of sleep duration. [b]Adjusted for age (continuous), regular physical activity (yes or no), current cigarette smoking (yes or no) and current alcohol drinking (yes or no). [c]Adjusted for age (continuous), regular physical activity (yes or no), current cigarette smoking (yes or no), current alcohol drinking (yes or no) and physical illnesses (yes or no). [d]Adjusted for age (continuous), regular physical activity (yes or no), current cigarette smoking (yes or no), current alcohol drinking (yes or no), physical illnesses (yes or no) and subcutaneous fat area (continuous). [e]Adjusted for age (continuous), regular physical activity (yes or no), current cigarette smoking (yes or no), current alcohol drinking (yes or no), physical illnesses (yes or no) and visceral fat area (continuous).

This study extends the understanding in the literature of sleep and obesity research in which sleep deprivation has been considered as a potential predictor of obesity, frequently defined by using BMI. BMI is not a valid proxy for body fat mass, and existing BMI cutoffs are not suitable for the classification of individuals as normal weight, overweight or obese in Asians.[26] Asians have proportionally more fat for a similar BMI level and are at increased cardiovascular risk at lower BMI levels as compared with Caucasians.[27] Findings from our study suggest that, in working Japanese men, short sleep duration is associated not only with

general obesity, but also with increased subcutaneous fat mass, supporting a role of chronic sleep restriction in obesity pathogenesis.

Reviews of several cross-sectional and prospective studies among child and adult populations around the world have found fairly uniform results that short sleep duration is associated with obesity[7] and weight gain.[16] However, in their most recent review of prospective studies, Nielsen *et al.*[2] concluded that short sleep duration is consistently associated with development of obesity in children and young adults, but the findings were less consistent in older adults. Furthermore, sleep duration was not associated with BMI in a population-based cohort study among Japanese aged 40 to 69 years,[17] as well as in a prospective multicenter cohort study among early-middle-aged adults (age range of 38 to 50 years) in the United States.[18] In a German study, the significant association between short sleep duration and BMI did not persist after controlling for physical health and emotional status.[21]

This study is the first in the field to formally assess physical and psychiatric illnesses and to assess the relationship between sleep duration and obesity independent of these factors. These confounders may lead to a relationship in the opposite direction; obesity predisposes to physical or psychiatric illnesses, which in turn cause reduced sleep duration. Previous studies have ignored this explanatory pathway or attempted to address it by using self-reported data obtained from a single question on the overall physical and mental health of the participants.[21] Such a measure is not sensitive and does not capture severity of the illnesses. In our analyses, we were not able to show a significant attenuation of the association between short sleep duration and obesity after excluding subjects with psychiatric illnesses and controlling for physical illnesses. These findings suggest that the association among our study population may not be explained by this pathway. Further studies are needed to investigate the possible confounding effects of physical and mental disorders on the relationship between sleep duration and obesity.

It is worth noting that short sleep duration did not show any significant association with general obesity and central abdominal fat areas among women in this study. Similar findings were also found in a study among a large Japanese working population in which no prospective association between sleep duration and obesity or weight gain was detected in women.[19] This finding is also consistent with results obtained from other studies in western populations.[28] In contrast, a study in Spain showed that the significant association between sleep duration and weight gain was observed in women, but not in men.[20] However, direct comparison with men might be made with caution as the mean age of women in our study was roughly 5 years older than that in men. In the Zurich Cohort Study, the relationship between sleep duration and weight weakened as participants aged.[29] Furthermore, our bivariate results show that sleep duration was not related to any obesity-related characteristics in women.

Based on experimental studies of sleep deprivation, a number of causal pathways linking short sleep duration with obesity have been suggested. One mechanism by which sleep deprivation might predispose to weight gain is by increasing caloric intake. In short-term trials, sleep restriction leads to reduction in circulating leptin, elevations in ghrelin, subjective hunger and preferences for calorie-dense, refined-carbohydrate foods,[30] which contribute to the development of obesity. Alternatively, some have argued that, in an environment where food is readily available, curtailed sleep may simply represent an increased opportunity to eat, especially if most of the wake-time is spent in sedentary activities such as watching television where snacking is common.[31] Chronic sleep deprivation clearly leads to feeling fatigue that may in turn lead to obesity-related behavior including decreased energy expenditure, irregular eating habit and low consumption of fruits and vegetables.[32] In addition, activation of inflammatory pathways by sleep restriction may also be implicated in the development of obesity.[33]

The strengths of this study include the large sample size of men, the use of CT scanner to measure central abdominal fat areas and the comprehensive assessments of important covariates. The relationship between sleep duration and obesity may vary in association with underlying risk factors such as insomnia and psychological disorders that are potential comorbidities of sleep deprivation and other severe medical conditions that might affect body composition. With a broad variety of data obtained from a standardized collection, we were able to exclude subjects with a history of psychiatric illnesses, insomnia, stroke, myocardial infarction, cancer and diabetes mellitus. In this way, we extended previous findings by systematically assessing the association between sleep duration and obesity independent from the effects of these potential confounding factors.

Several limitations should also be recognized. First, because of the cross-sectional design, a causal relationship cannot be definitively established. However, experimental studies have confirmed that sleep restriction can have metabolic effects that may be relevant to weight homeostasis.[31] Future studies should evaluate how changes in sleep duration are related to changes in weight and body fat composition over time. Second, daily sleep duration was self-reported, which is a continued limitation in sleep epidemiological studies. However, the Nurses' Health Study has shown a good validity for sleep duration measured by using a similar question against 1-week sleep diaries.[34] Third, long sleepers (>8 h) were not specifically separated from normal sleepers (7 to 8 h). As a result, we were unable to examine the relation between long sleep and obesity, as many studies have reported a U-shaped association.[12,35] Furthermore, information regarding sleep duration did not allow us to distinguish the real 'sleep duration' and 'time in bed'. Finally, although we excluded subjects with history of insomnia, no adjustment was made for other important sleep disorders such as obstructive sleep apnea, which is presumed to play an important role in both sleep disruption and obesity.[36] Future research should examine whether obstructive sleep apnea accounts for the gender differences in the association between sleep duration and adiposity as previous studies found that Asian men appear to have an increased risk of obstructive sleep apnea at lower BMI levels than observed in Caucasian men.[37]

In conclusion, our findings suggest that short sleep duration is associated not only with general obesity, but also with subcutaneous fat mass in Japanese working men. Further research is needed to further explicate the biological mechanisms behind this relationship and to see whether interventions addressing inadequate sleep or poor sleep quality could treat or prevent obesity by taking gender differences into consideration.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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