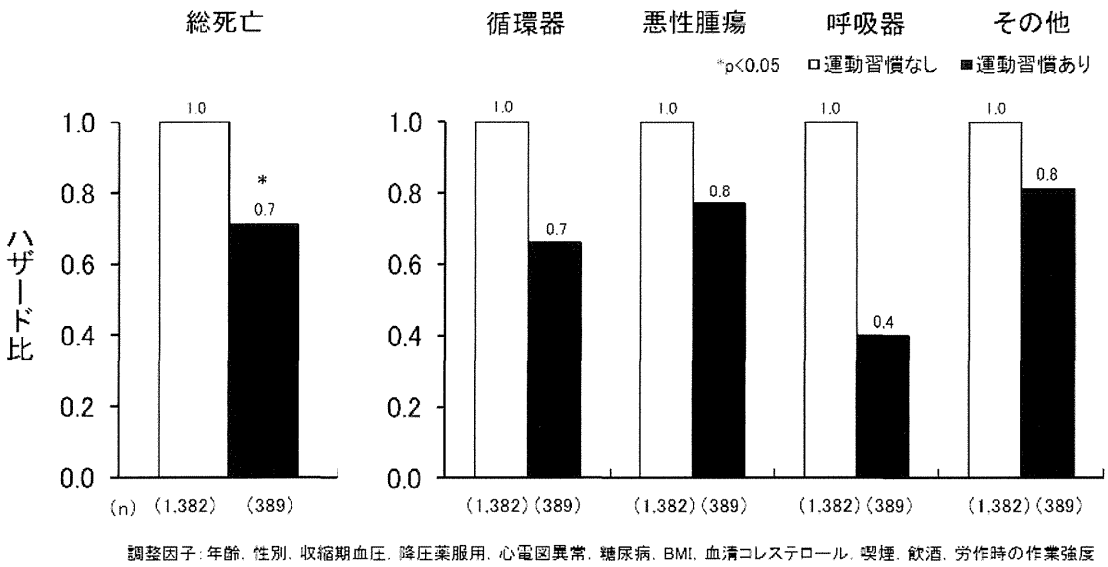

図 3. 運動習慣別にみた総死亡・死因別死亡のハザード比（久山町第 3 集団，65 歳未満男女 1771 名，1988～2005 年，多変量調整）

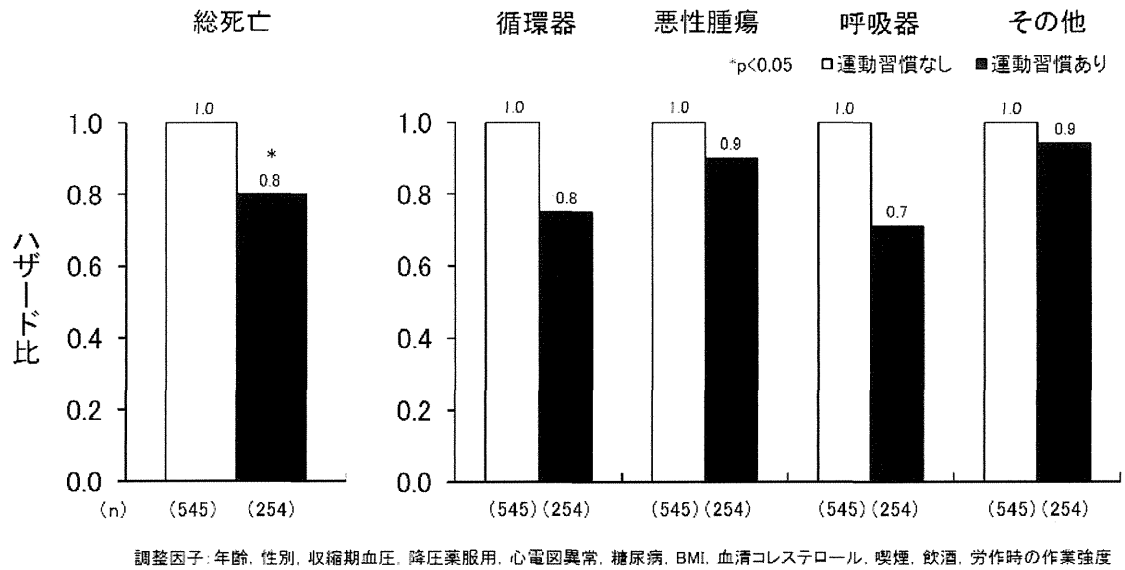

図 4. 運動習慣別にみた総死亡・死因別死亡のハザード比（久山町第 3 集団，65 歳以上男女 799 名，1988～2005 年，多変量調整）

別紙４

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原　著

歩行活動と生活活動を含めた総身体活動量と運動器疼痛との関連性について

― 地域在住高齢者を対象として ―

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森山　善彦[4)]　西内　久人[4)]
古賀　崇正[2)]　熊谷　秋三[5)]

Abstract: The study examined prevalence of MSP(Musculoskeletal pain), total physical activities, locomotive activities, household activities, cognitive functioning, depression, smoking habits, and socioeconomic factors involving 790 elderly subjects aged over 65. After adjustment of a confounding factor, higher activity group of the locomotive activities showed significantly lower prevalence in both groups of MSP and each part. On the other hand, higher activity group of the household activities showed significantly higher prevalence in the group of lower extremity, and lower activity group showed significantly higher prevalence in the group of axial skeleton. Furthermore, both group of the lower and higher groups that of the household activities showed significantly higher prevalence in the group of MSP. The results suggest that, independent of a confounding factor, locomotive activities serves as a protective factor to MSP, and also the relation between household activities and MSP is U-shaped.

Key words: Musculoskeletal pain, Locomotive activities, Household activities

はじめに

慢性的な運動器疼痛（MSP: Musculoskeletal pain）に対する身体活動の有効性は一般的に認められており[1,6,10,20]，余暇時の身体活動量の増加がMSPを含む慢性疾患や能力障害の予防もしくは治療において効果的であることが推察される。しかしながら，日常生活での高強度の活動が膝痛発生と関連するとの報告[11]や身体活動量の低下した者は腰痛有訴率が高いとの報告[5]などから，余暇時の身体活動量だけでなく，身体活動を歩行活動とそれ以外の生活活動に区別してMSP有訴率との関連性を部位別に検討していく必要性があ

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ると考える。特に高齢者では，家事活動などの生活活動が身体活動の大部分を占めることが指摘されており[13]，身体活動の測定範囲に生活活動を含めることは高齢者の実態を把握する上でも重要な知見と成り得ることが考えられる。さらに，これまでの先行研究では，身体活動が主に自記式質問紙によることから，身体活動量評価の方法論的な課題が残されている[6,10]。

そこで今回我々は，65歳以上の地域在住高齢者を対象に，客観的に測定された現在の身体活動量（歩行活動と生活活動を含む）と過去のMSP有訴率との関連性を部位別に検討することとした。

対　　象

本研究は，福岡県太宰府市（男女比率1: 1.10，高齢化率20.8%: 2009年）において2009年と2010年の8〜12月に行った測定会のデータを用いた横断的研究である。全44地区を年齢と性別で層別化し，それぞれの層から太宰府市全体の男女比率，高齢化率とほぼ一致した7地区に住む，2009年4月時点での65歳以上の全住民2,617名を抽出した。そのうち，要介護認定者，死亡，施設入所，転居および入院している者（452名）を除外した2,165名を対象者とし，さらに健康問題，多忙，調査主旨への不賛同者および返答なし者（1,233名）などを除いた932名から調査の協力を得られた（参加率43%）。そのうち，アンケートおよび体力測定不備（46名）および身体活動量計計測不備（96名）を除外した790名（男性366名，46.3%，女性424名，53.7%）を解析対象者とした（図1）。なお，本研究は，保健師，理学療法士，健康運動実践指導士などの管理下で行い，アンケート結果などは直接参加者に問診することで誤分類を防いでいる。本研究は，九州大学健康科学センター倫理委員会での審査，承認を得て実施され，参加者に研究の主旨を説明し，書面による同意を得た後に実施した。

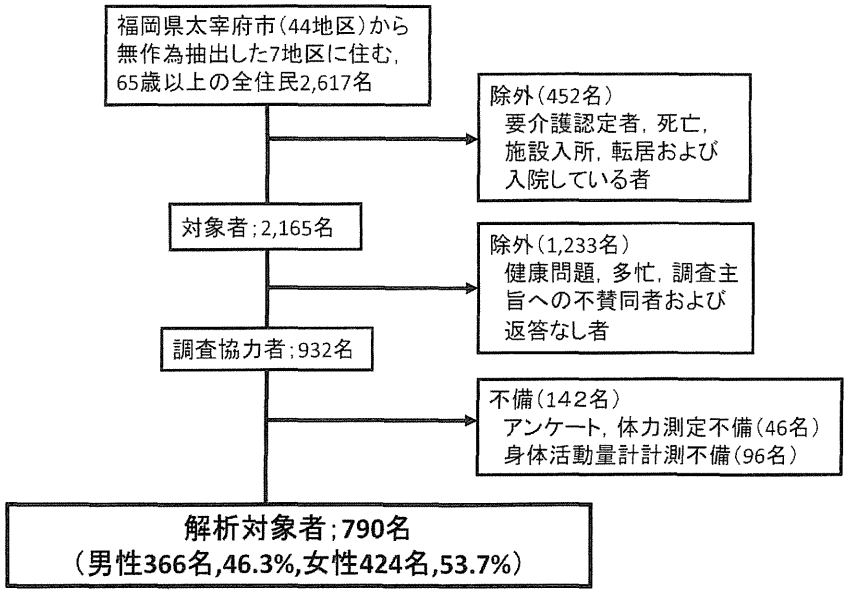

図1　研究のフローチャート

測定項目および測定方法

1. 運動器疼痛

MSPの定義は先行研究[6,10]に準拠し，検出率の高い質問内容とした。参加者には，「過去1年間で1ヶ月以上続く痛みがありましたか」と尋ね，“ある”と解答した者は次の身体の8ヶ所の中で疼痛のある部位を全て示すように指示した（肩関節，肘関節，手関節，股関節，膝関節，足関節，腰背部および頚部の周囲）。そのうち，肩・肘・手関節周囲に疼痛がある者を上肢（UE: Upper extremity）群，股・膝・足関節周囲に疼痛がある者を下肢（LE: Lower extremity）群，腰背部・頸部周囲に疼痛がある者を体軸骨格（AS: Axial skeleton）群，上記部位のいずれかに1ヶ所以上疼痛がある者をMSP群とした。なお，各群は複数回答による延べ人数とした。

2. 身体活動量

2006年に厚生労働省が策定した運動基準[7,8]によると，歩行に限らず掃除かけや家事などの日常生活活動を含む中等度以上の活動強度（3METs以上）の身体活動が推奨されている。そこで，本研究では，歩行とそれ以外の生活活動を識別できる機器である3軸加速度センサを活用した身体活動量計（オムロン活動量計；Active Style Pro HJA 350IT）[14]を使用した。参加者には，活動量計を入浴，水泳，就寝時などを除いて，1週間常時腰部に装着するように指示し，身体活動量を実測した。なお，参加者には活動量計装着後もこれまでと同じ普段通りの活動を行うように指示した。また，活動量計の表示画面はブラインド化することで参加者自身では見ることができないようにした。本研究では，1週間の身体活動量調査で「8時間以上の装着時間が1日以上あること」を条件とし，3METs以上の強度で合計されたMETs・時/週を算出した。さらに，総身体活動量，歩行活動量および生活活動量をそれぞれ三分位した。同じ機器を用いて測定した同様な集団での身体活動量平均値[13]（総身体活動量：男性21.8 ± 10.9，女性26.1 ± 12.8，歩行活動量：男性14.3 ± 9.2，女性11.8 ± 6.8，生活活動量：男性7.5 ± 5.2，女性14.3 ± 9.2）が，本研究の第2三分位数と比較的近似性があることが確認されたため，それぞれを低活動群，中活動群および高活動群に群分けした。

3. その他の因子

その他の因子[2]として，身長，体重，BMI（Body mass index），喫煙の有無，教育歴，所得（65歳以上の平均所得値にて2群に分類）を確認した。認知機能は，ファイブコグテスト[19]を用い，総合ランク得点が14点以下の者を認知機能低下とした。うつ症状は，CES-D（the Center for epidemiological studies depression Scale）[16]を用い，CES-D得点が16点以上をうつ症状ありと判断した。

統計解析

MSP有訴者とMSP非有訴者での諸特性の検討には，t検定ならびにχ^2検定を行った。三分位された総身体活動量，歩行活動量および生活活動量とMSP有訴率との関連性の検討にはロジスティック回帰分析を用いた。従属変数は，MSP群および各部位での有訴者数とし，独立変数は，総身体活動量，歩行活動量および生活活動量とした。基準値は，先行研究に準拠し総身体活動量と歩行活動量は低活動群[6,10]，生活活動量は中活動群[4]とした。調整因子は，年齢，性別，BMI，喫煙，教育年数，所得，認知機能低下およびうつ症状とした。統計解析は，身体活動量別にMSP有訴者数のオッズ比（OR; odds ratio）と95%信頼区間（CI; Confidence

interval）を算出した。有意水準は危険率5%未満とした。統計ソフトにはSAS（Var9.2）を用いた。

結　　果

本研究におけるMSP有訴率は60.9%（481名）であった。疼痛部位は，腰痛35.4%（280名），膝関節31%（245名），肩関節22.9%（181名）の順に多かった。MSP有訴者は非有訴者と比較して，高齢で女性が多く，BMI(kg/m^2)≧25，うつ症状，歩数，総身体活動量および歩行活動量の項目で有意差が認められた（**表1**）。

三分位された身体活動量別のMSP有訴率の結果を**表2**に示した。三分位された総身体活動量とMSP群および各部位の有訴率との間のロジスティク回帰分析の結果，交絡因子とは独立して高活動群は低活動群と比較して，LE群を除く部位でMSP有訴率が有意に低かった。次に，歩行活動量と生活活動量を区別して活動量別に有訴率のオッズ比を求めた結果，交絡因子とは独立して歩行活動量の高い群ほどMSP群および各部位の有訴率が有意に低かった。一方，LE群においては生活活動量の高い群で有意に有訴率が高く，AS群においては生活活動量が低い群で有意に有訴率が高かった。さらに，MSP群との関連性においては生活活動量が低い群と高い群では有意に有訴率が高かった。

考　　察

本研究におけるMSP有訴率は60.9%であった。諸外国での65歳以上の高齢者を対象とした大規模疫学調査によるとMSP有訴率は56.8%であったことが報告されており[3]，先行研究と比較的類似した有訴率であった。

本研究におけるMSP非有訴者とMSP有訴者の総身体活動量平均は，それぞれ21.4METs・時/週と18.6METs・時/週であり，MSP有訴者は非有訴者と比較して，総身体活動量が有意に低かった。健康づくりのための運動基準2006[7,8]によると，3METs以上の身体活動量基準値を23METs・時/週（19～26METs・時/週の範囲）としている。本研究におけるMSP非有訴者の総身体活動量は基準値と比較的近い値であり，総身体活動量がMSP有訴率に影響を及ぼしている可能性が示唆された。そこで，総身体活動量を三分位し，総身体活動量別に有訴率のオッズ比を求めた結果，交絡因子の調整後においても総身体活動量が高い群ほどLE群を除く部位で有訴率が有意に低かった。

先行研究によると，日常生活でのしゃがみ込み動作や階段昇降は膝痛発生の危険因子[11]とされている一方で，股・膝関節痛治療に対するガイドライン[20]では運動が効果的であることが証明され，歩行などを含む有酸素運動を中核的な治療として実施することを推奨している[1]。本研究で用いた活動量計は歩行活動とそれ以外の生活活動を識別できる機器であることから，それぞれの相反する作用（歩行活動では保護因子となり，生活活動では危険因子となる）が結果に影響を及ぼしたのではないかと考える。そこで，歩行活動と生活活動を区別して活動量別に有訴率のオッズ比を求めた結果，交絡因子の調整後においても，歩行活動量が高い群ほどMSP群および各部位での有訴率が有意に低かった。一方，LE群においては生活活動量の高い群で有意に有訴率が高く，AS群においては生活活動量が低い群で有意に有訴率が高かった。さらに，MSP群との関連性においては生活活動量が低い群と高い群では有意に有訴率が高くなることが示された。

そのような背景として，近年，MSPに対

特性	全体	MSP 非有訴者	MSP 有訴者	P-value[b]
n	790	309 (39.1%)	481 (60.9%)	
年齢（歳）[a]	72.8 (5.9)	72.3 (5.8)	73.2 (6.0)	P=0.04
性別，女性（%）	424 (53.7%)	146 (47.3%)	278 (57.8%)	P=0.004
BMI（kg / m²）≧ 25（%）	202 (25.6%)	65 (18.3%)	137 (25.8%)	P=0.004
喫煙者（%）	216 (27.3%)	84 (27.2%)	132 (27.6%)	P=0.91
教育年数（年）[a]	12 (2.4)	12.2 (2.5)	11.9 (2.4)	P=0.1
所得，16 万 / 月未満（%）（vs16 万 / 月以上群）	242 (30.6%)	88 (33.1%)	154 (37.5%)	P=0.24
認知機能低下者（%）	307 (38.9%)	135 (43.7%)	172 (35.8%)	P=0.06
うつ症状（%）	90 (11.4%)	19 (6.2%)	71 (14.9%)	P<0.001
歩数（歩）[a]	5351 (3584)	5900 (3400)	5000 (3657)	P<0.001
総身体活動量（METs・時 / 週）[a]	19.7 (16.1)	21.4 (15.4)	18.6 (16.8)	P=0.02
歩行活動量（METs・時 / 週）[a]	11 (13.3)	13.2 (12.6)	9.6 (13.3)	P<0.001
生活活動量（METs・時 / 週）[a]	8.8 (7.7)	8.3 (7.0)	9.0 (7.7)	P=0.15

MSP; Musculoskeletal pain, BMI; Body mass index, [a] 平均値±標準偏差 , [b] 対応のないｔ検定 ,x^2 検定

表 1　MSP 有訴者と MSP 非有訴者での諸特性の比較

Activity level	Odds Ratio (95%Confidence Interval)							
	n	UE 群	n	LE 群	n	AS 群	n	MSP 群
総身体活動量								
低活動	80	1.0【Reference】	111	1.0【Reference】	118	1.0【Reference】	174	1.0【Reference】
中活動	90	1.0 (0.6-1.0)	84	0.8 (0.7-0.9)*	101	0.7 (0.6-0.9)*	162	0.7 (0.6-0.8)*
高活動	73	0.7 (0.6-0.8)*	88	0.9 (0.8-1.1)	75	0.5 (0.4-0.6)*	145	0.6 (0.5-0.7)*
歩行活動量								
低活動	81	1.0【Reference】	115	1.0【Reference】	117	1.0【Reference】	177	1.0【Reference】
中活動	91	1.0 (0.8 1.1)	92	0.6 (0.5-0.7)	99	0.7 (0.4-0.6)*	165	0.6 (0.6-0.8)*
高活動	71	0.6 (0.5-0.7)*	76	0.5 (0.4-0.6)*	78	0.5 (0.4-0.6)*	139	0.4 (0.3-0.5)*
生活活動量								
低活動	78	1.1 (0.9-1.3)	95	1.0 (1.0-1.3)	111	1.3 (1.2-1.6)*	161	1.3 (1.2-1.6)*
中活動	83	1.0【Reference】	89	1.0【Reference】	91	1.0【Reference】	152	1.0【Reference】
高活動	82	1.0 (0.9-1.2)	99	1.6 (1.4-1.8)*	92	1.0 (0.8-1.1)	168	1.4 (1.2-1.6)*

UE; Upper extremity, LE; Lower extremity, AS; Axial skeleton, MSP; Musculoskeletal pain
調整因子；年齢，性別，body mass index，喫煙，教育年数，所得，認知機能低下およびうつ症状
*P value<0.05
総身体活動量（METs・時 / 週）; 男性：低活動< 11.3，中活動 11.3-23.9，高活動> 23.9
女性：低活動< 10.7，中活動 10.7-21.6，高活動> 21.6
歩行活動量（METs・時 / 週）; 男性：低活動< 5.0，中活動 5.0-16.3，高活動> 16.3
女性：低活動< 2.9，中活動 2.9- 8.5，高活動> 8.5
生活活動量（METs・時 / 週）; 男性：低活動< 3.4，中活動 3.4- 7.5，高活動> 7.5
女性：低活動< 5.1，中活動 5.1-11.5，高活動> 11.5

表 2　三分位された総身体活動量，歩行活動量および生活活動量と部位別有訴率との間のロジスティック回帰分析

する危険因子として身体不活動との関連性を観察した研究が散見され[6]，そのメカニズムとして不動に伴う軟骨代謝[15]，末梢組織（皮膚）[12]，脊髄後角[17]および皮質[9]などの可塑的変化が痛みと関連することが示唆されている。さらに，腰痛との関連性においてはU字型の関連性を示すことが証明されている[4]ことなどから，交絡因子とは独立して，MSPに対して歩行活動は保護因子となり，生活活動量はMSPに対して危険因子と保護因子の両方の可能性を併せ持つことが示唆された。先行研究においても身体活動の二面性は言及されており，過活動と不活動は危険因子となる一方で，中等度の活動は保護因子となることが指摘されている[18]。

本研究は，身体活動量を客観的な身体活動量計を用いて評価したことで先行研究の不十分な点を補い，さらに厚生労働省が提唱する身体活動の定義[7,8]に従って歩行活動を含む運動と生活活動を合わせて身体活動としたことが強みであるといえる。さらに，本研究の結果は，慢性的なMSPに対して身体活動量を向上させるような取り組みをする際には歩行活動と生活活動を区別して実施したほうが効果的であることを示唆する有益な知見を提供できたといえる。

本研究の限界としては，以下の4点が考えられる。まず第1に，参加率が43%と低いことである。低い参加率は，他の集団に一般化できない可能性がある。第2に，運動器疼痛を複数回答で群分けしているため，疼痛部位が重複している可能性があり，正確な部位別有訴率とはいえない。第3に，過去1年間でのMSPの有無を確認したため，現在の身体活動量を反映していない可能性が考えられる。第4に，横断研究であるため，その因果関係が不明な点である。今後は，それらの点も踏まえて縦断的に解明していく必要性が課題として残された。

ま と め

本研究の結果，認知機能低下，うつ症状，喫煙習慣および社会経済的要因とは独立してMSP群および各部位の疼痛に対して歩行活動は保護因子となるが，生活活動においては，MSP有訴率とはU字型の関連性を示すことが示唆された。しかしながら，本研究は横断研究であるため，その因果関係は不明のままであり，今後は両者の因果関係を縦断的に解明していく必要性が課題として残された。

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Serum Brain-Derived Neurotrophic Factor Levels Are Associated with Dyssomnia in Females, but not Males, among Japanese Workers

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Study Objectives: Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of growth factors that promote the growth and survival of neurons. Recent evidence suggests that BDNF is a sleep regulatory substance that contributes to sleep behavior. However, no studies have examined the association between the serum BDNF levels and dyssomnia. The present study was conducted to clarify the association between the serum BDNF levels and dyssomnia.

Methods: A total of 344 workers (age: 40.1 ± 10.5 years, male: 204, female: 140) were included in the study. The serum BDNF levels were categorized into tertiles according to sex.

Results: The prevalence of dyssomnia was 35.1% in males and 30.0% in females. In the females, the BDNF levels were found to be negatively associated with dyssomnia after adjusting for age, body mass index, hypertension, dyslipidemia, hyperglycemia, depression, smoking, alcohol intake, and regular exercise. Compared with the females in the high BDNF group, the multivariate odds ratio (95% CI) of dyssomnia was 2.08 (0.62-6.98) in females in the moderate BDNF group and 8.41 (2.05-27.14) in females in the low BDNF group. No such relationships were found in the males.

Conclusions: The serum BDNF levels are associated with dyssomnia in Japanese female, but not male, workers.

Keywords: Serum brain-derived neurotrophic factor, dyssomnia, sex, Japanese worker

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SCIENTIFIC INVESTIGATIONS

Dyssomnia is one of the most common health problems in the Japanese population. Recent surveys by the Japanese Ministry of Health Labor and Welfare have demonstrated that 21.1% of Japanese adults suffer from dyssomnia.[1] Many studies have suggested that dyssomnia is not only linked to mental disorders, including depression,[2] but also to endocrine disorders (e.g., obesity, diabetes mellitus) and cardiovascular disorders (e.g., hypertension, heart disease).[3-6]

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family of growth factors. In addition to its neurotrophic and synaptotrophic actions, including the promotion of growth and survival in neurons,[7,8] BDNF plays a role in learning and memory,[9] the regulation of food intake,[10] glucose and lipid metabolism and energy homeostasis.[11,12] BDNF is present in the nervous system and peripheral tissues and is also found in blood.[13-15] Accumulating evidence shows the serum BDNF levels to be associated with psychiatric and metabolic disorders, including depression,[16,17]Alzheimer disease,[18] and diabetes mellitus.[19-21] However, no studies have examined the association between the serum BDNF levels and dyssomnia.

Recent evidence interestingly suggests that BDNF is a sleep regulatory substance.[22-24] Faraguna et al.[25] showed the degree of BDNF expression during wakefulness to be causally linked to the extent of slow wave activity in the subsequent rest period. Moreover, Martinowich et al.[26] demonstrated that a genetic manipulation that leads to disruption of the activity-dependent BDNF expression results in impairments in sleep regulation. Based on this evidence showing a biological links between BDNF and sleep behavior, we hypothesized that serum BDNF levels may be associated with dyssomnia. In the present study, we examined this association in Japanese workers.

BRIEF SUMMARY

Current Knowledge/Study Rationale: BDNF is suggested to contribute to sleep behavior. However, there is no study on the association between serum BDNF and dyssomnia.

Study Impact: The serum BDNF levels were inversely associated with dyssomnia in females, but not in males. However, further studies are needed to answer whether or not the sex differences in BDNF are related to sex differences in dyssomnia.

METHODS

In Japan, the Industrial Safety and Health Law requires all employers to provide annual health check-ups for their employees. The annual health check-up consists of an interview regarding lifestyle; measurement of weight, height, and blood pressure; physical examination; electrocardiogram examinations; chest x-ray; urinalysis; and blood tests. Blood samples

from the study subjects were obtained from 08:00 to 10:00 after overnight fasting. In addition to performing these routine health check-up examinations, the serum BDNF levels were measured, and sleep quality and depressive symptoms were assessed with interviews by trained nurses.

Subjects

The subjects of this study were employees of the Creative Research Community (CRC) Company (Fukuoka, Japan), which provides services such as health check-up support, genetic testing, and clinical testing. A total of 400 workers, 20 years of age or older underwent an annual health check-up at their company in 2009. Among these workers, 30 did not agree to participate and 26 who did not complete the questionnaires or biochemical tests were excluded from the study. Ultimately, a total of 344 participants (204 males and 140 females) were included in this study. Two hundred eighty-two study subjects (82%) were day workers. All participants received oral and written information about the experimental procedures before giving their written informed consent. This study was approved by the Ethics Committee of St. Mary's College and monitored by the institutional review committee.

Serum BDNF Levels

After the blood was centrifuged 2000 × g for 10 min at 4°C, the serum was stored at -80°C until the analyses were performed. The serum BDNF concentrations were measured using an enzyme-linked immunoassay (ELISA) kit (Promega, Madison, WI) following the manufacturer's instructions. Briefly, 96 well plates were coated with anti-BDNF monoclonal antibodies and incubated at 4°C for 16 h. The plates were then incubated in a blocking buffer for 1 h. All of the incubation stages were conducted at room temperature. The serum samples were diluted to 1:200, and the plasma samples were diluted to 1:19 in Block & Sample 1 × Buffer. After adding the samples and the BDNF standard, the plates were incubated with shaking for 2 h, then washed in washing buffer. The plates were then incubated with anti-human BDNF polyclonal antibodies for 2 h. After being washed, the plates were incubated with anti-IgY HRP conjugate with shaking for 1 h and washed. Next, TMB One solution was added for 10 min, and the reaction was stopped with 1 M HCl. The absorbance at 450 nm was measured within 30 min after stopping the reaction.

Dyssomnia

Sleep quality was assessed according to the Pittsburgh Sleep Quality Index (PSQI). The PSQI is used worldwide as a tool for the assessment of sleep quality. The scores were obtained according to the PSQI-scoring method (0-1-2-3-4). The cutoff for the total score of the PSQI is 5.5 points, and scores above the cutoff are considered to indicate dyssomnia.[27]

Other Variables

BMI was calculated as the weight in kilograms divided by the height in meters squared. Obesity was defined as BMI ≥ 25 kg/m^2.[28] Antihypertensive medication use, antihyperlipidemic drug use, oral hypoglycemic intake or insulin administration, and current lifestyle factors, including smoking, alcohol intake, and regular exercise were determined by interviews with trained nurses. Hypertension was defined as blood pressure ≥ 140/90 mm Hg and/or current treatment with antihypertensive medications. Dyslipidemia was defined as LDL-cholesterol ≥ 140 mg/dL, triglyceride ≥ 150 mg/dL, HDL-cholesterol < 40 mg/dL and/or current treatment with antihyperlipidemic drugs. Hyperglycemia was defined as fasting plasma glucose concentrations ≥ 110 mg/dL and/or the use of antidiabetic medications.[29] Depressive symptoms were evaluated using the Japanese version of the Center for Epidemiological Studies Depression Scale (CES-D). Depression was defined as a CES-D score ≥ 16 points.[30]

Statistical Analyses

The serum BDNF levels were categorized into tertiles according to sex (males: < 10.91, 10.92 to 13.81, > 13.82 ng/mL; females: < 9.32, 9.33 to 12.12, > 12.13 ng/mL). The crude mean values and the frequencies of the variables were compared between the groups using the χ^2 test and one-way analysis of variance as appropriate. Dunnett test was employed for all post hoc tests. The odds ratios (OR) and 95% confidence intervals (95% CI) of dyssomnia for each BDNF tertile group were calculated by taking the highest tertile as the referent using the logistic regression models. A p-value less than 0.05 was considered to be statistically significant. All statistical analyses were performed using the SPSS software program (Statistical Package for Social Sciences, version 18.0, SPSS Inc., Chicago, IL, USA).

RESULTS

Characteristics of Participants

The prevalence of dyssomnia was 35.1% in the males and 30.0% in the females. The serum BDNF levels were significantly higher in the males (12.72 ± 4.08 ng/mL) than in the females (11.13 ± 3.28 ng/mL, $p < 0.001$).

Table 1 presents the characteristics of the male participants by tertile of the serum BDNF levels. There were no significant differences in PSQI scores or prevalence of dyssomnia among the 3 groups of males. The frequency of regular exercise was significantly higher in the low BDNF group than in the high BDNF group. There were no significant differences in any of the other parameters among the 3 groups of males. **Table 2** presents the characteristics of the female participants by tertile of the serum BDNF levels. The mean PSQI scores in the low and moderate BDNF groups were significantly higher than that in the high BDNF group among females ($p < 0.01$, $p = 0.02$, respectively). Additionally, there were significant differences in the prevalence of dyssomnia among the 3 groups ($p < 0.001$). The prevalence of dyssomnia in the low BDNF group was significantly higher than that in the high BDNF group ($p < 0.01$). There were no significant differences in any of the other parameters among the 3 groups of females.

Association between Serum BDNF Levels and Dyssomnia by Sex

Table 3 shows the association between the serum BDNF levels and dyssomnia. Compared with the females in the high BDNF group, the age-adjusted OR (95% CI) of dyssomnia was 2.04 (0.68-6.09) in females in the moderate BDNF group and 8.18 (2.89-23.13) in females in the low BDNF group. These associations remained statistically significant even after ad-

Table 1—Characteristics of participants by tertile of serum BDNF levels in men (n = 204)

	Serum BDNF level ng/mL			
	High (≥ 13.82)	Middle (10.92-13.81)	Low (≤ 10.91)	p value
Number of subjects	69	69	69	
Age (years)	43.1 ± 10.0	41.8 ± 10.9	42.6 ± 11.6	0.78
BMI (kg/m^2)	24.1 ± 4.0	23.0 ± 2.7	24.0 ± 3.2	0.11
Obesity	26 (37.7%)	16 (23.2%)	22 (33.2%)	0.17
SBP (mm Hg)	135.2 ± 18.8	133.6 ± 16.9	136.4 ± 16.4	0.65
DBP (mm Hg)	84.0 ± 16.6	82.8 ± 12.3	81.9 ± 12.4	0.69
Hypertension	29 (42.0%)	30 (43.5%)	30 (45.5%)	0.92
TC (mg/dL)	218.7 ± 33.4	216.7 ± 31.9	207.2 ± 33.4	0.10
HDL-C (mg/dL)	59.2 ± 14.2	61.7 ± 15.3	60.4 ± 11.4	0.56
LDL-C (mg/dL)	126.5 ± 30.2	126.5 ± 28.9	120.7 ± 27.4	0.41
TG (mg/dL)	147.2 ± 110.6	123.4 ± 67.6	11.2 ± 62.7	0.05
Dyslipidemia	33 (47.8%)	34 (49.3%)	26 (39.4%)	0.46
FBG (mg/dL)	102.9 ± 26.3	98.1 ± 15.5	101.4 ± 19.6	0.40
HbA1C (%)	5.0 ± 0.8	4.8 ± 0.5	4.9 ± 0.7	0.32
Hyperglycemia	11 (15.9%)	6 (8.7%)	16 (24.2%)	0.05
PSQIG score	5.4 ± 2.4	4.8 ± 2.3	5.0 ± 2.4	0.32
Dyssomnia	29 (43.3%)	19 (27.5%)	23 (34.8%)	0.73
CESD score	12.0 ± 6.5	10.1 ± 6.3	11.1 ± 7.1	0.25
Depression	16 (23.5%)	11 (15.9%)	15 (22.7%)	0.49
Smoking	27 (39.7%)	30 (43.5%)	28 (42.4%)	0.90
Alcohol drinking	41 (60.2%)	43 (62.3%)	50 (75.7%)	0.12
Regular exercise	25 (36.8%)	22 (32.4%)	37 (55.4%)	0.02
Service form				
Day worker	52 (77.6%)	55 (80.9%)	55 (84.6%)	0.59
Two shift worker (the day and night)	15 (22.4%)	13 (19.1%)	10 (15.4%)	

Data presented are number (row percentages) or mean value ± standard deviation. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein- cholesterol; LDL-C, low-density lipoprotein-cholesterol; FBG, Fasting blood glucose; BDNF, brain-derived neurotrophic factor.

justing for age, BMI, dyslipidemia, diabetes mellitus, depression, regular exercise, and so on (moderate: OR 1.73, 95% CI 0.51-5.90; low: OR 8.77, 95% CI 2.71-28.38). In contrast, compared with the males in the high BDNF group, the males in the low BDNF group showed a decreased age-adjusted OR for dyssomnia (OR 0.47, 95% CI 0.23-0.97). However, this association disappeared after adjusting for confounding factors (OR 0.58, 95% CI 0.23-1.28).

Association between Serum BDNF Levels and Patterns of Dyssomnia

Table 4 shows the association between serum BDNF levels and the scores of 7 components of PSQIG. Serum BDNF levels in females were significantly inversely correlated with the score of sleep duration ($r = -0.191$, $p < 0.05$), sleep disturbance ($r = -0.179$, $p < 0.05$), daytime dysfunction ($r = -0.270$, $p < 0.01$), and global ($r = -0.295$, $p < 0.001$). No such correlations were found in males.

DISCUSSION

We found the serum BDNF levels to be negatively associated with dyssomnia in females. Because the serum BDNF levels have been reported to change according to age,[31] body weight, BMI,[32] depression,[16,17] metabolic disorders, including diabetes mellitus,[19-21] and regular exercise,[33,34] we adjusted the model for these potential confounding factors. The association between the serum BDNF levels and dyssomnia remained statistically significant even after adjusting for these confounders. Among females, the multivariable-adjusted odds ratio of dyssomnia in the low BDNF group was eight times higher than that in the high BDNF group. However, these associations were not observed in the male subjects. To our knowledge, this is the first study to demonstrate an association between the serum BDNF levels and dyssomnia.

There are many kinds of dyssomnia, and it is an important issue to determine what types of dyssomnia correlate with the serum BDNF levels. Low level of serum BDNF is considered to associate with intrinsic circadian rhythm disorder, since the majority of study subjects were day workers. Therefore, the association between serum BDNF levels and extrinsic circadian rhythm disorder should be investigated in the future. The results of this study showed that serum BDNF levels were negatively associated with sleep duration, sleep disturbance, and daytime dysfunction in the female, although the degrees of these associations seem to be weak. Thus, further large-scale studies are recommended to confirm how serum the BDNF level correlates with the occurrence of dyssomnia.

An association between the serum BDNF levels and dyssomnia is biologically plausible. Since BDNF can cross the blood-

Table 2—Characteristics of participants by tertile of serum BDNF levels in women (n = 140)

	Serum BDNF level ng/mL			
	High (≥ 12.13)	Middle (9.33-12.12)	Low (≤ 9.32)	p value
Number of subjects	47	47	46	
Age (years)	37.1 ± 8.8	36.0 ± 8.5	36.6 ± 9.6	0.82
BMI (kg/m^2)	20.6 ± 2.8	20.9 ± 3.8	21.2 ± 2.5	0.69
Obesity	2 (4.3%)	4 (8.5%)	4 (8.7%)	0.64
SBP (mm Hg)	122.3 ± 15.5	118.1 ± 11.4	118.1 ± 12.8	0.21
DBP (mm Hg)	75.3 ± 11.1	74.8 ± 8.6	74.0 ± 9.1	0.74
Hypertension	7 (14.9%)	4 (8.5%)	6 (13.0%)	0.62
TC (mg/dL)	218.7 ± 33.8	206.2 ± 39.5	203.4 ± 26.0	0.49
HDL-C (mg/dL)	75.4 ± 15.5	77.0 ± 14.8	75.1 ± 13.6	0.37
LDL-C (mg/dL)	114.3 ± 29.2	111.9 ± 26.8	110.3 ± 22.6	0.76
TG (mg/dL)	77.1 ± 50.0	64.0 ± 27.0	75.3 ± 44.9	0.26
Dyslipidemia	10 (21.3%)	6 (13.0%)	11 (23.4%)	0.41
FBG (mg/dL)	93.1 ± 15.1	91.4 ± 14.4	90.2 ± 7.2	0.54
HbA1C (%)	4.7 ± 0.3	4.7 ± 0.6	4.6 ± 0.2	0.66
Hyperglycemia	3 (6.4%)	4 (8.5%)	1 (2.2%)	0.41
PSQIG score	4.3 ± 2.2	3.9 ± 2.2	5.6 ± 2.4	< 0.01
Dyssomnia	6 (12.8%)	11 (23.4%)	25 (54.3%)	< 0.001
CESD score	9.7 ± 7.7	9.6 ± 7.2	11.5 ± 8.2	0.41
Depression	6 (12.8%)	10 (21.3%)	13 (28.3%)	0.18
Smoking	8 (17.0%)	6 (13.0%)	4 (8.7%)	0.49
Alcohol drinking	21 (44.7%)	22 (46.8%)	28 (60.9%)	0.24
Regular exercise	16 (34.0%)	15 (32.6%)	16 (36.4%)	0.93
Service form				
Day worker	39 (83.0%)	42 (91.3%)	39 (84.8%)	0.47
Two shift worker (the day and night)	8 (17.0%)	4 (8.7%)	7 (15.2%)	

Data presented are number (row percentages) or mean value ± standard deviation. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein- cholesterol; LDL-C, low-density lipoprotein-cholesterol; FBG, Fasting blood glucose; BDNF, brain-derived neurotrophic factor.

Table 3—Distribution of Japanese workers with and without dyssomnia according to serum BDNF levels, with corresponding OR and 95%CI

Serum BDNF level	Number of participants	Dyssomnia case	Age- and Sex-adjusted OR (95%CI)	p value	Multivariable-adjusted OR (95%CI)	p value
Male						
High	69	29	1		1	
Middle	69	19	0.67 (0.33-1.36)	0.32	0.51 (0.23-1.12)	0.09
Low	66	23	0.47 (0.23-0.97)	0.05	0.58 (0.23-1.28)	0.18
Female						
High	47	6	1		1	
Middle	47	11	2.04 (0.68-6.09)	0.02	1.73 (0.51-5.90)	0.38
Low	46	25	8.18 (2.89-23.13)	< 0.001	8.77 (2.71-28.38)	< 0.001

Multivariable-adjusted OR: The odds ratios (OR) and 95% confidence intervals (95% CI) of dyssomnia for each BDNF tertile group were calculated by taking the highest tertile as the referent using the logistic regression models, adjusted for age, BMI, dyslipidemia, hyperglycemia, depression, smoking, alcohol drinking, and regular exercise, service form.

brain barrier in both directions[35] and brain tissue is the main contributor to circulating BDNF,[36] low serum BDNF levels may reflect decreased BDNF levels in the brain. An experimental animal study suggested that BDNF in the brain contributes to the regulation of sleep behavior and promotes NREM sleep.[22] Hence, decreased levels of brain BDNF may be related to poor control of sleep behavior.

On the other hand, decreased serum BDNF levels may be caused by dyssomnia. Recent studies in humans suggest that acute or chronic sleep deprivation affects the hypothalamic-pituitary-adrenal (HPA) system and changes the secretion of cortisol.[37,38] Vgontzas et al.[38] demonstrated that 24-h mean cortisol secretion in chronic insomniacs is higher than that in normal controls.[24] Intriguingly, glucocorticoids have been reported

Table 4—The association between serum BDNF level and PSQIG subscores (n = 344)

	All n = 344	Male n = 204	Female n = 140
Sleep quality	0.038	0.111	-0.138
Sleep latency	-0.043	-0.014	-0.106
Sleep duration	-0.019	0.072	-0.191*
Sleep efficiency	0.000	0.005	-0.049
Sleep disturbance	-0.044	0.063	-0.179*
Hypnotic medication	-0.031	-0.030	-0.089
Daytime dysfunction	0.001	0.125	-0.270**
Global	-0.044	0.079	-0.295***

*p < 0.05, **p < 0.01, ***p < 0.001.

to suppress the BDNF expression in the hippocampus.[39] Additionally, a human study demonstrated a negative association between the cortisol levels and the BDNF levels in the blood.[40] Therefore, dyssomnia may reduce the BDNF levels in the brain and the blood by altering the activity of the HPA system to increase the secretion of cortisol.

Many epidemiological studies have suggested gender differences are associated with dyssomnia.[5] However, it remains unclear as to whether or not the sex differences in BDNF observed in the results of the present study are related to sex differences in dyssomnia.

Several limitations should be noted. First, the cross-sectional design of the study limits the interpretation of causality between the serum BDNF levels and dyssomnia. Second, since the sample size was relatively small and the subjects were workers, the subjects may not be representative of the entire Japanese population. Third, we obtained only one serum sample at morning for measurement of serum BDNF level from study subjects. Therefore, we could not investigate the association between the circadian change of serum BDNF levels and dyssomnia in this study. This association should be investigated in future study, since the serum level of BDNF has been demonstrated to be influenced by several conditions, such as meal intake and level of activity.[10-12] Finally, we did not measure any other hormones or mediators which were reported to correlate with dyssomnia. Thus, further study is needed to clarify how serum BDNF levels associate with those hormones and mediators, such as cortisol, growth hormone, sex hormones, and melatonin.

CONCLUSION

In this study, serum BDNF levels were associated with dyssomnia in females but not in males. The association observed in the female subjects remained statistically significant even after adjusting for possible confounding factors, including age, BMI, hypertension, dyslipidemia, diabetes mellitus, depression, smoking, drinking, and regular exercise. Our results support the emerging concept that BDNF is a sleep regulatory substance and may contribute to improving understanding of the pathogenic mechanisms of dyssomnia. Further longitudinal studies of large populations are required to elucidate the precise relationship between the serum BDNF levels and dyssomnia.

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Effect of Exercise Training for the Chronic Hemodialysis Patients

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The present study was conducted to investigate the effect of exercise training on the glucose level in hemodialysis (HD) patients. Sixteen HD patients aged 60.8±9.5 years old participated in this study. They were asked to engage in 30 minutes of exercise training three times a week on the non-hemodialysis days for three months. Both the physical fitness and the serum creatinine levels increased significantly after the exercise training in comparison to the levels at baseline. The degree of the change in the blood glucose level was negatively associated with the degree of change in the serum BDNF level ($r=-0.59$, $p<0.05$). The results of the present study suggest that home-based exercise training may improve the physical fitness as well as increasing the muscle mass in HD patients. However, further studies are needed to explain the role of BDNF, which was suggested to play a role in glucose metabolism in our study.

Key words: hemodialysis, exercise training, brain-derived neurotrophic factor, glucose metabolism.

INTRODUCTION

Chronic hemodialysis patients (HD patients) show insulin-resistance, which increases their glucose and triglyceride (TG) levels [1]. HD patients sometimes suffer from depression [2-5]. The improvements in HD treatment in Japan have given Japanese HD patients the highest survival rate in the world [6]. However, as the survival rate has increased, the number of HD patients who receive HD therapy for a long duration of time has increased in Japan. Patients with long-term HD treatment are likely to suffer from cardiovascular and bone diseases [7, 8], which may cause physical inactivity [9, 10].

Prolonged physical inactivity diminishes physical strength and increases the risk of osteoporosis [7, 8], and also decreases the activities of daily living (ADL) and the quality of the life (QOL) in HD patients. Several investigators have reported that exercise may improve physical strength [11, 12], glucose metabolism [12-15] and depression [11] in HD patients.

Many studies have revealed that reduced levels of brain-derived neurotrophic factor (BDNF) in the brain and the blood may be involved in the pathogenesis of mental disorders, including depression [16-19] and Alzheimer's disease [20, 21]. Furthermore, BDNF can cross the blood–brain barrier in both directions [22], and brain tissue is the main contributor to circulating BDNF [23]. Moreover, Karege et al. [24] showed that serum BDNF in rats correlated positively with cortical BDNF levels.

More recent studies have noted that BDNF may also be a mediator of glucose and lipid metabolism [25-29]. Moreover, some studies suggested that acute and regular exercise increased the serum BDNF levels [30, 31]. Although the role of BDNF in the pathogenesis of these mental disorders is still undefined, our previous study revealed that the serum BDNF level was lower in HD patients in the healthy group, thus suggesting that BDNF may play a role in the hyperglycemia and mental disorders in HD patients [32]. However, there have been few studies that have examined the serum BDNF levels

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