

図1 国立長寿医療研究センター・老化に関する長期縦断疫学研究(NILS-LSA)の経緯

NILS-LSAでは地域在住の中高齢者約2,400人の10年以上にわたるデータが蓄積されている。

トは、同じ人数のあらたな補充を行い、定常状態として約2,400人のダイナミックコホートをめざしている。

施設内に設けられた専用の検査センターで朝9時から夕方4時までの間に分刻みでスケジュールを組んで、1日7名、週4日、年間を通して詳細な老化に関連する検査を行っている。平成12年(2000)4月に2,267名の基礎集団が完成し、以後は2年ごとに検査を繰り返し行っており、現在は第7次調査を行っている。調査項目は頭部MRIや超音波断層、骨密度測定、腹部CTなど最新の機器を利用した医学検査のみならず、詳細な生活調査、栄養調査、運動機能調査、心理検査など広汎で精度の高い内容である(図2)。運動器疾患に関連した検査としては、DXA法による全身骨、腰椎、左右大腿骨頸部の4スキャンでの骨密度測定、末梢骨定量CT検査法(pQCT)による橈骨16スキャン、左右膝X線撮影、胸椎腰椎X線撮影、膝関節機能検査、転倒調査、膝痛調査、腰痛調査、骨折調査、骨代謝マーカー検査などを実施している。調査開始当初より、調査参加者のほぼ全員からの血液サンプルを用いてDNAを蓄積している。これほど背景因子が詳細に検討されている一般住民のDNA試料の蓄積は、国内外でもほかにはほとんどないと思われる^{8,9)}。

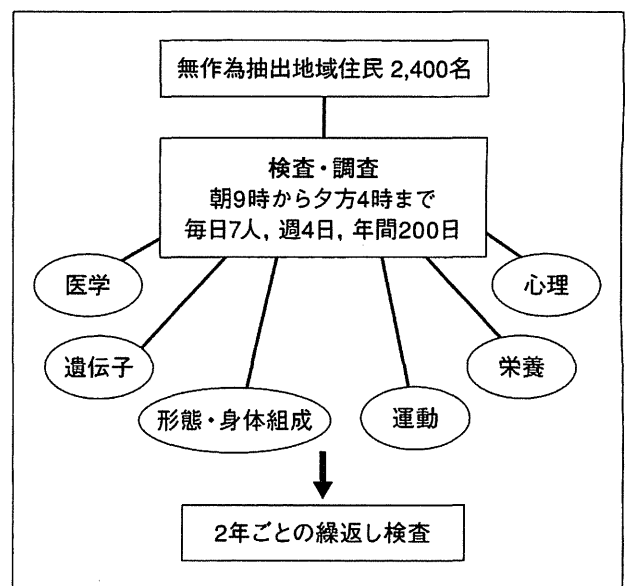


図2 国立長寿医療研究センター・老化に関する長期縦断疫学研究(NILS-LSA)の概要

加齢に伴う運動器疾患罹患の実態

NILS-LSAの第5次調査に参加した40~88歳の男性1,200名、女性1,219名の合計2,419名を対象として、立位で両膝のX線写真を撮影し、Kellgren-Lawrence分類(KL分類)¹⁰⁾にて変形性膝関節症をgrade 0からgrade IVまでに分類し、grade II以上を変形性膝関節症と診断した。また、grade III以上を膝関節高度変形として、10歳ごとの年齢別および性別に有病率を算定した。図3に示すように、変形性膝関節症は男性よりも女性に多く、年

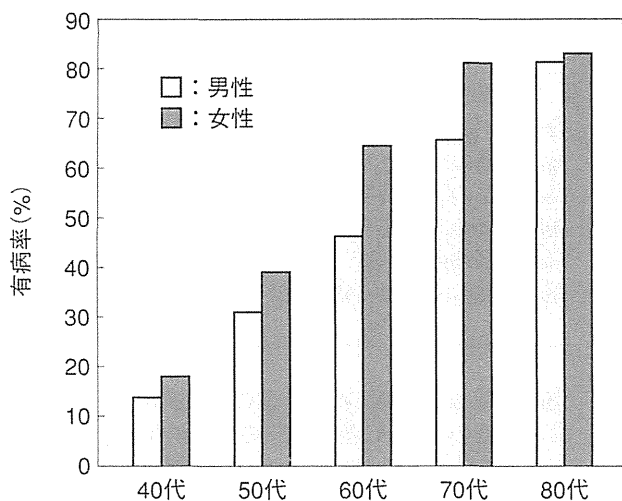


図3 年代別、性別の膝変形性関節症の有病率 (Kellgren-Lawrence 分類 grade II 以上)

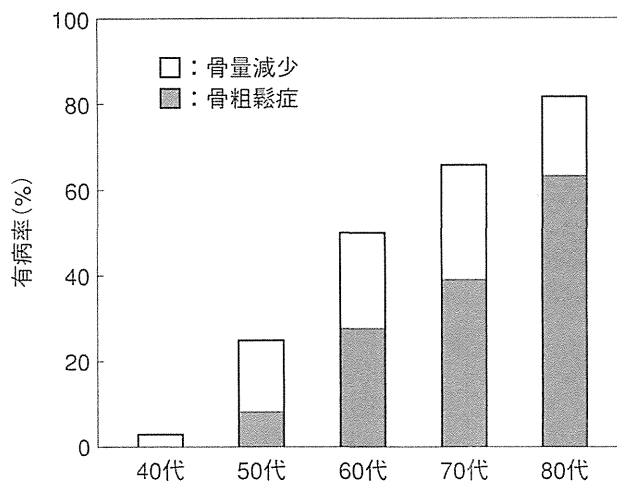


図4 女性の年代別の骨粗鬆症および骨量減少の有病率 (日本骨代謝学会診断基準による腰椎骨密度からの判定)

年齢とともに有病率は上昇する。40歳以上の女性全体での有病率は52.3%、男性で43.5%であった。また、KL分類 grade III以上の膝高度変形保有率は女性のほうが男性よりも2倍以上多く、また女性では年齢とともにその率は大きく上昇していた。上記の有病率を用いて日本人全体の人口構成から有病率を計算すると、男性1,278万人、女性1,950万人の合計3,228万人と推定された。

日本骨代謝学会の診断基準¹¹⁾を用いて、DXA法で計測した腰椎骨密度(第2, 3, 4腰椎の平均骨密度)および右大腿骨頸部骨密度により、性別、年齢別に骨粗鬆症の有病率を算定した(図4)。50歳以上の女性の有病率は、腰椎BMDの判定の場合26.1%、大腿骨頸部BMD判定の場合21.3%であった。骨粗鬆症・骨量減少の年代別有病率は、どちらの部位の判定でも加齢で高くなり、とくに60歳代で急に高くなった。腰椎に比べ、大腿骨頸部判定の場合、50, 60歳代での有病率は低かった。50歳以上の男性の骨粗鬆症有病率は、腰椎BMDの判定の場合7.6%、大腿骨頸部BMD判定の場合10.3%であった。骨粗鬆症・骨量減少の年代別有病率は、大腿骨頸部の判定において60歳代以降、男性でも加齢で高くなっていった。この結果をもとに、今回得られた骨粗鬆症有病率から見積もられる骨粗鬆症患者数は、腰椎骨密度による有病率を用いると50歳以上の女性で約811万人、50歳以上の男性で189万人と推計され、大腿骨頸部では女性685万人、男性250万人となる。男女合

計で骨粗鬆症患者数は900万~1,000万人と推定された。

骨粗鬆症疾患ゲノム研究

骨粗鬆症は生活習慣病であり、カルシウム摂取の不足ややせ、運動不足などの危険因子が指摘されている²⁾。一方で、骨粗鬆症の危険因子として家族歴がある。他の多くの生活習慣病や老年病と同じように、骨粗鬆症は遺伝的素因と生活習慣や加齢などが複雑に影響しあって発症する多因子疾患であると考えられている。疾患によって遺伝的要因の影響の強さは異なる。人種差や環境、生活習慣による違いはあろうが、アメリカのFraminghamスタディの報告では、骨密度の遺伝率(heritability)は約60%と推定されており、遺伝的な要因は比較的大きいと思われる¹²⁾。NILS-LSAでは、これまでに骨密度と有意な関連のあった31種類の遺伝子多型についてあらたに発見、あるいは確認の報告を行っている(表1)⁷⁾。

骨粗鬆症や骨密度への遺伝子多型の影響は、直接的な影響よりもむしろ生活習慣や環境因子による骨への影響を遺伝子多型が修飾する部分が多い可能性がある。図5は著者らの調査の解析結果である。閉経女性のDXA法による骨密度と除脂肪体重との関係へのエストロゲン受容体(ER α)遺伝子Xba I多型の影響について検討した¹³⁾。除脂肪体重として求めた筋量が多ければ骨密度は高いが、その影響はAA型よりもAG/GG型のほうが

表 1 NILS-LSAにおいて骨密度との関連をあらたに発見または確認した遺伝子多型

略号	遺伝子多型	骨密度への影響
カルシウム向性ホルモンおよび受容体		
<i>VDR</i>	vitamin D receptor (A-3731G)	男性の CC 型で大腿骨頸部の骨密度が高い
<i>ESR1</i>	estrogen receptor α (PP/pp)	高齢女性の CC 型で骨密度が低い
<i>ESR1</i>	estrogen receptor α (XX/xx)	高齢女性の GG 型で骨密度が低い
<i>OST</i>	osteocalcin (C298T)	閉経女性の TT 型で骨密度が低い
<i>ADR</i>	androgen receptor (CAG repeat)	未閉経女性の CAG リピートが多いと骨密度が低い
<i>CYP17A1</i>	cytochrome P450, family 17, subfamily A, polypeptide 1 (T-34C)	閉経女性の CC 型で骨密度が低い
サイトカイン, 成長ホルモンおよび受容体		
<i>IL-6</i>	interleukin-6 (C-634G)	閉経女性の GG 型で橈骨遠位の骨密度が低い
<i>TGF-β</i>	transforming growth factor- β 1 (T29C)	高齢女性の TT/TC 型で橈骨の骨密度が低い
<i>OPG</i>	osteoprotegerin (T950C)	未閉経女性の CC 型で橈骨近位の骨密度が低い
<i>OPG</i>	osteoprotegerin (T245G)	閉経女性の GG 型で大腿骨頸部骨密度が低い
<i>CCR</i>	chemokine receptor 2 (G190A)	若年男性と閉経女性の GG/GA で骨密度が低い
骨基質関連蛋白		
<i>MMP1</i>	matrix metalloproteinase-1 (1G/2G at-1607)	閉経女性の GG/GG 型で橈骨遠位骨密度が低い
<i>MMP9</i>	matrix metalloproteinase-9 (C-1562T)	男性の CT/TT 型で骨密度が低い
<i>COL</i>	collagen type 1 (G-1997T)	閉経女性の GG 型で骨密度が低い
<i>ICAM-1</i>	intercellular adhesion molecule-1 (Lys469Glu)	閉経女性の AA 型で骨密度が低い
<i>PLOD1</i>	procollagen-lysine 2-oxyglutarate 5-dioxygenase (Ala99Thr)	未閉経・閉経女性の GA/AA 型で骨密度が低い
<i>CX37</i>	connexin 37 (Pro319Ser)	男性の TT 型で骨密度が低い
その他		
<i>KLOT</i>	klotho (G-395A)	閉経・未閉経女性の GG 型で骨密度が低い
<i>MTP</i>	microsomal triglyceride transfer protein (G-493T)	未閉経女性の TT 型で骨密度が高い
<i>VLDLR</i>	VLDL receptor (triplet repeat)	男性の CGG リピート 8 以上で骨密度が高い
<i>ALAP</i>	adipocyte-derived leucine aminopeptidase (Lys528Arg)	未閉経女性の GA/AA 型で骨密度が低い
<i>LIPC</i>	hepatic lipase (C-514T)	閉経女性の TT 型で骨密度が低い
<i>CNR2</i>	cannabinoid receptor 2 gene (A/G, rs2501431)	未閉経・閉経女性の AA/AG 型で骨密度が低い
<i>PON1</i>	paraoxonase-1 (Gln192Arg)	閉経女性の GG 型で骨密度が低い
<i>PON1</i>	paraoxonase-1 (Met55Leu)	閉経女性の TT 型で骨密度が低い
<i>PON2</i>	paraoxonase-2 (Cys311Ser)	閉経女性の CC 型で骨密度が低い
<i>DRD4</i>	dopamine D4 receptor (C-521T)	男性の CC 型で骨密度が低い
<i>FOXC2</i>	forkhead box C2 (C-512T)	男女ともに T アリルで骨密度が低い
<i>PLN</i>	perilipin (C1243T)	男性の C アリルで骨密度が低い
<i>MAOA</i>	monoamine oxidase A (uVNTR)	未閉経・閉経女性のリピート 4 未満で骨密度低い
<i>SH2B1</i>	Src-homology-2-B (Ala484Thr)	未閉経・閉経女性の A アリルで骨密度が低い

強い。AG/GG 型の多型をもつ人は筋量を増やすことが、AA 型の人よりも骨粗鬆症の予防には効果的であることがわかる。筋量が少ない集団では AA 型のほうが骨密度は高いが、筋量が多い集団では AG/GG 型のほうが骨密度は高いという逆転が生じており、このため対象集団の筋量が異なれば、遺伝子多型の骨密度との関係はまったく逆になってしまう。遺伝子以外の個体差が十分に検討されていないことが、ゲノム研究での再現性が乏しいことの要因のひとつになっている可能性がある。感受性遺伝子多型をもっている人も発症しない人

もいる。その要因を探るというアプローチもある。感受性遺伝子多型をもっていて発症した人、発症していない人について生活習慣などの要因を詳細に比較検討することで、感受性遺伝子をもっている人も骨粗鬆症をどうすれば予防できるかを明らかにすることができる。さらに生活習慣などの修飾可能な危険要因については、その縦断的变化についての検討も必要である。特定の遺伝子多型をもつ人が、たとえば身体活動量を 2 倍にしたとき骨密度はどう変化するのか、遺伝子多型によってその効果にどのような差があるのかを明らかにする

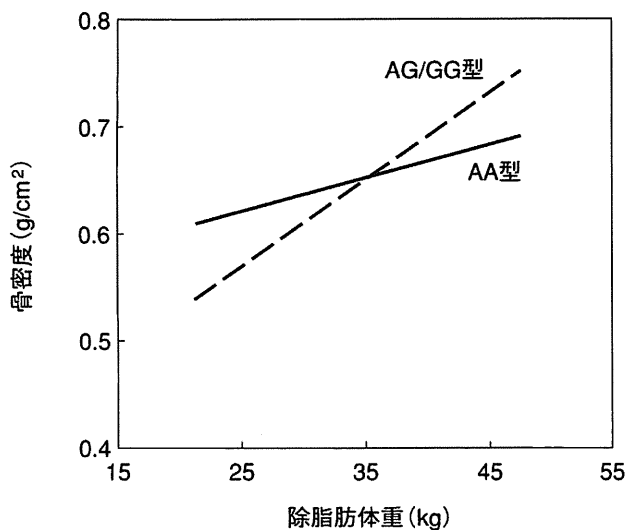


図 5 閉経女性のDXA法による骨密度と除脂肪体重との関係へのエストロゲン受容体(ER α)遺伝子 Xba I 多型の影響¹³⁾

除脂肪体重、すなわち筋量が多ければ骨密度は高いが、その影響はAA型よりもAG/GG型のほうが強い。

ことが、遺伝子多型を利用した実際の予防指導の際には重要である。こうしたデータを蓄積するためには、多数の集団で長期にわたった詳細な生活習慣や環境要因の調査が必要である(「サイドメモ」参照)。

運動器疾患のリスク予想と予防

骨代謝マーカー測定によって骨粗鬆症や骨量減少の予測ができるかをNILS-LSAで検討した。骨代謝マーカーとしてオステオカルシン(OC)、骨型アルカリホスファターゼ(BAP)、尿中I型コラーゲン架橋N-ペプチド(NTx)、デオキシピリジノリン(DPD)を測定したところ、女性の腰椎でOC、BAP、NTxが、女性の大腿骨頸部でDPD、BAP、NTxが、男性の大腿骨頸部でBAPが6年後の骨粗鬆症や骨量減少の発症に有意に関連しており、これらのマーカーから将来の骨粗鬆症や骨量減少の発症を予測できる可能性が示された¹⁴⁾。

NILS-LSAでは、生活習慣や環境要因との相互関係を考慮した骨粗鬆症の遺伝要因の検討も順次進めている。DXA法による骨粗鬆症診断結果と、握力、脚筋力など運動・体力に関する要因、カルシウム、ビタミンDなど栄養に関する要因、BMI、除脂肪体重など体格・体型に関する要因、そのほか嗜好、閉経、骨代謝マーカーを含む血液尿検査

結果などの項目の追跡による縦断的なデータについて網羅的に検討を行うことで、それぞれ骨粗鬆症と関連の強い要因を抽出する。抽出された要因と遺伝子多型との相互作用を網羅的に検討し、その結果から最終的に骨粗鬆症と関連する生活習慣要因、遺伝子多型、生活習慣要因と遺伝子多型の交互作用を抽出し、骨粗鬆症の予測を行う総合的なシステムの構築を行っている。長期縦断研究によりこうしたシステムが完成すれば、骨粗鬆症の医療や予防の実用化へ一歩前進するものと期待される。

おわりに

高齢化が急速に進む日本の社会において、高齢者の健康維持・増進はきわめて重要な課題である。高齢者が健康に長生きできることは国民の共通の願いであり、これを実現することが急務である。高齢者の運動器疾患は直接の死因とはならない場合がほとんどではあるが、高齢者のQOLを阻害し、寝たきりや廃用症候群を引き起こし、認知症や肺炎の要因ともなる。高齢者の運動器疾患の予防と治療は高齢者の健康長寿を考える場合には欠かすことができない。そのためのエビデンスを集積する研究として、疾患そのものだけでなく、

サイドメモ

縦断研究

加齢による変化を検討する方法には大きく分けて、横断的方法と縦断的方法の2つがある。縦断的研究は同一の個人を継続して観察し、加齢による実際の心身の変化、加齢に関連する要因、発育、発達、老化、寿命などをとらえようとするものである¹⁻⁴⁾。一方、さまざまな年齢を含む集団を設定して種々の検査を一度に実施し、1歳ごとの、あるいは5歳、10歳ごとの年齢群で検査値がどのように異なるのかを検討し、その差を加齢変化とする方法が横断的研究である。一度の調査で終了してしまう横断研究に比べて経時的な追跡を行う縦断研究は、結論が出るまでに一般に数年から10年以上もの期間を要し、調査を継続するための費用や人材の確保も必要である。しかし、加齢変化の観察を行うためには横断的観察のみでは加齢による変化を正確にとらえることができない。

遺伝子や栄養，運動までを含めた学際的な長期縦断疫学研究の進展が望まれる。

文献

- 1) Yoshimura, N. et al. : *J. Bone Miner. Metab.*, **27** : 620-628, 2009.
- 2) 下方浩史：新老年学改訂第3版(大内尉義，秋山弘子編)。東京大学出版会，2010，pp.333-346.
- 3) 安藤富士子，下方浩史：*Medicina*, **45** : 430-433, 2008.
- 4) Shimokata, H. et al. : *J. Epidemiol.*, **10** : S1-S9, 2000.
- 5) 下方浩史：*Geriatric Med.*, **36** : 21-26, 1998.
- 6) 下方浩史：*Geriatric Med.*, **45** : 13-17, 2007.
- 7) 下方浩史，安藤富士子：日本老年医学会雑誌，**45** : 563-572, 2008.
- 8) 下方浩史・他：*Mol. Med.*, **39** : 576-581, 2002.
- 9) 下方浩史，安藤富士子：*Clin. Calcium*, **18** : 155-161, 2008.
- 10) Kellgren, J. H. and Lawrence, J. S. : *Ann. Rheum. Dis.*, **15** : 1-11, 1956.
- 11) 折笠 肇・他：日本骨代謝学会雑誌，**18** : 76-82, 2001.
- 12) Karasik, D. et al. : *J. Bone Miner. Res.*, **179** : 1718-1727, 2002.
- 13) Kitamura, I. et al. : *Bone*, **40** : 1623-1629, 2007.
- 14) 竹村真理枝・他：*Osteoporos. Jpn.*, **15** : 28-32, 2007.

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Impact of Caregiver Burden on Adverse Health Outcomes in Community-Dwelling Dependent Older Care Recipients

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Objective: *To determine whether caregiver burden is associated with subsequent all-cause mortality or hospitalization among dependent community-dwelling older care recipients. Methods:* *A prospective cohort study of 1,067 pairs of community-dwelling 65-year-old or older care recipients and their informal caregivers was conducted. The 1,067 pairs completed the baseline assessment including caregiver burden assessed by the Zarit Burden Interview and a 3-year follow-up for all-cause mortality and hospitalization. Results:* *During the 3-year follow-up, 268 recipients died and 455 were admitted to hospitals. The multivariate Cox proportional hazards model revealed that the recipients with caregivers with a baseline ZBI score in the highest quartile were 1.54 and 1.51 times more likely to show increased risks of all-cause mortality and hospitalization, respectively, in comparison with those with caregivers in the lowest quartile after adjustment for potential confounders. The highest quartile of caregiver burden was associated with all-cause mortality and hospitalization within nonusers of respite services including day-care services, home-help services, and nursing-home respite stay services. No apparent association was observed within the users of these services except for day-care services, for which users showed a statistically significant association between the highest quartile and the risk of hospitalization. Conclusions:* *Heavy caregiver burden is associated with mortality and hospitalization among community-dwelling dependent older adults, even after adjusting for potential confounders. The reduction of caregiver burden and improvement of caregiver well-being may not only prevent the deterioration of caregiver health but also reduce adverse health outcomes for care recipients. (Am J Geriatr Psychiatry 2011; 19:382–391)*

Key Words: Caregiver burden, mortality, hospitalization, adverse health outcomes of care recipient

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The current trend toward a community-based healthcare system means that when older people require care, much of it is provided at home. Thus, family members are providing care for ill or disabled older relatives. Family caregiving has been intensively studied in the past decade, particularly the impact on caregivers of providing home care to a family member. Caregiver burden has been defined as a negative reaction to the impact of providing care on the caregiver's social, occupational, and personal roles.¹⁻³ It is well documented that informal care for the disabled elderly places heavy burdens on family caregivers.¹⁻³ Previous studies demonstrated that caregiver burden is associated with the substantial care needs of seriously ill patients, which are in turn associated with the presence of dementia, behavioral problems, poorer physical functioning, and factors that are not readily modifiable.⁴⁻⁷ Caregiver burden can lead to a chronic stress response that can worsen caregiver health, contribute to psychiatric morbidity in the form of increased depression,⁸ contribute to the risk of health problems such as wound healing impairment, elevated blood pressure, and coronary heart disease risk and immune function impairment,⁹⁻¹¹ and is an independent risk factor for mortality.¹²

Thus, most of the previous studies on caregiver burden have focused on examining its cause(s) and extensively examining caregiver health. However, conversely, much less attention has been paid to the impact of caregiver burden or distress on the health of the partner, the care recipient. In fact, it remains uncertain whether caregiver burden or distress has any influence on the health-related outcomes of care recipients, although the association of caregiver burden with long-term care placement has been well demonstrated.^{13,14} In this study, we investigated whether caregiver burden is associated with adverse health outcomes of the care recipients, including all-cause mortality and hospitalization for acute illness, during a 3-year study period. In addition, we examined the effect of community-based respite care services, including day-care, home-help, and nursing-home respite stay services on the adverse outcomes of care recipients.

METHODS

Study Setting and Cohort Participants

In this study, we employed baseline data on the care recipient and caregiver pairs in the Nagoya Longitudinal Study for Frail Elderly (NLS-FE) and data on the mortality and hospitalization of the care recipients during the 3-year follow-up period. Japan introduced a universal-coverage long-term care insurance (LTCI) program in 2000. Under the LTCI program, each applicant's care levels are determined according to eligibility criteria. Eligibility status is classified into six levels ("needs support" and care levels 1-5) by the estimation of care needs based on an assessment of the current physical and mental status of the patient and their use of medical procedures.¹⁵ The NLS-FE was designed to compare the outcomes of different uses of community-based care services provided by the LTCI program.^{16,17} The study sample consisted of 1,875 community-dwelling elderly (632 men and 1,243 women, age 65 years or older) with some degree of physical or mental disability. They were eligible for the LTCI program, lived in Nagoya City, Japan, and received various kinds of community-based services from the Nagoya City Health Care Service Foundation for Older People, which has 17 visiting nursing stations associated with care-managing centers. These 1,875 NLS-FE participants and 1,502 caregivers (373 of the 1,875 participants lacked a primary caregiver), who were enrolled between December 1, 2003, and January 31, 2004, were scheduled to undergo comprehensive in-home assessments by trained nurses at the baseline and at 6, 12, and 24 months. At 3-month intervals, data were collected about any important events in the lives of the participants, including mortality and admission to the hospital for acute illness during the 3-year follow-up. Written informed consent for participation was obtained from the participants, care recipients, and caregivers, or, for those with substantial cognitive impairment, from a surrogate (usually the closest relative or legal guardian), according to procedures approved by the Institutional Review Board of Nagoya University Graduate School of Medicine.

Data Collection

The data were collected at the clients' homes through structured interviews with care recipients or surrogates and caregivers and from care-managing center records taken by trained nurses. The data included each participant's demographic characteristics, general socioeconomic status, living arrangements, subjective economic status, use of medical services, and the utilization of a total of seven community-based services available under LTCI programs, including the day-care service, visiting nurse service, home-help service, visiting bathing service, visiting rehabilitation, assistive device leasing, and nursing-home respite stay (overnight respite, temporary stays at nursing facilities). The data also included depressive symptoms as assessed by the 15-item Geriatric Depression Scale (GDS-15) (range: 0–15, with higher values indicating more depressive symptoms)¹⁸ and a rating for eight basic activities of daily living (bADL) using summary scores ranging from 0 (total disability) to 20 (no disability). The information on the following physician-diagnosed chronic conditions was obtained from care-managing center records: ischemic heart disease, congestive heart failure, cerebrovascular disease, diabetes mellitus, dementia, chronic obstructive pulmonary disease, cancer, hypertension, and other diseases comprising the Charlson Comorbidity Index,¹⁹ which represents a sum of weighted indexes that takes into account the number and seriousness of preexisting comorbid conditions (range: 0–19, with a higher value indicating higher comorbidity).

Data were also obtained from caregivers concerning their own personal demographic characteristics including caregiver relationship to care recipient (spouse or not), and the presence of behavioral disturbance of the care recipient according to the primary assessment dataset of the public LTCI, including wandering, hallucinations, physically aggressive behaviors, verbal aggression, delusions, altered sleep-wake cycles, sexually disinhibited behaviors, aberrant behaviors, abnormal eating behaviors, and resistance to care. Depressive symptoms were assessed by the GDS-15, and the caregiver's subjective burden was assessed by the Japanese version of the Zarit Burden Interview (ZBI), which is a 22-item self-report inventory that examines the burden associated with functional behavioral impairments in the home care situation (range: 0–88, with higher values

indicating a greater burden). The primary caregivers were also asked to rate their current overall health in three categories of subjective health status (poor, fair, and good to excellent).

Subjects for the Analysis

Among the original 1,502 pairs at baseline, 276 caregivers could not complete or refused to assess the ZBI, and the data on comorbidity condition or sociodemographic characteristics were lacking for 159 participants. The study sample, therefore, consisted of 1,067 community-dwelling disabled elderly (387 men, 680 women, age range: 65–104 years) and paired caregivers (256 men, 811 women, age range: 31–90 years). There were no statistical differences in mortality and hospitalization rates during the follow-up period between participants with and without caregiver ZBI measurements among the 1,502 participants. Of these 1,067 pairs, 259 care recipients could not complete the GDS-15 because of severe cognitive impairment or communication impairment, and 101 caregivers because of refusal to do the assessment.

Statistical Analysis

The ZBI score was categorized into quartiles (quartile 1: score, 0–15, N = 284; quartile 2: 16–26, N = 253; quartile 3: 27–39, N = 269; quartile 4: 40–84, N = 261). Baseline characteristics of the study participants, including both care recipients and caregivers, were examined using the Jonckheere–Terpstra test or the General Linear Models for trends across the quartiles of the ZBI score. Analysis of variance for multiple comparisons was used to determine differences among the quartiles of the ZBI score for continuous variables, and the Pearson χ^2 test was used to test categorical variables. The end point of this study was defined as the time to all-cause death or hospitalization because of acute illness, whichever occurred first, during follow-up. Cox proportional hazard models and the Kaplan–Meier method (differences between strata of the ZBI score levels determined using log-rank tests) were used to assess the association of quartiles of the ZBI score with those adverse outcomes after enrollment during a 3-year period (3-month intervals). To create an ideal model for a multivariate Cox proportional hazards model, we first evaluated the association between

each covariate and all-cause death or hospitalization, using the univariate Cox proportional hazards model. Covariates included, for the recipient, sociodemographic characteristics, the presence or absence of regular medical checkups, the number of community-based services, economic status, bADL score, the Charlson comorbidity index, and the presence or absence of selected major comorbidities and behavioral problems. Covariates also included, for the caregiver, sociodemographic characteristics, subjective health status, and categorized ZBI score. In the multivariate analysis, the covariates included were variables associated with each event with $p < 0.05$ in univariate analysis. In models considering the quartiles of the caregiver ZBI score, we compared hazard ratios (HRs) with a corresponding 95% confidence interval (CI) in the second, third, and fourth quartiles with those in the first quartile (referent).

Additional analyses stratified by the use or nonuse of community-based respite care services including day-care, home-help, and nursing-home respite stay services were also performed using a consistent set of covariates to examine the data for possible interactions of these variables with the adverse health outcomes of care recipients. Student's *t*-test and analysis of covariance (ANCOVA) were used to compare the caregiver ZBI score according to the service use and nonuse groups. Covariates of ANCOVA included recipient gender, age, bADL score, the Charlson comorbidity index, the presence or absence of dementia and behavior problems, caregiver gender, and caregiver age.

The data were analyzed using the SAS, Release 9.13. Probability value of < 0.05 was considered significant.

RESULTS

The baseline distribution of the sociodemographic characteristics of the care recipients and caregivers according to the quartiles of the ZBI score is shown in Table 1. We used analysis of variance or Pearson χ^2 test to evaluate differences among the quartiles of the ZBI score. The bADL score decreased, and the number of community-based services used, the Charlson comorbidity index, and recipient GDS-15 score increased as the level of the ZBI quartile increased. The care recipients whose caregivers' ZBI

scores were in higher quartiles were more likely to show a higher prevalence of dementia (χ^2 test: $\chi^2 = 61.09$, degrees of freedom [*df*] = 3, $p < 0.001$; Jonckheere-Terpstra test: *z* statistics, *Z* value = 7.51, $N = 1,067$, $p < 0.001$), behavioral problems ($\chi^2 = 14.75$, $df = 3$, $p = 0.002$; Jonckheere-Terpstra test, *Z* value = 8.58, $N = 1,067$, $p < 0.001$) and a history of cerebrovascular disease ($\chi^2 = 10.31$, $df = 3$, $p = 0.016$; Jonckheere-Terpstra test, *Z* value = 2.37, $N = 1,067$, $p = 0.018$). The caregiver's GDS-15 score increased (General Linear Model, *F* value = 313.48, $df = 1,964$, $p < 0.001$), and the prevalence of good to excellent subjective health status of the caregiver decreased with increasing quartiles of the ZBI score (Jonckheere-Terpstra test, *Z* value = 5.37, $N = 1,067$, $p < 0.001$). There were no differences in the rate of regular medical checkups (χ^2 test, $\chi^2 = 5.66$, $df = 3$, $p = 0.130$), living arrangements (living alone or with one person versus living with two or more, $\chi^2 = 1.46$, $df = 3$, $p = 0.692$), and three categories of economic status ($\chi^2 = 6.70$, $df = 3$, $p = 0.349$) among the quartiles of the ZBI score.

During the 3-year period, 268 care recipients died and 455 were admitted to hospitals (Table 2). The participants whose caregivers' ZBI scores were in the higher quartiles were more likely to die and be hospitalized during the follow-up period than those whose caregivers' scores were in the lower quartile categories (χ^2 test, $\chi^2 = 9.78$, $df = 3$, $p = 0.020$; $\chi^2 = 11.09$, $df = 3$, $p = 0.007$, respectively).

Kaplan-Meier curves of survival and the cumulative incidence of hospitalization during the 3-year period among care recipients according to the quartile of the caregivers' ZBI scores demonstrated that all-cause mortality and hospitalization increased with higher quartiles of caregiver ZBI at baseline (log-rank χ^2 test, mortality: $\chi^2 = 17.29$, $df = 3$, $p < 0.001$; hospitalization: $\chi^2 = 23.61$, $df = 3$, $p < 0.001$; Fig. 1).

The univariate Cox proportional hazards model revealed that the recipients whose caregivers' ZBI scores were in the highest quartile were 1.93 times and 1.86 times more likely to suffer all-cause mortality and hospitalization, respectively, during the 3-year period than those in the lowest quartile (95% CI: 1.38–2.71, Wald χ^2 test, $\chi^2 = 14.80$, $df = 1$, $p < 0.001$; 95% CI: 1.43–2.42, Wald $\chi^2 = 21.16$, $df = 1$, $p < 0.001$). The GDS-15 score of the care recipients and caregivers was not associated with mortality and hospitalization in univariate analysis (mortality: HR: 1.03; 95% CI: 0.98–1.07, Wald χ^2

Impact of Caregiver Burden on Adverse Health Outcomes

TABLE 1. Baseline Characteristics of Study Participants According to ZBI Score Quartile of Caregivers

	Quartile Group of Caregiver ZBI Score				F	p
	1st, Score: 0-15, n = 284	2nd, Score: 16-26, n = 253	3rd, Score: 27-39, n = 269	4th, Score: 40-84, n = 261		
Care recipients (n = 1067)						
Men/women, N (% of men)	89/195 (31.3)	88/165 (34.8)	100/169 (37.2)	110/151 (42.1)		0.065
Age, M (SD), year ^a	81.0 (7.1)	81.1 (7.7)	81.2 (7.8)	80.8 (8.5)	0.10	0.962
Basic ADL (range: 0-20), M (SD) ^a	14.2 (6.1)	12.5 (6.2)	11.0 (6.5)	10.4 (6.3)	20.07	<0.001
Charlson comorbidity index, M (SD) ^a	1.8 (1.5)	2.2 (1.5)	2.3 (1.5)	2.4 (1.7)	7.06	<0.001
GDS-15 (range: 0-15), M (SD) ^{a,b}	5.4 (3.4)	6.2 (3.2)	6.6 (3.4)	8.1 (3.7)	21.19	<0.001
No. of service uses (range: 0-7), M (SD) ^a	2.0 (1.1)	2.2 (1.2)	2.4 (1.3)	2.5 (1.3)	8.97	<0.001
Presence of chronic disease, no. (%)						
Ischemic heart disease	36 (12.7)	31 (12.3)	36 (13.4)	29 (11.1)		0.882
Congestive heart failure	17 (6.0)	20 (7.9)	22 (8.2)	27 (10.3)		0.321
Cerebrovascular disease	93 (32.7)	110 (43.5)	120 (44.6)	111 (42.5)		0.016
COPD	11 (3.9)	11 (4.3)	14 (5.2)	18 (6.9)		0.400
Dementia	66 (23.2)	92 (36.4)	135 (50.2)	135 (51.7)		<0.001
Cancer	29 (10.2)	22 (8.7)	14 (5.2)	28 (10.7)		0.098
Presence of behavioral problems, no. (%)	8 (2.8)	11 (4.3)	21 (7.8)	26 (10.0)		0.002
Caregiver variables (n = 1067)						
Men/women, no. (% of men)	71/213 (25.0)	69/184 (27.3)	56/213 (20.3)	60/201 (23.0)		0.350
Age, M (SD), year ^a	64.1 (13.0)	65.4 (12.2)	63.5 (12.6)	65.8 (11.3)	2.05	0.106
GDS-15 (range: 0-15), M (SD) ^{a,c}	3.4 (3.0)	4.7 (3.2)	5.8 (3.5)	8.5 (3.4)	107.98	<0.001
Relationship to care recipient, no. (%)						
Spouse	115 (40.5)	119 (47.0)	106 (39.4)	128 (49.0)		0.061
Nonspouse	169 (59.5)	134 (53.0)	163 (60.6)	133 (51.0)		
Health status, no. (%)						
Good to excellent	150 (52.8)	101 (39.9)	98 (36.4)	80 (26.2)		<0.001
Fair	103 (36.3)	127 (50.2)	148 (55.0)	169 (55.4)		
Poor	31 (10.9)	25 (9.9)	23 (8.6)	56 (18.4)		
ZBI score (range: 0-88), M (SD) ^a	9.4 (4.7)	21.0 (3.1)	32.6 (4.0)	52.5 (9.8)	2553.05	<0.001

Notes: M: mean; SD: standard deviation; COPD: chronic obstructive pulmonary disease.

^aAnalysis of variance for multiple comparisons was used to determine differences among the quartiles of the ZBI score for continuous variables (*df* = 3,1063 except for recipient GDS-15 [*df* = 3, 804] and caregiver GDS-15 [*df* = 3,962]), and the Pearson χ^2 test was used to test categorical variables (*df* = 3).

^bn = 808.

^cn = 966.

TABLE 2. Adverse Events During 3-year Period According to the Quartile Group of ZBI Score

	Quartile Group of ZBI Score				Total, n = 1,067	p ^a
	1st, n = 284	2nd, n = 253	3rd, n = 269	4th, n = 261		
Adverse outcomes, no. (% of each quartile)						
All-cause death	58 (20.4)	63 (24.9)	64 (23.8)	83 (31.8)	268 (25.1)	0.020
Hospitalization	98 (34.5)	111 (43.9)	119 (44.2)	127 (48.7)	455 (42.6)	0.007

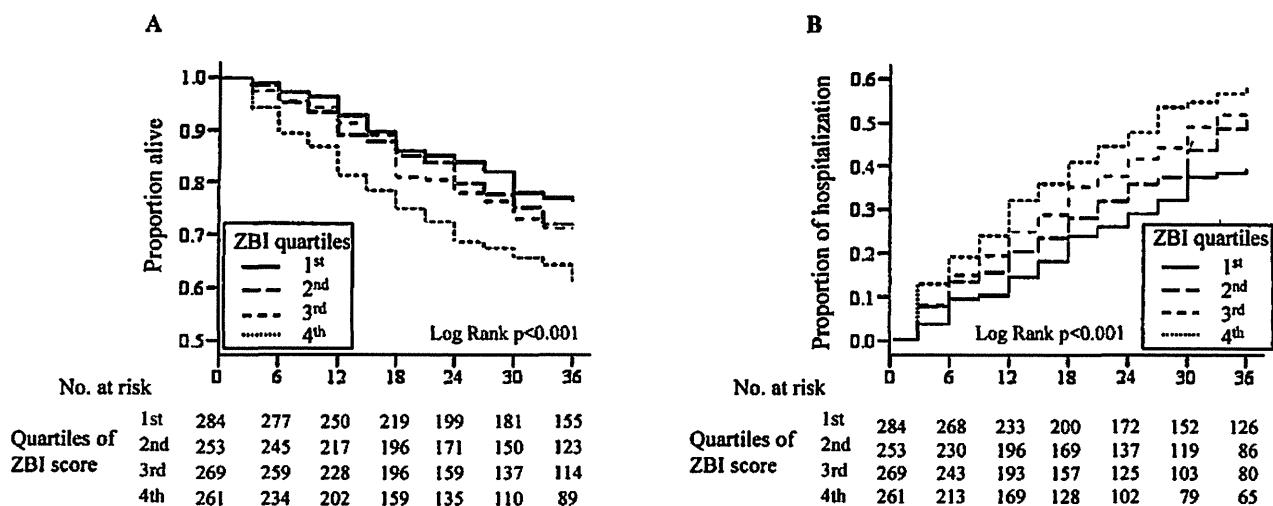
^aPearson χ^2 test. Degree of freedom is equal to 3.

test, $\chi^2 = 1.52$, *df* = 1, *p* = 0.218, and HR: 1.02; 95% CI: 0.98-1.05, Wald $\chi^2 = 1.072$, *df* = 1, *p* = 0.301, respectively; hospitalization: HR: 1.02; 95% CI: 0.99-1.05; Wald χ^2 test, $\chi^2 = 1.54$, *df* = 1, *p* = 0.215, and HR: 1.01; 95% CI: 0.99-1.04; Wald $\chi^2 = 0.81$, *df* = 1, *p* = 0.369, respectively).

As shown in Table 3, multivariate adjustment for confounders, including recipient gender and age,

bADL score, number of community-based services used, the Charlson comorbidity index, caregiver gender and age, presence or absence of behavioral problems (only for all-cause mortality analysis), and the subjective health status of the caregiver (only for hospitalization analysis), showed that the highest quartile of caregivers' ZBI scores (compared with the lowest quartile) was associated with a 1.54-fold risk

FIGURE 1. Kaplan–Meier Plot for Probability of Event-Free Survival (A) and Probability of Hospital Admission (B) According to Increasing Quintiles of the Zarit Burden Interview Score



Log-rank χ^2 test, mortality (A): $\chi^2 = 17.29$, $df = 3$, $p < 0.001$; hospitalization (B): $\chi^2 = 23.61$, $df = 3$, $p < 0.001$.

of all-cause death and a 1.51-fold risk of recipient hospitalization. When the analyses were conducted using the ZBI score as a continuous variable, the recipients who had caregivers with higher ZBI scores were associated with higher risk of mortality and hospitalization (HR: 1.01, 95% CI: 1.00–1.02, Wald χ^2 test, $\chi^2 = 6.92$, $df = 1$, $p = 0.009$, and HR: 1.01, 95% CI: 1.00–1.01, Wald $\chi^2 = 8.86$, $df = 1$, $p = 0.003$, respectively). The HRs of the top quartile were similar when the comorbidity index score was replaced with the presence or absence of chronic diseases that were identified as risk factors by univariate analysis in each event (Table 3).

Based on ANCOVA adjusted for recipient gender, age, bADL score, the Charlson comorbidity index, the presence or absence of dementia and behavior problems, caregiver gender, and caregiver age, no differences in the adjusted average ZBI scores were detected between users and nonusers of these services (ANCOVA, adjusted mean ZBI score (standard deviation): day-care service, nonuse, 27.9 (16.4) versus use, 29.3 (16.5), F value = 1.92, $df = 1, 1057$, $p = 0.166$; home-help service: nonuse, 29.0 (16.4) versus use, 27.9 (16.4), F value = 1.06, $df = 1, 1057$, $p = 0.304$) except for the nursing-home respite service, for which users showed higher ZBI scores than nonusers (nonuse, 28.1 [16.4], versus use, 32.1 [16.8], F value = 5.26, $df = 1, 1057$, $p = 0.022$).

In Table 4, using the multivariate Cox proportional hazards model, we examined the association between higher versus lowest quartile of the ZBI score and care recipient all-cause mortality and hospitalization within subgroups of various community-based respite service use status. Overall, within nonusers of these respite care services, the highest quartile of caregiver burden was associated with all-cause mortality and hospitalization. No apparent association was observed within users of these services except for users of the day-care service, who showed a statistically significant association between the highest quartile and the risk of hospitalization (HR: 1.56, 95% CI: 1.03–2.36, Wald χ^2 test, $\chi^2 = 4.50$, $df = 1$, $p = 0.034$).

DISCUSSION

In the present study, we observed that the recipients with caregivers with a baseline ZBI score in the highest quartile were 1.54 and 1.51 times more likely to show increased risk of all-cause mortality and hospitalization during a 3-year follow-up period, respectively, in comparison with those with caregivers in the lowest. These relationships existed independently of various other risk factors for mortality and hospitalization, including gender, age, number of community-based services used, ADL status, and

TABLE 3. Multivariate Cox Proportional Hazards Models and Association Between Baseline Characteristics and Risk of Mortality and Hospitalization During 3-year Follow-up

	All Death						Hospitalization					
	Model 1 ^a			Model 2 ^b			Model 1 ^c			Model 2 ^d		
	Wald χ^2	p	HR (95% CI)	Wald χ^2	p	HR (95% CI)	Wald χ^2	p	HR (95% CI)	Wald χ^2	p	HR (95% CI)
Care recipient variables												
Men (versus women)	22.41	<0.001	1.98 (1.49–2.63)	24.25	<0.001	2.06 (1.54–2.75)	3.39	0.065	1.23 (0.99–1.54)	3.05	0.081	1.22 (0.98–1.52)
Age ^e	66.21	<0.001	1.07 (1.05–1.09)	45.71	<0.001	1.06 (1.04–1.08)	6.08	0.014	1.02 (1.00–1.03)	3.24	0.072	1.01 (1.00–1.03)
Basic ADL score ^e	26.01	<0.001	0.94 (0.92–0.96)	32.04	<0.001	0.93 (0.91–0.96)	7.89	0.005	0.97 (0.96–0.99)	12.95	<0.001	0.97 (0.95–0.99)
No. of service uses ^e	0.84	0.360	0.94 (0.83–1.05)	0.90	0.343	0.93 (0.83–1.05)	2.28	0.131	1.07 (0.97–1.17)	1.75	0.186	1.06 (0.97–1.16)
Charlson comorbidity index ^e	8.84	0.003	1.12 (1.04–1.22)			—	2.13	0.145	1.05 (0.98–1.12)			—
Chronic disease (versus absence)												
Congestive heart failure		—		5.16	0.023	1.54 (1.06–2.23)		—			—	
COPD		—				—		—		3.090	0.079	1.40 (0.96–2.03)
Dementia		—		4.298	<0.001	1.33 (1.02–1.74)		—			—	
Cancer		—		14.64	<0.001	1.99 (1.40–2.82)		—		18.10	<0.001	1.84 (1.39–2.44)
Behavioral problems (versus absence)	0.20	0.657	1.11 (0.72 to 1.70)	0.23	0.629	1.12 (0.72–1.74)		—			—	
Caregiver's variables												
Men (versus women)	0.03	0.863	1.02 (0.74–1.42)	0.01	0.984	0.99 (0.71–1.38)	0.01	0.942	0.99 (0.77–1.27)	0.13	0.714	0.95 (0.74–1.22)
Age ^e	0.36	0.551	1.00 (0.99–1.02)	0.47	0.492	1.00 (0.99–1.02)	0.07	0.788	1.00 (0.99–1.01)	0.04	0.847	1.00 (0.99–1.01)
Subjective caregiver health status (versus good to excellent)												
Fair		—				—	2.95	0.086	1.21 (0.97–1.50)	2.52	0.113	1.19 (0.96–1.48)
Poor		—				—	2.99	0.084	1.32 (0.96–1.82)	2.69	0.101	1.31 (0.95–1.80)
ZBI score (versus 1st quartile)												
2nd	0.13	0.717	1.07 (0.75–1.53)	0.23	0.629	1.09 (0.76–1.57)	2.06	0.151	1.22 (0.93–1.61)	2.51	0.113	1.25 (0.95–1.64)
3rd	0.01	0.942	1.01 (0.71–1.46)	0.06	0.809	1.05 (0.73–1.51)	2.93	0.087	1.27 (0.97–1.68)	3.95	0.047	1.32 (1.00–1.75)
4th	5.80	0.016	1.54 (1.09–2.17)	4.44	0.035	1.45 (1.03–2.05)	8.62	0.003	1.51 (1.15–1.98)	8.29	0.004	1.50 (1.14–1.97)

Notes: Degree of freedom is equal to 1. COPD: chronic obstructive pulmonary disease.

^aModel 1 included gender, age, bADL score, number of community-based services used, regular medical checkups, Charlson comorbidity index, behavioral problems, caregiver's age and gender, the Zarit categories that are associated with mortality in univariate analysis.

^bModel 2 for analysis of all-death, which included variables used in Model 1 plus presence or absence of heart failure, dementia, and cancer, which are associated with all-death in univariate analysis, instead of Charlson comorbidity index.

^cModel 1 included gender, age, bADL score, number of community-based services used, regular medical checkups, Charlson comorbidity index, caregiver's age and gender, subjective caregiver health status, and the Zarit categories that are associated with mortality in univariate analysis.

^dModel 2 for analysis of hospitalization, which included variables used in Model 1 plus presence or absence of cancer and COPD, which are associated with all-death in univariate analysis, instead of Charlson comorbidity index.

^eContinuous variables.

TABLE 4. Subgroup Cox Hazard Analysis According to Quartiles of the ZBI Score

Use or Nonuse	No. of Case Total	Quartile Group of ZBI Score (1st: Reference)								
		2nd			3rd			4th		
		Wald χ^2	p	HR (95% CI)	Wald χ^2	p	HR (95% CI)	Wald χ^2	p	HR (95% CI)
All death^a										
Day-care service										
Nonuse	165/573	1.03	0.310	1.26 (0.81-1.96)	0.07	0.791	0.95 (0.58-1.54)	5.06	0.024	1.66 (1.07-2.59)
Use	103/494	0.31	0.579	0.84 (0.45-1.58)	0.15	0.695	1.12 (0.64-1.97)	0.75	0.387	1.29 (0.72-2.31)
Home-help service										
Nonuse	155/618	0.76	0.382	1.25 (0.76-2.05)	0.16	0.688	1.11 (0.67-1.85)	12.7	<0.001	2.32 (1.46-3.69)
Use	113/449	0.10	0.757	0.92 (0.54-1.57)	0.23	0.633	0.88 (0.52-1.49)	0.63	0.426	0.80 (0.46-1.39)
Nursing-home respite stay service										
Nonuse	237/959	0.34	0.558	1.12 (0.76-1.65)	0.09	0.768	1.06 (0.72-1.56)	9.75	0.002	1.79 (1.24-2.58)
Use	31/108	0.42	0.517	0.70 (0.24-1.79)	0.77	0.381	0.63 (0.23-1.76)	1.86	0.173	0.46 (0.15-1.41)
Hospitalization^b										
Day-care service										
Nonuse	250/573	1.72	0.189	1.27 (0.89-1.82)	3.46	0.063	1.43 (0.98-2.10)	5.07	0.024	1.54 (1.06-2.24)
Use	205/494	0.86	0.353	1.23 (0.80-1.88)	0.93	0.334	1.22 (0.81-1.84)	4.50	0.034	1.56 (1.03-2.36)
Home-help service										
Nonuse	260/618	3.56	0.059	1.45 (0.99-2.14)	4.88	0.027	1.54 (1.05-2.25)	18.00	<0.001	2.25 (1.55-3.27)
Use	195/449	0.01	0.945	1.01 (0.68-1.51)	0.01	0.930	1.02 (0.67-1.54)	0.40	0.528	0.87 (0.57-1.33)
Nursing-home respite stay service										
Nonuse	400/959	2.30	0.130	1.25 (0.94-1.67)	2.09	0.148	1.24 (0.93-1.67)	9.32	0.002	1.57 (1.18-2.10)
Use	55/108	0.21	0.646	1.26 (0.47-3.34)	0.65	0.419	1.43 (0.60-3.41)	0.02	0.891	1.06 (0.44-2.56)

Notes: Multivariate Cox proportional hazard models. Degree of freedom for all variables is equal to 1.

^aModel included gender, age, basic activities of daily living (bADL) score, number of community-based services used, Charlson comorbidity index, behavioral problems, caregiver's age and gender, and the Zarit categories.

^bModel included gender, age, bADL score, number of community-based services used, Charlson comorbidity index, caregiver's age and gender, subjective caregiver health status, and the Zarit categories.

comorbidity. To our knowledge, this is the first report addressing the relationships between caregiver burden and mortality or hospitalization for dependent older care recipients living in the community.

In addition, subgroup analysis revealed that the association between a high caregiver burden and adverse health outcomes of care recipients was mainly observed in nonusers of community-based respite services, including day-care, home help, or nursing-home respite stay services. No association was found between high caregiver burden and adverse health outcomes of care recipients among users of these services except for users of day-care services with a hospitalization risk.

There are a number of possible mechanisms for these associations. Previous research has found caregiver burden to be a factor in determining the quality of care given and, specifically, a negative indicator of the willingness of caregivers to continue in the caregiving role.^{2,20} The caregiver burden may lead to a lower quality of care, leading over time to abuse or neglect and, ultimately, to negative health outcomes for the care recipient.^{21,22} In fact, it has been demon-

strated that a lack of needed care for disabled older individuals or a decreased quality of family caregiving results in poor outcomes for care recipients.²³⁻²⁵ Thus, caregiver burden and emotional distress can be a detriment to the health and well-being of care recipients through inadequate provision of care.

In this study, we demonstrated that the GDS-15 score of the caregiver as well as the care recipient increased as the level of the ZBI quartile increased. These results may indicate that caregiver burden is associated with depressive symptoms in the care recipients and that there may be interrelationships between the emotional distress of the caregiver and depressive symptoms in care recipients. A number of reports have suggested that depressive symptoms have been shown to be an important risk factor for mortality and to increase the risk of physical disability through poorer adherence to healthy life styles.²⁶⁻²⁸ However, the GDS-15 scores of care recipients were not associated with all-cause mortality and hospitalization in this cohort. There are several possible reasons for this difference between our cohort and others. The subjects of the current

Impact of Caregiver Burden on Adverse Health Outcomes

investigation had multiple medical problems and functional limitations and were probably at higher mortality and hospitalization risk than those in these prior studies.²⁶⁻²⁸

It has been demonstrated that the death or serious illness of a spouse increases the risk of death or affects the health of a partner.^{29,30} A possible mechanism of this association is that spousal illness or death may deprive a partner of social, emotional, or other practical support.^{29,30} In the present study, subjective poor health status of the caregiver was associated with risk of hospitalization for the care recipient but not with mortality in this cohort. The highest level of caregiver burden was associated with hospitalization for dependent elderly care recipients, even after adjustment for the subjective health status of the caregivers, making it unlikely that our findings were confounded by the poor health status of the caregiver, at least at baseline.

Community-based long-term care services are believed to relieve stress on family caregivers and enable older people with disabilities to remain at home for a longer period of time.³¹ However, the usefulness of these services for reducing caregiver burden is still controversial. Some studies have demonstrated a positive effect of respite service on caregiver burden, but others have shown no effect or a negative relationship between respite service use and caregiver burden.³²⁻³⁶ In our cohort, no difference in the caregiver ZBI score was observed between users and nonusers of day-care services and home-help services, and a rather higher average ZBI score in users of nursing-home respite stay services compared with nonusers was observed, although cross-sectional determination of respite care service use and the ZBI measurement do not allow evaluation of the causal and consequent relationships between service use and caregiver burden. However, the present study found that the adverse outcome for care recipients with caregivers with the highest burden is more evident in nonusers of respite services than in service users. It is possible that the use of these long-term care services decreased the adverse health outcomes of care recipients through other factors beyond caregiver burden.

Our study has several strengths, including the relatively large number of paired participants and outcome events, a prospective design, and a well-defined population. Our analyses took into account potential confounders including age, gender, BADL,

comorbidity, and subjective health status of the caregiver. We also adjusted for the number of community-based services used and conducted an analysis stratified by the use or nonuse of community-based respite care services.

This study has potential limitations. Subjects with acute illness at enrollment were excluded from participating in the NLS-FE, and the present study used statistical control of potential confounding variables to rule out third factors that might produce an association between caregiver burden and care recipient adverse health outcomes during the follow-up period. However, because of the observational design of the present study, differences in unmeasured factors, including social circumstances, caregiver's competence in caring for a disabled recipient, the health condition of the caregivers during the study period not at baseline, and the length of caregiving may in part account for the findings. We used only the presence or absence of selected major comorbidities and behavioral problems as covariates in the analyses. The lack of assessment of the severity of the recipient's medical illness or significant behavioral problems, both of which would require more time for care providing, may have influenced the results in the present study. The present findings may not be generalizable to other populations, given that health practices, a variety of social and economic factors, ethnic attitudes about caring for very old people, and the cost of healthcare may have influenced these results. It should be noted that multiple analyses in the present study increased the chances of making high likelihood of Type I errors.

We demonstrated high caregiver burden as an important risk of the adverse health outcomes of care recipients, including all-cause mortality and hospitalization. This risk of care recipient adverse health outcomes associated with a heavy caregiver burden was attenuated in community-based respite care service users. In the community setting, interventions directed toward the reduction of caregiver burden and improving caregiver well-being may not only delay long-term care placement and prevent the deterioration of caregiver health but also reduce care recipient adverse health outcomes. A community-based service may thus yield benefits for care recipients and may favorably affect the complex and interrelated variables of the caregiver and the recipient. These efforts may facilitate the continuation of home care of the disabled elderly.

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References

- George LK, Gwyther LP: Caregiver well-being: a multidimensional examination of family caregivers of demented adults. *Gerontologist* 1986; 26:253-259
- Zarit SH, Todd PA, Zarit JM: Subjective burden of husbands and wives as caregivers. *Gerontologist* 1986; 26:260-266
- Schulz R, Visintainer P, Williamson GM: Psychiatric and physical morbidity effects of caregiving. *J Gerontol* 1990; 45:181-191
- Torti FM Jr, Gwyther LP, Reed SD, et al: A multinational review of recent trends and reports in dementia caregiver burden. *Alzheimer Dis Assoc Disord* 2004; 18:99-109
- Covinsky KE, Goldman L, Cook EF, et al: The impact of serious illness on patients' families. SUPPORT Investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment. *JAMA* 1994; 272:1839-1844
- Scholte op Reimer WJ, de Haan RJ, et al: The burden of caregiving in partners of long-term stroke survivors. *Stroke* 1998; 29:1605-1611
- Vitaliano PP, Katon W, Unützer J: Making the case for caregiver research in geriatric psychiatry. *Am J Geriatr Psychiatry* 2005; 13:834-843
- Gallicchio L, Siddiqi N, Langenberg P, et al: Gender differences in burden and depression among informal caregivers of demented elders in the community. *Int J Geriatr Psychiatry* 2002; 17:154-163
- Kiecolt-Glaser JK, Marucha PT, Malarkey WB, et al: Slowing of wound healing by psychological stress. *Lancet* 1995; 346:1194-1196
- Kiecolt-Glaser JK, Glaser R, Gravenstein S, et al: Chronic stress alters the immune response to influenza virus vaccine in older adults. *Proc Natl Acad Sci USA* 1996; 93:3043-3047
- von Känel R, Mausbach BT, Patterson TL, et al: Increased Framingham Coronary Heart Disease Risk Score in dementia caregivers relative to non-caregiving controls. *Gerontology* 2008; 54:131-137
- Schulz R, Beach SR: Caregiving as a risk factor for mortality: the Caregiver Health Effects Study. *JAMA* 1999; 282:2215-2219
- Yaffe K, Fox P, Newcomer R, et al: Patient and caregiver characteristics and nursing home placement in patients with dementia. *JAMA* 2002; 287:2090-2097
- Gaugler JE, Kane RL, Kane RA, et al: Caregiving and institutionalization of cognitively impaired older people: utilizing dynamic predictors of change. *Gerontologist* 2003; 43:219-229
- Tsutsui T, Muramatsu N: Care-needs certification in the long-term care insurance system of Japan. *J Am Geriatr Soc* 2005; 53:522-527
- Kuzuya M, Masuda Y, Hirakawa Y, et al: Day care service use is associated with lower mortality in community-dwelling frail older people. *J Am Geriatr Soc* 2006; 54:1364-1371
- Kuzuya M, Masuda Y, Hirakawa Y, et al: Underuse of medications for chronic diseases in the oldest of community-dwelling older frail Japanese. *J Am Geriatr Soc* 2006; 54:598-605
- Yesavage JA: Geriatric Depression Scale. *Psychopharmacol Bull* 1988; 24:709-711
- Charlson ME, Pompei P, Ales KL, et al: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40:373-383
- Pearlin LI, Mullan JT, Semple SJ, et al: Caregiving and the stress process: an overview of concepts and their measures. *Gerontologist* 1990; 30:583-594
- Lachs MS, Pillemer K: Abuse and neglect of elderly persons. *N Engl J Med* 1995; 332:437-443
- Beach SR, Schulz R, Williamson GM, et al: Risk factors for potentially harmful informal caregiver behavior. *J Am Geriatr Soc* 2005; 53:255-261
- Blazer DG, Sachs-Ericsson N, Hybels CF: Perception of unmet basic needs as a predictor of mortality among community-dwelling older adults. *Am J Public Health* 2005; 95:299-304
- Sands LP, Wang Y, McCabe GP, et al: Rates of acute care admissions for frail older people living with met versus unmet activity of daily living needs. *J Am Geriatr Soc* 2006; 54:339-344
- Lachs MS, Williams CS, O'Brien S, et al: The mortality of elder mistreatment. *JAMA* 1998; 280:428-432
- Schulz R, Drayer RA, Rollman BL: Depression as a risk factor for non-suicide mortality in the elderly. *Biol Psychiatry* 2002; 52:205-225
- Cronin-Stubbs D, de Leon CF, Beckett LA, et al: Six-year effect of depressive symptoms on the course of physical disability in community-living older adults. *Arch Intern Med* 2000; 160:3074-3080
- Williams LS, Ghose SS, Swindle RW: Depression and other mental health diagnoses increase mortality risk after ischemic stroke. *Am J Psychiatry* 2004; 161:1090-1095
- Martikainen P, Valkonen T: Mortality after the death of a spouse: rates and causes of death in a large Finnish cohort. *Am J Public Health* 1996; 86:1087-1093
- Christakis NA, Allison PD: Mortality after the hospitalization of a spouse. *N Engl J Med* 2006; 354:719-730
- Zarit SH, Gaugler JE, Jarrott SE: Useful services for families: research findings and directions. *Int J Geriatr Psychiatry* 1999; 14:165-177
- Sörensen S, Pinquart M, Duberstein P: How effective are interventions with caregivers? An updated meta-analysis. *Gerontologist* 2002; 42:356-372
- Shaw C, McNamara R, Abrams K, et al: Systematic review of respite care in the frail elderly. *Health Technol Assess* 2009; 13:1-224
- Cox C: Findings from a statewide program of respite care: a comparison of service users, stoppers, and nonusers. *Gerontologist* 1997; 37:511-517
- Baumgarten M, Lebel P, Laprise H, et al: Adult day care for the frail elderly: outcomes, satisfaction, and cost. *J Aging Health* 2002; 14:237-259
- Grant I, McKibbin CL, Taylor MJ, et al: In-home respite intervention reduces plasma epinephrine in stressed Alzheimer caregivers. *Am J Geriatr Psychiatry* 2003; 11:62-72

表1 65歳以上の高齢者の通院者率上位5傷病(複数回答)

性別	第1位	第2位	第3位	第4位	第5位
男性	高血圧症 24.0%	眼の病気 10.7%	糖尿病 10.7%	腰痛症 9.5%	前立腺肥大症 8.2%
女性	高血圧症 25.3%	眼の病気 14.6%	腰痛症 13.2%	脂質異常症 9.4%	骨粗鬆症 8.1%

(文献¹⁾より)

康状況は加齢とともに悪くなり、85歳以上の男性の38.4%、女性の41.7%が自覚症状、通院、健康状態に起因する生活への影響のすべてがあると回答している(図1)。

高年齢者と超高齢者の死因

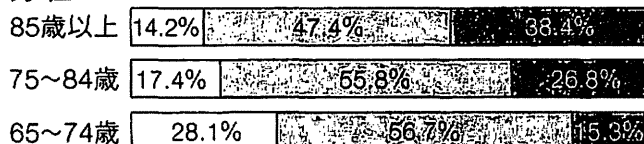
人口動態統計による平成21年度の年齢階級別死因は、55～84歳までが悪性新生物、心疾患、脳血管疾患の順であり²⁾、これよりも若い世代では自殺、不慮の事故が上位にあるのが特徴である。中年者でも高齢者でも基本的には死因に大きな違いはない。しかし、90歳以上の超高齢者では悪性新生物による死亡の割合が低下し、心疾患による死亡の割合が増加する。肺炎による死亡も超高齢者では増加している。また死因としての「老衰」が第5位までに登場しているのも超高齢者の特徴である(表2)。

高齢者疾患の臨床的特徴

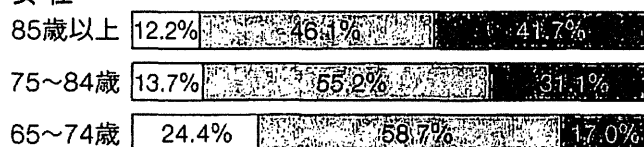
高齢者疾患には認知症や骨粗鬆症、加齢性難聴、白内障など高齢者特有の疾患もあるが、腰痛症や関節症などの整形外科的な疾患、高血圧症や糖尿病、脂質異常症、癌、動脈硬化性疾患など一般成人にも見られる疾患も多い。

しかも高齢者では、これらの疾患を同時に持っており、また症状が出にくく診断が難しかったり、治療への反応が悪く慢性化しやすかったりする。特に疾患がなくても、筋肉量

男性



女性



- 自覚症状・通院・生活への影響ともなし
- 自覚症状・通院・生活への影響いずれかあり
- 自覚症状・通院・生活への影響ともあり

図1 性別・年齢別に見た高齢者の健康状態の構成割合(入院中、回答不詳の者を除く)

(文献¹⁾より)

が減少するサルコペニアと呼ばれる状態や、日常生活活動に支障の生じている脆弱高齢者、要介護高齢者も多い³⁾。

高齢者疾患を診る場合には、栄養問題を考慮することがきわめて重要である⁴⁾。老化に伴う生理学的変化として、消化吸收機能が低下し、エネルギー消費量が減って、食欲が低下する。感覚機能、特に食欲に密接に関わる味覚、臭覚、視覚などの機能の低下がいつそう食欲不振を増強させる。高齢者に多い心疾患に使われるジギタリス薬などには食欲を減退させる副作用が往々にして見られる。

また亜鉛欠乏は味覚障害を起し、食欲低下の原因となる。亜鉛欠乏症は若年者に多いが、最近では高齢者にも多く見られる。亜鉛

大きくなっていることにも注意しなければならない。高齢者では肥満よりもやせの重要性を認識すべきである。高度の肥満に伴う高血圧症や糖尿病などが無い限り、高齢者に食事制限を勧めるべきではない。



高齢者における検査値の見方

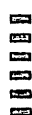
高齢者における検査値の判定には注意が必要である⁵⁾。検査値に異常を来す要因としては、検査手技などの技術的要因、体質性黄疸など遺伝的要因による個人差、さらに同じ個人でも、検査の時刻や季節、体位、運動や食事の影響などによる個人内変動がある。技術的要因としては、高齢者では静脈が脆く、しばしば採血が困難であり、採血時の溶血が問題となる場合が多い。溶血により血清カリウムやLDHが高値になることがある。

同一個人でも測定時の条件で異常値になることがある。こうした個人内変動は検体採取時の時刻や体位、生活習慣による影響、薬物の影響などによることが多い。時間的要因には日内変動、日差、季節差が挙げられる。日内変動を示す検査値としては血糖値、血清鉄、中性脂肪、脂肪酸、ビリルビン、遊離脂肪酸、副腎皮質ホルモンなどがある。これらの検査では採血の時刻に留意しなければならない。

筋組織からの逸脱酵素であるCK、AST、LDHの上昇が運動後に見られる。その上昇は運動翌朝に最大となる。これらの検査値は登山などの負荷の大きい運動でなくても、高齢者ではレクリエーション程度の軽度の運動で上昇が見られることもある。逆に、CKは寝たきり状態では低値になる。

安静に横になっている場合と、起立し活動している場合では循環血漿量が異なる。立位で活動をしている場合には血液の濃縮が起こ

り、血清蛋白質の濃度が上昇する。血清総蛋白量や血清アルブミンのみならず血清蛋白に結合して血清中に存在するカルシウムやビリルビン、コレステロールなどの測定値も立位活動時に上昇し、安静仰臥時では低下する。この低下は立位を30分ほど取ることで回復するが、同じ患者でも外来と入院で、また寝たきりの患者と自由に歩き回っている患者で、検査値の判定について考慮する必要がある。



おわりに

高齢者は多彩な自覚症状、多数の疾患を同時に有していることが多い。個々の疾患や症状について、それぞれの分野の専門医が対応しては、検査や治療が増えて適切な対応ができない。老年内科の標榜を目指すためには、臓器別、分野別の縦割り医療ではなく、内科全般にわたる幅広い知識を持ち、高齢者の特性を理解することが必要である。さらに介護保険制度や高齢者医療、在宅医療など、家庭や社会的な環境についての理解と知識が重要であろう。高齢者、特に後期高齢者、超高齢者が今後急速に増えていく日本の社会で、老年内科医の果たすべき役割は大きい。老年内科医の今後の活躍に期待したい。

*文献

- 1) 厚生労働省大臣官房統計情報部：平成19年国民生活基礎調査の概況，2008。
- 2) 厚生労働省大臣官房統計情報部：平成21年人口動態統計，2010。
- 3) 下方浩史，他：Geriatr Med 49：303，2011。
- 4) 下方浩史，他：成人病と生活習慣病 40：1026，2010。
- 5) 下方浩史：老年医学テキスト 改訂第3版，日本老年医学会編，メジカルビュー社，東京，2008，p156。

Dietary patterns of antioxidant vitamin and carotenoid intake associated with bone mineral density: findings from post-menopausal Japanese female subjects

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Abstract

Summary Recent studies show that antioxidants may reduce the risk of osteoporosis. This study showed the associations of bone mineral density with dietary patterns of antioxidant vitamins and carotenoids. The findings suggest the combination of vitamin C and β -cryptoxanthin intakes might provide benefit to bone health in post-menopausal Japanese female subjects.

Introduction Recent epidemiological studies show antioxidants may reduce the risk of osteoporosis, but little is known about the dietary patterns of antioxidant vitamin and carotenoid intakes and their relation with bone mineral density (BMD).

Methods A total of 293 post-menopausal female subjects who had received health examinations in the town of Mikkabi, Shizuoka Prefecture, Japan, participated in the study. Radial

BMD was measured using dual-energy X-ray absorptiometry. Dietary intakes of antioxidant vitamins and carotenoids were assessed by using a validated food-frequency questionnaire. Dietary patterns were identified on a selected set of antioxidants through principal component factor analysis.

Results Three dietary patterns were identified. The “retinol” pattern, characterized by notably high intakes of preformed retinol, zeaxanthin, and vitamin E, was positively associated with the risk for low BMD. In contrast, the “ β -cryptoxanthin” pattern, characterized by notably high intakes of β -cryptoxanthin and vitamin C, was negatively associated with low BMD. The odds ratios for low BMD in the highest tertiles of dietary intakes of preformed retinol, vitamin C, and β -cryptoxanthin against the lowest tertiles were 3.22 [95% confidence interval (CI), 1.38–7.51], 0.25 (CI, 0.10–0.66), and 0.40 (CI, 0.17–0.92), respectively, after adjustments for confounders. However, negative associations of vitamin C and β -cryptoxanthin with low BMD were not significant after further adjustment for intake of β -cryptoxanthin or vitamin C, respectively. Higher intakes of both vitamin C and β -cryptoxanthin were significantly associated with low BMD ($P < 0.05$).

Conclusions The combination of vitamin C and β -cryptoxanthin may be associated with radial BMD in post-menopausal Japanese female subjects.

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Keywords Bone mineral density · Carotenoid ·
Dietary pattern · Preformed retinol · Vitamin

Introduction

Osteoporosis and related fractures are a major public health problem [1]. Osteoporosis is a chronic disease characterized by low bone mineral density and microarchitectural