Table 1 Comparison of base-line characteristics between participants and non-participants in the 1993 exercise class

| | Participants | Non-participants | *P* |
|---|---|---|---|
| No. of subjects | 119 | 878 | |
| Age | 72.5 years | 73.4 years | ns |
| Male | 42.9% | 27.7% | 0.0012 |
| Fall incidence | | | |
| "I scarcely fall." *n* (%) | 105 (88.2) | 760 (86.6) | ns |
| "I sometimes fall." | 14 (11.8) | 106 (12.1) | |
| "I often fall and it is problematic in daily life." | 0 | 1 (0.1) | |
| "I have experienced a fall-related bone fracture or serious injury." | 0 | 11 (1.3) | |
| ADL | | | |
| Persons independent in ADL (21 points) *n* (%) | 117 (98.3) | 832 (94.8) | ns |
| Persons dependent in ADL (≤20 points) | 2 (3.5) | 46 (6.3) | |
| Depressive state | | | |
| Mean GDS (points) | 4.6 ± 3.3 | 5.1 ± 3.6 | ns |
| GDS of ≥10, *n* (%) | 10 (8.4) | 124 (14.2) | ns |
| GDS of <10 | 109 (91.6) | 750 (85.8) | |
| History of stroke | | | |
| Yes | 1 (0.9) | 41 (4.9) | 0.05 |
| No | 114 (99.1) | 794 (95.1) | |
| Taking drugs (including antihypertensive drugs) | | | |
| Yes | 48 (40.3) | 350 (40.6) | ns |
| No | 71 (59.7) | 512 (59.4) | |
| Taking antihypertensive drugs | | | |
| Yes | 33 (27.7) | 243 (28.2) | ns |
| No | 86 (72.3) | 619 (71.8) | |
| Urinary incontinence | | | |
| Yes | 0 (0) | 15 (1.7) | ns |
| No | 119 (100) | 844 (98.3) | |
| Cognitive impairment | | | |
| ≥Grade IIa in classification of dementia-related dependency | 6 (5.3) | 83 (10.6) | ns |
| ≤Grade I | 107 (94.7) | 703 (89.4) | |

ADL, activities of daily living; GDS, 15-item geriatric depression scale.

analysis in two models according to the mode of participation in exercise. We analyzed the odds ratio of participants versus non-participants on the subjects whose fall incidence increased as the dependent variable. In the 8-year period 1993–2001, 119 subjects attended exercise class (model 1). In those 119 subjects, 19 attended exercise class only during the 3-year period 1993–1995, 29 subjects attended exercise class only during the 5-year period 1996–2001, and 71 subjects attended exercise class in both the 1993–1995 and 1996–2001 periods (model 2). As shown in model 2, worsening of fall incidence was strongly suppressed in the participants in both the 1993–1995 and 1996–2001 periods (odds ratio, 0.20; $P = 0.008$), however, each group who participated only 1993–1995 or only 1996–2001 failed to reach a significant odds ratio.

Table 4 shows odds ratios in monovariate analysis for worsening of fall incidence during the 8-year period of other confounding variables. Age, female sex, dependence in ADL, depressive state (GDS, ≥10) and taking drugs were found to be associated with worsening of fall incidence, but history of stroke, taking antihypertensive drugs, urinary incontinence and cognitive impairment were not associated with falls.

Table 5 shows effects of participation in the exercise class on preventing of fall incidence during the 8-year period in all subjects and non-fallers in 1993 in multivariate analysis. As shown in Table 5, only participation in both the 1993–1995 and 1996–2001 periods was a significant independent variable even after the adjustment for age, sex, ADL, depression scale and presence/absence of oral drugs (odds ratio, 0.20; $P = 0.007$). Even

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Table 2 Comparison of falling state, ADL and depressive state between participants and non-participants in 2001

| | Participants | | Non-participants | |
|---|---|---|---|---|
| | 1993 | 2001 | 1993 | 2001 |
| Fall incidence | | | | |
| "I scarcely fall." *n* (%) | 105 (88.2) | 104 (87.4) | 760 (86.6) | 669 (76.2)* |
| "I sometimes fall." | 14 (11.8) | 12 (10.1) | 106 (12.1) | 158 (18.0) |
| "I often fall and it is problematic in daily life." | 0 | 1 (0.8) | 1 (0.1) | 16 (1.8) |
| "I have experienced a fall-related bone fracture or serious injury." | 0 | 2 (1.7) | 11 (1.3) | 35 (4.0) |
| ADL | | | | |
| Persons independent in ADL (21 points) *n* (%) | 117 (98.3) | 98 (82.4) | 831 (94.8) | 603 (70.0)** |
| Persons dependent in ADL (≤20 points) | 2 (3.5) | 21 (17.6) | 46 (6.3) | 259 (30.0) |
| Depressive state | | | | |
| Mean GDS (points) | 4.6 ± 3.3 | 5.6 ± 3.8 | 5.1 ± 3.6 | 6.2 ± 3.6 |
| GDS of ≥10, *n* (%) | 10 (8.4) | 19 (17.1) | 124 (14.2) | 163 (21.1) |
| GDS of <10 | 109 (91.6) | 92 (82.9) | 750 (85.8) | 609 (78.9) |

*$P < 0.05$, **$P < 0.01$, participants vs non-participants in 2001 ($\chi^2$ test).

Table 3 Factors associated with worsening of fall incidence during the 8-year period (monovariate analysis): two models according to the mode of participation in exercise

| | Odds ratio | *P* |
|---|---|---|
| Model 1 | | |
| In the 8-year period 1993–2000, | | |
| Participated in exercise class ($n = 119$) | 0.42 | 0.01 |
| No participation in exercise class at all ($n = 878$) | 1.0 | |
| Model 2 | | |
| Participated in exercise class only in the 3-year period 1993–1995 ($n = 19$) | 1.24 | ns |
| Participated in both the 3-year period 1993–1995 and the period 1996–2001 ($n = 71$) | 0.20 | 0.008 |
| Participated only in the 5-year period 1996–2001 ($n = 29$) | 0.54 | ns |
| No participation in exercise class at all ($n = 878$) | 1.0 | |

when the same analysis was performed only in the subjects who were non-fallers in 1993 ($n = 865$ subjects), the result was almost the same, as shown in the right part of Table 5.

From 1993–2000, participation for exercise class was effective for prevention of successive death (odds ratio, 0.43; $P = 0.03$) after the adjustment for confounding variables.

## Discussion

We revealed the effect of participation in the exercise classes on the prevention of falls in community-dwelling elderly people. Worsening of fall incidence was suppressed to a significantly more favorable extent in the 71 subjects who participated in both 1993–1995 and 1996–2001 periods after the adjustment of the confounding factors such as age, sex, ADL, depression scale and presence/absence of oral drugs (odds ratio, 0.20; $P = 0.007$) compared with non-participants, 19 participants during only 1993–1995, or 29 participants during only 1996–2001. Although subjects who participated in exercise classes during only the earlier or later period did not show a significant effect of exercise on preventing falls, the subjects who participated only during 1996–2001 were supposed to fail to reach a significance because of the smallness of subjects number.

In the previous reports, many kinds of exercises such as tai chi, balance training, muscle strengthening training and agility training have been reported to be effective for the prevention of falling.[8–18] In this study, all kinds of exercise were involved, including underwater exercise. Although there have been many reports on exercise programs to prevent falls in older people, few have studied the effect of exercise sessions on the whole community population for a long time. We compared the effect of preventing falls between the participating and non-participating subjects in the exercise class in



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Table 4 Other factors associated with worsening of fall incidence during the 8-year period (monovariate analysis)

| | | |
|---|---|---|
| Age | 1.1 | <0.0001 |
| Sex | | |
| Female | 1.8 | 0.002 |
| Male | 1.0 | |
| ADL | | |
| Independence | 0.33 | 0.0006 |
| Dependence | 1.0 | |
| Depression scale | | |
| GDS of ≥10, *n* (%) | 1.83 | 0.006 |
| GDS of <10 | 1.0 | |
| History of stroke | | |
| Yes | 1.44 | ns |
| No | 1.0 | |
| Taking drugs (including antihypertensive drugs) | | |
| Yes | 1.78 | 0.001 |
| No | 1.0 | |
| Taking antihypertensive drugs | | |
| Yes | 1.29 | ns |
| No | 1.0 | |
| Urinary incontinence | | |
| Yes | 0.78 | ns |
| No | 1.0 | |
| Cognitive impairment | | |
| ≥Grade IIa in classification of dementia-related dependence | 1.4 | ns |
| ≤Grade I | 1.0 | |

the entire community-dwelling elderly throughout the town during the long period of 8 years. This study is not a controlled study. But the controlled study had been already carried out in this exercise class in the participants during the 6 months in 1993, revealing that exercise was effective in neurobehavioral function especially in the TUG test.[2] In another study of ours, the TUG test was the independent predictor of falls both in our cross-sectional and longitudinal studies.[4] After finishing the controlled study in the first year of 1993, the exercise class was opened for any community-dwelling people and many subjects participated in the class each year freely. Although some study limitations, such as non-controlled study and that some subjects participated irregularly, may exist, persistent open sessions for exercise were proved to be effective in the whole community for a long time in this study. That is why this community-based study is very valuable notwithstanding it being a non-controlled study.

## Conclusion

In conclusion, unlike a short program, long-continuing exercise is effective in preventing falls in elderly people for a long time after the adjustment of age, ADL, depression and other confounding variables. Community-dwelling elderly people who have risks of falling are recommended to join supervised group exercise sessions to maintain or improve geriatric comprehensive functions.

Table 5 Effect of participation in the exercise class (two models) on worsening of fall incidence during the 8-year period in all subjects and non-fallers in 1993 (multiple logistic regression)

| | All subjects including fallers and non-fallers in 1993 (997 subjects) Odds ratio | *P* | Non-fallers in (865 subjects) Odds ratio | *P* |
|---|---|---|---|---|
| Model 1 | | | | |
| In the 8-year period 1993–2001 | 0.44 | 0.01 | 0.44 | 0.02 |
| Participated in exercise class | 1.0 | | 1.0 | |
| No participation in exercise class at all | | | | |
| Model 2 | | | | |
| Participated in exercise class only in the 3-year period 1993–1995 | 1.46 | ns | 1.95 | ns |
| Participated in both the 3-year period 1993–1995 and the period 1996–2001 | 0.20 | 0.007 | 0.19 | 0.008 |
| Participated only in the 5-year period 1996–2001 | 0.66 | ns | 0.59 | ns |
| No participation in exercise class at all | 1.0 | | 1.0 | |

Corrected with the confounding factors such as sex, age, ADL, depression scale and presence/absence of taking drugs in two models.

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## A CLOSE ASSOCIATION BETWEEN HEARING IMPAIRMENT AND ACTIVITIES OF DAILY LIVING, DEPRESSION, AND QUALITY OF LIFE IN COMMUNITY-DWELLING OLDER PEOPLE IN JAPAN

*To the Editor:* The prevalence of impaired hearing increases greatly with age.[1] In the article entitled, "The relationship between hearing impairment and depression in older veterans,"[2] the authors showed that hearing impairment (HI) is strongly correlated with depression in older people. To confirm these findings, we compared quantitative scores in activities of daily living (ADLs), subjective quality of life (QOL), and depression of elderly subjects with HI and those without in community-dwelling older people living in three towns in Japan.

The study population consisted of 434 community-dwelling older people with HI aged 65 and older (210 men, 224 women; mean age 76.9 ± 6.9) and 2,170 age- and sex-matched older people without HI (adjusted ratio = 1:5, male:female = 1,050:1,120, mean age 76.9 ± 6.7) living in three towns: Tosa, Kahoku, and Urausu, in Kochi and Hokkaido Prefectures, Japan. Hearing function was assessed using a self-reported questionnaire, and the subjects were classified into four classes using a hearing function scale: those able to hear well (include those requiring a hearing aid) = 3, those able to hear loud voices only = 2, those able to hear only when the speaker shouts into his/her ear = 1, and those who can scarcely hear = 0. Subjects with HI were defined as those with a score of 0 to 2 and subjects without HI as those with a score of 3. Seven basic ADL items (walking, ascending and descending stairs, feeding, dressing, using the toilet, bathing, grooming) were assessed, each on a 4-level scale, whereby 3 = completely independent, 2 = needs some help, 1 = needs much help, and 0 = completely dependent. Scores for each item were summed to generate a total basic ADL score ranging from 0 to 21.[3] For higher-level daily activities, assessed using the Tokyo Metropolitan Institute of Gerontology (TMIG) Index of Competence, a 13-item index was used that included three sublevels of competence, each rated on a yes/no basis: (1) instrumental ADL: instrumental self-maintenance (5 items: the ability to use public transport, buy daily

Table 1. Comparison of Activity of Daily Living (ADL), Depression, and Quality-of-Life (QOL) Scores Between Community-Dwelling Elderly Subjects in Japan with and without Hearing Impairment (HI)

| Variable | With HI (n = 434) | Without HI (n = 2,170) | *P*-value* |
|---|---|---|---|
| Age, mean ± SD | 76.9 ± 6.9 | 76.9 ± 6.7 | NS |
| Male, n (%) | 210 (48.3) | 1,050 (48.3) | NS |
| ADL scores, mean ± SD | | | |
| Basic ADLs (range 0–21) | 18.1 ± 5.2 | 19.9 ± 3.0 | <.01 |
| Instrumental ADLs (range 0–5) | 3.5 ± 1.9 | 4.3 ± 1.5 | <.01 |
| Intellectual ADLs (range 0–4) | 2.3 ± 1.4 | 3.1 ± 1.2 | <.01 |
| Social Role (range 0–4) | 2.4 ± 1.5 | 3.1 ± 1.2 | <.01 |
| Tokyo Metropolitan Institute of Gerontology - Index (range 0–13) | 8.3 ± 4.1 | 10.6 ± 3.3 | <.01 |
| Depression | | | |
| Taking antidepressive drugs, n (%) | 14 (6.7) | 40 (3.7) | .045 |
| GDS score (range 0–15), mean ± SD | 7.3 ± 4.0 | 5.4 ± 3.9 | <.01 |
| With depression (GDS score ≥ 10), n (%) | 122 (31.8) | 351 (17.8) | <.01 |
| QOL score (range 0–100), mean ± SD | | | |
| Subjective health | 46.0 ± 22.5 | 59.7 ± 21.8 | <.01 |
| Family relationship | 67.9 ± 25.3 | 77.4 ± 21.0 | <.01 |
| Friend relationship | 65.2 ± 24.1 | 75.9 ± 20.5 | <.01 |
| Financial satisfaction | 47.3 ± 24.6 | 56.9 ± 24.4 | <.01 |
| Subjective life satisfaction | 52.5 ± 25.3 | 62.9 ± 24.4 | <.01 |

*Based on Student *t* test for continuous variables and chi-square test for categorical variables.
SD = standard deviation; NS = not significant; GDS = Geriatric Depression Scale.

necessities, prepare a meal, pay bills, handle banking matters); (2) intellectual activities (4 items: the ability to fill out forms, read newspapers, and read books or magazines and interest in television programs or news articles on health-related matters); and (3) social roles (4 items: the ability to visit friends, give advice to relatives and friends, visit someone in the hospital, and initiate a conversation with younger people).[4] The 15-item Geriatric Depression Scale (GDS-15) was used to screen the subjects for depression. Quantitative subjective QOL was assessed using a 100-mm visual analog scale (the worst QOL being on the left end of the scale and the best on the right) with the following five items: subjective sense of health, relationship with family, relationship with friends, financial satisfaction, and subjective happiness.[5,6]

Table 1 shows ADL scores, mean GDS-15 scores, the prevalence of depression (GDS cut-off = 10), the number of subjects taking antidepressive drugs, and QOL scores of subjects with and without HI. Scores on all ADL items (including basic ADLs, instrumental ADLs, intellectual ADLs, social roles, and the TMIG Index), mean GDS scores, and all quantitative QOL scores were significantly lower in elderly subjects with HI than those without. Moreover, the rate of depression as assessed according to the GDS was higher in those with HI than those without.

These findings in community-dwelling older people in Japan coincide with the findings reported in two other studies.[2,7] It is therefore suggested that the close association between HI and ADLs, depression, and QOL in older people is a universal phenomenon. Moreover, in addition to HI, other sensory functions might also be related to ADLs, depression, and QOL in older people. In conclusion, these findings suggest that more attention should be paid to routine evaluation of sensory impairment during comprehensive geriatric assessment and to trying to improve such impairment where possible.

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# Stroke-Independent Association Between Metabolic Syndrome and Functional Dependence, Depression, and Low Quality of Life in Elderly Community-Dwelling Brazilian People

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OBJECTIVES: Metabolic syndrome (Met.S) is a risk factor for stroke, dementia, and ischemic heart disease (IHD). It is unclear whether Met.S is an independent risk factor for functional dependence, depression, cognitive impairment, and low health-related quality of life (HRQoL) in a population free of clinical stroke.

DESIGN: Cross-sectional.

SETTING: Two communities in southern Brazil.

PARTICIPANTS: Four hundred twenty people aged 60 and older.

MEASUREMENTS: An adapted (body mass index $\geq$30 kg/m$^2$ and blood pressure $\geq$140/90) Adult Treatment Panel III definition was used in diagnosing Met.S. Depression (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Revised*) and Mini-Mental State Examination were evaluated along with activities of daily living (ADLs) and instrumental activities of daily living (IADLs). HRQoL was measured using a visual analogue scale (0–10). All values were adjusted for age, sex, and presence of IHD.

RESULTS: Forty (9.5%) subjects had a stroke and were excluded from the final analysis. Met.S was present in 37.4% of the stroke-free population. Met.S was significantly and independently associated with 2.24 times as much ADL dependence, 2.39 times as much IADL dependence, a 2.12 times higher risk of depression, a 2.27 times higher likelihood of cognitive impairment, and a 1.62 times higher chance of low self-perceived HRQoL (all $P<0.05$). Adjustment for its own components reduced the strength of the above associations but did not eliminate their statistical significance. If Met.S were removed from this population, dependence, depression, cognitive impairment, and low QoL would be reduced 15.0% to 21.4%.

CONCLUSION: Met.S was significantly associated with functional dependence, depression, cognitive impairment, and low HRQoL, and its effects were independent of clinical stroke, IHD, and its own individual components. J Am Geriatr Soc 55:374–382, 2007.

Key words: metabolic syndrome; functional dependence; depression; cognitive impairment; QoL

One of the most widely accepted theories of aging is the combined oxidative stress/protein-glycation theory, whereby accumulation of these effects over time leads to aging, age-associated diseases, neurofunctional dependence, cognitive impairment, frailty, and death.[1]

Metabolic syndrome (Met.S) consists of a cluster of obesity, glucose intolerance, hypertension, low high-density lipoprotein cholesterol (HDL-C), and high triglycerides; most of these have been shown to be risk factors for stroke and ischemic heart disease (IHD).[2] The pathophysiological unified basis of the syndrome seems to involve hyperinsulinemia,[3] which, in turn, is strongly associated with obesity.[4] Met.S itself has also been shown to be a risk factor for IHD,[5] stroke,[5–7] and dementia,[8] including Alzheimer's disease.[9] A recent study has found Met.S to be an independent risk factor for asymptomatic stroke.[10]

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The Met.S phenotype seems to be the consequence of chronic exposure to the effects of obesity,[4] sedentarism,[11] and an unhealthy diet[11] upon a susceptible genotype.[12] Obese individuals with Met.S may be considered the subfraction of obese individuals subjected to more oxidative stress and therefore manifesting to a higher degree the adverse metabolic consequences of obesity.[4] In addition to its usual association with obesity, Met.S seems to accelerate biological aging by promoting protein glycation,[1] insulin resistance, and telomere attrition.[13] In this sense, subjects with Met.S might represent a better population model of overfeeding[14] and accelerated aging (reverse of caloric restriction) than those with isolated obesity. In particular, Met.S might be a more consistent risk factor in older people, in whom obesity itself loses much of its risk.[15]

"Successful" aging might be defined as aging without major chronic, debilitating diseases and keeping functional independence and proper cognitive and affective neurofunctions to a maximum extent before death,[16,17] although in practice, in modern societies, "usual" aging is more often associated with debilitating diseases and progressive loss of autonomy, in which advanced cases the "usual" gives place to the clearly "pathological" cases.[16]

Many aging changes that have been interpreted as age-intrinsic have turned out to be "usual" only in modern societies (i.e., they were shown not to belong to the physiology of aging itself, as evidenced in primitive communities).[18] Met.S may be considered the modern society chronic syndrome epidemic par excellence, for it encompasses most of the main atherogenic risk factors for cardiovascular diseases.[19]

Functional dependence, cognitive impairment, and depression are central reasons that many people do not experience successful aging.[17] Many associations have been reported between the metabolic factors of Met.S (hyperinsulinism, obesity, glucose intolerance, low HDL-C, and hypertension) and features of pathological aging (functional dependence, cognitive impairment, and depression).[20–26]

Clinically manifested stroke is the most common condition responsible for functional decline in older people.[27] After stroke, IHD is one of the most important causes or correlates of functional dependence, cognitive impairment, and (vascular) depression in older people.[27] Met.S, in turn, is strongly associated with and predicts the occurrence of stroke[5–7] and IHD.[5]

Given these considerations, it would be expected that Met.S would be associated with functional dependence, cognitive impairment, depression, and low health-related quality of life (HRQoL), even in a stroke-free population, yet no comprehensive study could be found to document these relationships. It is also unclear whether Met.S is, independently of its individual components, associated with the above outcomes in stroke-free subjects and when controlling for IHD.

In this study, it was hypothesized that Met.S would be an independent determinant of functional decline, depression, cognitive impairment, and lower self-perceived health in stroke-free community-dwelling Brazilian older adults.

## METHODS

### Population and Setting

This study invited 450 older adults (≥60) living in two towns (~30,000 inhabitants each) in the southernmost Brazilian state, Rio Grande do Sul. This randomized sample was selected from a list provided by the Department of Social Assistance of each town that contained virtually all people aged 60 and older in the town (n = 4,547 for both towns). Whenever an older person was identified, his or her spouse was also identified and, if older than 60, invited to participate in the research by the local health agent. Of the final sample of 422 (response rate = 93.8%), 238 (56.4%) were married, and 111 couples participated in the research (52.6%).

Brazil is a heterogeneous society, made up primarily of whites (53.4%) and Mestizos (40.4%) inhabitants.[28] Two towns, Estancia Velha and Charqueadas, were selected to better ethnically represent southern Brazilian older people. Estancia Velha has a predominantly white population, whereas Charqueadas' inhabitants are mainly Mestizo.[28] A preliminary analysis did not evidence any major differences in terms of prevalence of Met.S, functional dependence, depression, or average HRQoL between these two towns. Data were therefore pooled and analyzed together to account for a reliable sample of southern Brazilian older people.

Dependent individuals were brought to the research site and taken home in an appropriate vehicle.

### Measurements

Trained (1 full day) sixth-year medical students performed the interviews and the battery of geriatric tests. At the end of the questionnaire, all subjects submitted to blood examination, a battery of geriatric assessment scales, and geriatric evaluation. The blood examinations consisted of analysis of fasting glucose, hemoglobin, albumin, total cholesterol, HDL-C, triglycerides, and creatinine levels.

For diagnosis of Met.S, an adapted form of the Adult Treatment Panel (ATP) III[2] definition using two of the World Health Organization (WHO)[29] criteria was applied for use in Brazilian older people, whereby body mass index (BMI) of 30 kg/m$^2$ and higher and blood pressure of 140/90 mmHg or higher were used to diagnose the obesity and hypertensive component of the syndrome, respectively. The WHO definition of Met.S does not allow Met.S to be treated as a continuous variable, as was done in this study (Figure 1). In addition, the ATP III definition uses waist circumference (WC) instead of BMI and adopts a criterion for normal blood pressure as systolic less than 130 and diastolic less than 85 mmHg, which is not as clear a "low risk" category as it is in young adults.[30] Therefore, a cutoff point of 140/90 mmHg was adopted to define hypertension in older people, as in the WHO Met.S definition.[29] In this study, BMI was used instead of WC for several reasons. WC is strongly ethnicity-specific,[31] and there is not yet a standard cutoff point for use in South American men and women; some studies, including one conducted in Brazil,[32] have shown that the WC criteria for Met.S does not significantly improve the prediction of Met.S-associated cardiovascular outcomes when compared with BMI of 30 kg/m$^2$ or greater; and WC was not evaluated in this population.

The diagnosis of Met.S, according to these modified ATP III criteria, required three or more of the following five criteria: obesity (BMI $\geq$30 kg/m$^2$), HDL-C less than 40 mg/dL in men or less than 50 mg/dL in women, triglycerides of 150 mg/dL or greater, blood pressure of 140 mmHg or greater for systolic or 90 mmHg or greater for diastolic, and fasting glucose of 110 mg/dL or greater (glucose intolerance plus frank diabetes mellitus). People without Met.S were the control group. In addition, according to the newest ATP definition,[2] the use of drugs for hypertension, high glucose and triglyceride, and low HDL-C was also considered to be a positive score for each respective Met.S component.

In addition, the WHO criteria for Met.S were used solely to compare its prevalence with the prevalence of the modified ATP III definition and to enable prevalence comparisons with reports from other countries. The WHO defines Met.S as the presence of diabetes mellitus or impaired glucose tolerance (as above) plus the presence of two or more obesity, hypertension (as above), and dyslipidemia (hypertriglyceridemia as above or HDL-C <40 mg/dL for women and <35 mg/dL for men).

Unless otherwise stated, Met.S refers to the modified ATP III criteria.

Mini-Mental State Examination (MMSE)[33] score was used to evaluate cognitive function. Cognitive impairment was defined as a MMSE score of 23 points or less. Depressive symptoms were assessed using the 15-item Geriatric Depression Scale (GDS), Brazilian Portuguese validated version.[34] A psychiatrist diagnosed depression according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Revised.*[35] Cases were screened using two questions: Have you dropped many of your activities and interests? Do you often feel sad or depressed? Cases with positive answers to either question were selected for the psychiatry interview. Major and minor (dysthymia) depression were considered as a single "depression" variable.

Functional status was assessed using an standardized questionnaire and included activities of daily living (ADLs),[36,37] instrumental activities of daily living (IADLs), and advanced (social and intellectual) ADLs (the last two constituting the Tokyo Metropolitan Institute of Gerontology (TMIG) scale).[38] Difficulty performing one or more of any of the ADLs was considered to be dependence for the respective ADL.

HRQoL was assessed using a 10-cm visual analogue scale,[39] ranging from 0 (worst possible score) to 10 (best). The median score was used as the cutpoint when categorizing into low and high score groups.

The validity and reproducibility of all of the above scales and methods have been well established; detailed methodologies being described elsewhere.[33–39]

Comorbidities were assessed using a standardized questionnaire and medical history. Diabetes mellitus type 2 was defined as fasting plasma glucose of 126 mg/dL or higher or current use of antidiabetic drugs.[40] Stroke diagnosis was performed on the basis of clinical history, findings on the neurological examination, and previous brain computed tomography (CT) scans. Paper medical charts from the local health unit were reviewed for confirmation in case of history of stroke without present neurological localization. Cases were entered as positive if at least one brain CT scan or magnetic resonance image scan confirming the stroke was registered.

IHD was defined as presence of angina pectoris, use of nitrates, history of myocardial infarction; positive ECG, effort-ECG, or coronary angiography; or history of coronary angioplasty or bypass. Heart disease was defined as any heart abnormality that might have been causing symptoms to the patient and included IHD, heart failure, and arrhythmias, as identified in the clinical history or medical examination.

### Statistical Analysis

For statistical analyses, SPSS version 11.5 (SPSS Inc., Chicago, IL) was used. Multivariate logistic regression analysis was used to assess the relationships between categorical variables. Independent *t* test was used for comparisons between two groups and analysis of variance for comparisons between more than two groups. Analysis of covariance was used to adjust means to age, sex, and IHD. A 95% confidence interval (CI) was used and calculated on the basis of the binomial distribution. Except where otherwise stated, all values were adjusted for age, sex, and IHD.

Initial baseline analysis included stroke distributions (Table 1). In a second step, cases with stroke were removed from the analysis involving the relationship between Met.S, functional status, depression, cognitive impairment, and HRQoL (from Figure 1 and Table 2 on).

Population attributable risk (PAR) is defined as the fraction of total disease experience in the population that would not have occurred if the effect associated with the risk factor of interest had been removed.[41] To directly calculate the adjusted PAR, the Interactive Risk Assessment Program (IRAP) was used.[41] PAR was adjusted for age, sex, and presence of heart disease.

The ethics committee of the Catholic University of Rio Grande do Sul State, Brazil, approved this project. Informed consent was obtained from all participants. Surrogates were also asked to sign the informed consent form when subjects' MMSE scores were 23 points or less.

## RESULTS

Of the 450 subjects initial invited, 422 (93.8%) participated in the research. Mean age was 68.3 (range 60–91), and women represented 63.3%. Met.S was present in 166 (39.3%) subjects according to the modified ATP III criteria and 152 (36.0%) individuals using the WHO criteria. Dependence in ADLs was present in 107 (25.4%) subjects, dependence in IADLs in 119 (28.2%), and dependence in advanced ADLs in 208 (49.3%). Depression was diagnosed in 72 (17.1%) subjects and cognitive impairment in 144 (34.1%).

Women were 2.96 times as likely to be dependent in ADLs, 4.23 times as likely to be dependent in IADLs, 2.29 times as likely to be depressed, and 2.48 times as likely to have cognitive impairment (all $P = .006$); women were not more likely to have Met.S (95% CI = 0.54–1.36) or to have a lower self-rating of their HRQoL (95% CI = 0.62–1.37). Moreover, the associations between Met.S and evaluated outcomes described below were not restricted to women, and associated risk was in general not notably dissimilar between the sexes (not shown).

Table 1. Baseline Characteristics According to the Presence or Absence of Metabolic Syndrome

| Characteristic | Metabolic Syndrome: No n = 256 (60.7%) | Metabolic Syndrome: Yes n = 166 (39.3%) | *P*-value* |
|---|---|---|---|
| Age, mean | 68.5 | 68.1 | .46 |
| Female, n (%) | 168 (65.6) | 99 (59.6) | .18 |
| White/Mestizo, % | 54.8/45.2 | 55.2/44.8 | .59 |
| Monthly income, US$ | 712 | 662 | .34 |
| Education, years, mean | 3.11 | 2.88 | .20 |
| Anemia, n (%) | 66 (25.8) | 35 (21.1) | .31 |
| Albumin, mg/dL | 4.23 | 4.28 | .37 |
| Systolic BP, mmHg | 152.3 | 159.4 | .003 |
| Diastolic BP, mmHg | 88 | 91 | .004 |
| Hypertension, n (%) | 207 (80.9) | 157 (94.6) | <.001 |
| BMI, kg/m$^2$ | | | |
| Mean | 26.4 | 30.4 | <.001 |
| ≥30.0 (obese) | 33 (12.9) | 143 (86.2) | <.001 |
| High-density lipoprotein cholesterol, mg/dL | | | |
| Mean | 48.9 | 34.8 | <.001 |
| <40 men; <50 women, n (%) | 69 (27.0) | 153 (92.2) | <.001 |
| Triglycerides, mg/dL | | | |
| Mean | 119.6 | 168.2 | <.001 |
| ≥150, n (%) | 22 (8.6) | 115 (69.3) | <.001 |
| Glucose | | | |
| Mg/dL, mean | 110.7 | 144.1 | <.001 |
| Intolerance, n (%) | 19 (7.4) | 59 (35.6) | <.001 |
| Diabetes mellitus type 2, n (%) | 30 (11.7 | 73 (44.0) | <.001 |
| Metabolic syndrome components, mean | 1.48 | 3.52 | <.001 |
| Taking prescribed and regular drugs, n (%) | 230 (89.8) | 148 (89.2) | .79 |
| Alcohol, ≥1/week | 63 (24.6) | 31 (18.7) | .29 |
| Smoking, n (%) | | | |
| Past | 61 (23.8) | 43 (25.9) | .36 |
| Present | 32 (12.5) | 20 (12.0) | .85 |
| Bone fracture, n (%) | 78 (30.5) | 46 (27.7) | .57 |
| Osteoarthrosis, n (%) | 119 (46.5) | 82 (49.4) | .55 |
| Heart disease, n (%) | 73 (28.5) | 52 (31.3) | .60 |
| Ischemic heart disease, n (%) | 21 (8.2) | 24 (14.5) | .119 |
| Stroke, n (%) | 18 (7.0) | 22 (13.3) | .109 |
| Actively working, n (%)† | 171 (66.8) | 91 (54.8) | .008 |
| Regular exercise, n (%)‡ | 106 (41.4) | 32 (19.3) | .003 |

*T test for numeric variables and chi-square test for categorical variables.
†Remunerated (mainly manual labor), part-time included.
‡≥three times a week.
*†‡Because physical activity decreases the risk of obesity and improves insulin sensitivity independent of its effect upon body mass index (BMI),[42] adjusting for either of these two variables in Tables 2–4 would be considered overadjusting.
BP = blood pressure.

As expected, most metabolic-associated atherogenic risk factors were higher in the Met.S group (Table 1). Stroke was present in 40 individuals (9.5%). Stroke prevalence was higher in the Met.S group, but it not significantly so. Three hundred eighty-two individuals were free of stroke; 143 (37.4%) of these had Met.S.

Figure 1 illustrates significantly worse scores for all evaluated variables as the number of Met.S components increased in the stroke-free population ($P<.05$ for all variables).

Table 2 depicts the mean adjusted score for each applied test or scale according to the presence or absence of Met.S. Even though advanced ADL scores were lower in the Met.S group, these trends did not reach significance. For all other variables, mean scores were significantly lower in the Met.S group.

Table 3 shows the mean value or prevalence for several individual components of Met.S according to dependence in ADLs. After adjusting for age and IHD, women were 2.96 times as likely to be dependent in ADLs as men ($P<.001$). After adjusting for age, sex, and IHD, a one-digit increase in BMI (kg/m$^2$) increased the risk of being dependent in ADLs 7% ($P=.007$). Obesity was associated with a 1.91 times higher likelihood of dependence ($P=.004$). Ten

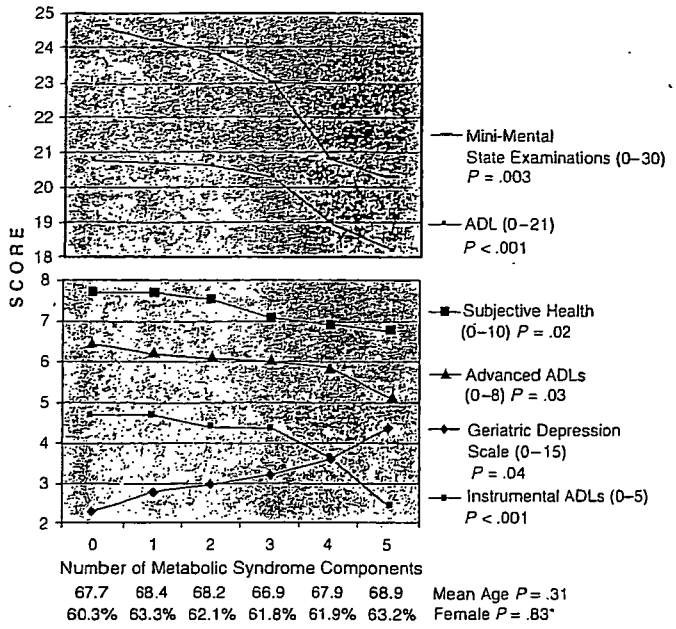


Figure 1. Cognitive, affective, and physical functions according to the number of Metabolic Syndrome components in the stroke-free population. *Chi-square test; analysis of variance for other *P*-values. ADL = activities of daily living.

mg/dL higher serum fasting glucose level was associated with a 1.6 times higher chance of dependence ($P = .03$), and diabetes mellitus increased the chance of dependence in ADLs by 1.98 times ($P = .004$).

Met.S was associated with a 2.24 (95% CI = 1.13–4.44; $P = .02$) greater chance of being dependent in ADLs. After controlling for all Met.S individual components, Met.S was still associated with a 1.71 times greater likelihood of being dependent in ADLs (95% CI = 1.02–2.87; $P = .04$).

Table 4 shows the CI, odds ratio (OR; if $P < .05$), and PAR of Met.S as an associated risk factor for low performance in the several evaluated neurofunctional variables and HRQoL. Met.S was significantly associated with greater dependence for all variables except advanced ADL scale. Met.S was significantly associated with a 2.27 times higher risk of cognitive deficit, a 2.12 times higher likelihood of depression, 2.24 times more dependence in ADLs, 2.39 times more dependence in IADLs, and 1.88 times higher odds for low HRQoL (all $P < 0.05$). Further adjustment for the individual components of Met.S reduced but did not eliminate the strength or significance of the association.

If Met.S were theoretically removed from the population (PAR), prevalence of cognitive impairment would decrease 21.3%, depression 20.1%, dependence in ADLs 20.5%, and dependence in IADLs 21.4%, and the number of people self-rating their HRQoL as low would decrease 15.0% (all $P = .05$).

## DISCUSSION

Even after adjusting for IHD and individual components of Met.S, the Met.S construct was still independently associated with 1.58 to 2.02 greater odds for dependence in ADLs, IADLs, cognitive impairment, depression, and low HRQoL. This phenomenon suggests that Met.S, in addition to its unified hyperinsulinemic pathophysiological process, is also a valid clinical construct in geriatrics, because it represents a useful concept of risk.

As expected, regular practice of exercise and being actively working (mainly manual labor in this population) were negatively associated with Met.S (both $P < .01$), although because physical activity decreases the risk of obesity and improves insulin sensitivity independent of its effect on BMI,[42] adjusting for either of these variables would be considered overadjusting. For this reason, values in Tables 1–4 were not adjusted for either of these two variables.

Obesity was associated only with dependence in ADLs, whereas glucose intolerance (including frank diabetes mellitus) was associated with dependence in ADLs and cognitive impairment. Low HDL-C was associated only with low self-perceived health status. It has been previously reported that, in older people, low HDL-C is associated with low functional status,[43] but the finding that low

Table 2. Cognitive, Affective, Functional, and Health-Related Quality of Life (HRQoL) Mean Scores According to the Presence or Absence of Metabolic Syndrome in the Stroke-Free Population

| | Metabolic Syndrome | | |
|---|---|---|---|
| | No n = 239 (62.6%) | Yes n = 143 (37.4%) | |
| Cognitive, Affective, Functional, and HRQoL Scales | Mean ± Standard Deviation | | *P*-value* |
| Geriatric Depression Scale score (0–15) | 2.77 ± 2.8 | 3.79 ± 3.1 | .04 |
| Mini-Mental State Examination score (0–30) | 24.15 ± 4.4 | 22.09 ± 4.9 | .01 |
| ADL scale score (0–21) | 20.51 ± 1.5 | 18.78 ± 2.5 | <.001 |
| Instrumental ADL scale score (0–5) | 11.19 ± 1.2 | 10.49 ± 1.5 | <.001 |
| Social ADL score (0–4) | 3.60 ± 0.79 | 3.32 ± 0.89 | .07 |
| Intellectual ADL score (0–4) | 2.66 ± 1.3 | 2.26 ± 1.2 | .09 |
| Tokyo Metropolitan Institute of Gerontology scale score (0–13) | 10.67 ± 2.5 | 8.89 ± 2.9 | <.001 |
| HRQoL score (0–10) | 7.46 ± 2.4 | 6.59 ± 2.4 | .03 |

*Note:* Mean scores were adjusted for age, sex, and the presence of ischemic heart disease.
* Analysis of covariance.
ADL = activity of daily living.

Table 3. Metabolic Syndrome (Met.S), Its Individual Components, and Presence of Ischemic Heart Disease (IHD) According to Activity of Daily Living (ADL) Dependence Status in the Stroke-Free Population

| Characteristic | ADL | | Adjusted Analysis* | | |
|---|---|---|---|---|---|
| | Independent n = 295 (77.2%) | Dependent n = 87 (22.8%) | P-value | OR | 95% CI |
| Female, n (%) | 173 (58.6) | 72 (82.8) | <.001 | 2.96 | 1.80–4.87 |
| Age, mean | 68.1 | 68.5 | .37 | — | — |
| Body mass index, kg/m$^2$ | | | | | |
| Mean | 27.5 | 29.11 | .007 | 1.07 | 1.02–1.12 |
| ≥30.0 (obese), n (%) | 77 (26.1) | 32 (36.8) | .004 | 1.91 | 1.17–3.12 |
| Fasting glucose, mg/dL, mean | 120.8 | 134.7 | .03 | 1.06 | 1.01–1.11 |
| Diabetes mellitus type 2, n (%) | 64 (21.7) | 30 (34.5) | .004 | 1.98 | 1.29–3.04 |
| Systolic BP, mmHg, mean | 153.1 | 153.7 | .36 | — | — |
| Diastolic BP, mmHg, mean | 86.4 | 86.5 | .79 | — | — |
| Hypertension (BP 140/90), n (%) | 253 (85.8) | 76 (87.4) | .27 | — | — |
| High-density lipoprotein, mg/dL | | | | | |
| Mean | 43.2 | 43.6 | .44 | — | — |
| <40 men, <50 women, n (%) | 150 (50.8) | 45 (51.7) | .71 | — | — |
| Triglycerides, mg/dL | | | | | |
| Mean | 137.9 | 140.4 | .32 | — | — |
| ≥150, n (%) | 92 (31.2) | 26 (29.9) | .46 | — | — |
| Met.S Adult Treatment Panel III score, n (%) | 110 (37.3) | 45 (51.7) | .02 | 2.24 | 1.13–4.44 |
| Number of Met.S components, mean | 1.63 | 2.13 | .001 | 1.42 | 1.16–1.74 |
| IHD, n (%) | 26 (8.2) | 14 (13.2) | .13 | 1.45 | 0.69–2.96 |

* Logistic regression, adjusted for age, sex, and presence of IHD. For numeric variables, odds ratio (OR) and 95% confidence interval (CI) correspond to a change in 1 unit in each respective variable.
BP = blood pressure.

HDL-C is associated with low self-perceived health independently of functional status seems to be a new finding. Because both extremes of BMI tend to have low HDL-C, and frail older people tend to be underweight, those with a BMI less than 20 kg/m$^2$ were excluded, but this did not modify the strength of the above association.

Hypertension was not associated with any evaluated outcome. Patients with systolic heart failure and dementia tend to have lower blood pressure,[44] although after excluding patients with heart failure and MMSE scores less than 24, systolic blood pressure was negatively correlated with MMSE (correlation coefficient = –0.12; $P = .048$) but not with other evaluated variables (not shown).

As for functional dependence, the findings were in accord with those of the Rotterdam Study,[45] in which diabetes mellitus and overweight, but not hypertension, were cross-sectionally associated with a 1.5 to 2.0 times higher chance of locomotor disability. Hypertriglyceridemia was another Met.S component that was not associated with any of the evaluated outcomes.

Mean advanced (intellectual and social) ADL score had a significant tendency to worsen with increasing number of Met.S components (Figure 1), although lower mean advanced ADL score in those with Met.S was just of borderline significance (Table 2) and was not significantly associated with Met.S in the logistic regression (Table 4). These findings are in accordance with results from a study conduced in Japan in which the IADL subdimension of the TMIG scale was more consistently associated with hypertension and diabetes mellitus than the intellectual and social dimensions of this scale were.[46]

The concept of Met.S was the only variable that showed a consistent association with dependence in ADLs and IADLs, cognitive impairment, depression, and low HRQoL. This suggests that the metabolic alterations of Met.S itself (rather than its obesity component alone) promote pathological aging, physical dependence, depression, cognitive impairment, and decreased HRQoL.

### Possible Mediative Mechanisms

Several pathophysiological factors might mediate the associations between Met.S, functional dependence, cognitive impairment, and depression found in this study. On a population level, peripheral arterial disease is just minimally associated with increased attributable risk for functional dependence (2.5%)[27] and would hardly explain the approximately 21% to 22% PAR for ADLs and IADLs associated with Met.S in this study. Hyperglycemia has been associated with general weakness, muscle cramps, blurred vision, and dizziness.[57] Decreased proprioception due to peripheral neuropathy may also bring dependence.[47]

Nevertheless, except for small-vessel disease, none of the above causes can explain the association between Met.S, cognitive impairment, and depression.[48] Moreover, ORs for cognitive impairment, depression, and functional dependence (ADL and IADL) were all strikingly similar (2.12–2.39), suggesting a common pathophysiological mediator process. Indeed, the three above neurofunctional outcomes were strongly associated between themselves, even after adjusting for age and sex (OR = 2.45–4.26; all

Table 4. Metabolic Syndrome (Met.S) and Its Individual Components as Associated Factors for Low Performance in Several (Neuro)Functional Variables and Low Health-Related Quality of Life (HRQoL) in the Stroke-Free Population

| Met.S Components | Cognitive Impairment | Depression | Dependence in ADLs | Dependence in Instrumental ADLs | Dependence in Advanced ADLs | Low HRQoL |
|---|---|---|---|---|---|---|
| | Odds Ratio (95% Confidence Interval) | | | | | |
| Obesity | 1.13 (0.72–1.78) | 1.20 (0.55–2.60) | 1.93 (1.20–3.01)* | 1.17 (0.73–1.88) | 0.80 (0.52–1.23) | 0.98 (0.64–1.50) |
| Hypertension | 0.80 (0.70–1.63) | 1.04 (0.69–2.27) | 1.25 (0.63–2.47) | 1.77 (0.93–3.35) | 1.10 (0.62–1.94) | 0.85 (0.48–1.51) |
| Diabetes mellitus or glucose intolerance | 1.56 (1.03–2.26)* | 1.33 (0.85–2.08) | 2.03 (1.25–3.3)* | 1.39 (0.91–2.13) | 1.09 (0.70–1.71) | 1.27 (0.81–1.99) |
| High-density lipoprotein cholesterol, mg/dL, <40 (men) or <50 (women) | 1.28 (0.88–1.85) | 1.17 (0.73–1.87) | 1.16 (0.72–1.87) | 1.47 (0.95–2.28) | 1.14 (0.71–1.60) | 1.87 (1.24–2.83)* |
| Triglycerides ≥150 mg/dL | 1.03 (0.71–1.49) | 0.97 (0.61–1.54) | 1.24 (0.77–2.00) | 1.05 (0.71–1.55) | 0.91 (0.60–1.39) | 1.39 (0.91–2.12) |
| Met.S† | 2.27 (1.21–4.26)* | 2.12 (1.05–4.28)* | 2.24 (1.13–4.44)* | 2.39 (1.20–4.76)* | 1.34 (0.81–2.23) | 1.88 (1.14–3.10)* |
| Met.S adjusted for components‡ | 1.82 (1.06–3.12)* | 2.02 (1.11–3.68)* | 1.71 (1.04–2.81)* | 1.58 (0.99–2.52)* | 1.70 (0.89–3.25) | 1.59 (1.02–2.48)* |
| Met.S population attributable risk, %† | 21.3 | 20.1 | 20.5 | 21.4 | — | 15.0 |

Logistic regression: adjusted for age, sex, and presence of ischemic heart disease.
* $P < .05$.
† Calculated from odds ratio (OR) adjusted for age, sex, and IHD but not Met.S components.
‡ Further adjusted for all Met.S individual components.
ADLs = activities of daily living.

$P = .002$; not shown), suggesting that they may belong to a single syndromic entity.

Mean physical and cognitive functions decline steeply after the seventh decade of life; but this decline is heterogeneous.[49] Small-vessel disease might be one of the pathological hallmarks of this transition and might also explain its heterogeneous character.[49] Met.S and hyperinsulinism are preferentially associated with cerebral microangiopathy.[20] Indeed, Met.S seems also to potentiate age-related leukoaraiosis,[20] which has been reported to be associated with frontal-subcortical lacunar strokes and selective cognitive, affective, and neuromotor dysfunctions.[48] Together, these neurofunctional abnormalities constitute what has been considered a new geriatric nosological entity, namely the frontal-subcortical (ischemic) geriatric syndrome.[48] Frontal-subcortical dysfunction may be a key point in explaining the concomitant and interrelated decline in cognitive, affective, and neuromotor functions in older people.[48]

A study of identical elderly male twins showed that the most significant determinant of late-life white-matter lesions were glucose levels, HDL-C, and systolic blood pressure, all of which are Met.S components.[26] Moreover, insulin levels are significantly higher in patients with lacunar stroke, subcortical atherosclerotic encephalopathy, and microangiopathy than in normal control subjects.[20]

Small-vessel disease and clinical stroke are involved in the etiology of cognitive impairment in older people.[49] In this study, Met.S was more strongly associated with cognitive impairment in the stroke-free population (OR = 2.27; $P < .01$) than with stroke in the original population (OR = 1.5; $P = .19$). These findings suggest that Met.S might be more associated with features of small-vessel cerebrovascular disease than with clinical stroke. In fact, Met.S (but not its conventional risk factors) was recently shown to be independently associated with intracranial atherosclerosis and lacunar (often silent) stroke.[7]

Met.S might have increased the risk of depression simply by promoting more functional dependence, although even after adjusting for functional status, Met.S was still significantly associated with a 1.53 (1.03–2.27) higher chance of having depression. This result points to a straightforward effect of Met.S on depression and suggests that its influence on the brain directly mediates this effect.[48] In addition to promoting stroke and cerebral small-vessel disease, Met.S seems also to accelerate age-associated loss of serotoninergic innervation and responsivity, a phenomenon associated with higher risk of depression.[21,22]

Finally, Met.S might lead to decreased neuromotor and cognitive functions via an accelerated biological neuroaging process itself.[4,13]

## Limitations

This study has several limitations. Because epidemiological studies, especially those of cross-sectional design such as this one, cannot prove cause and effect when the end-point is an outcome of a chronic noncommunicable condition, findings from this study can be cited only as being consistent with the hypothesis in question.

Because present-diagnosed Met.S was independently associated with most evaluated neurofunctional variables, hyperinsulinism and other Met.S components are probably

still acting in synergy to promote vascular disease at older age. However, due to the cross-sectional nature of this research, these values might account for just a fraction of all the cumulative variance on neurofunctional decline attributable to Met.S. For a given cardiovascular risk factor, the maximum explanatory variance upon outcomes might be found some 10 to 20 years, or even more, before this outcome; this rule is also valid for the brain.[26] This phenomenon may account, at least in part, for the lack of association between hypertension and any of the evaluated outcomes in this study.

### Final Remarks

The above results are consistent with a growing body of evidence that links obesity, Met.S, vascular disease, and subclinical inflammation to cognitive, affective, neuromotor, and functional decline.[20–36,46] The relationship between insulin resistance, cerebrovascular and neural aging is tantalizing in its potential to offer an integrated model for aging of the body and the brain.[24]

To the authors' knowledge, this is the first study to comprehensively show that Met.S is associated with functional dependence, cognitive impairment, depression, and low HRQoL in older people. Moreover, it also suggests that Met.S may be a risk factor for the above outcomes independent of its own individual components (which might act in synergy), stroke, and IHD. It also demonstrated that, if Met.S were theoretically removed from this population, dependence in ADLs and IADLs—and the prevalence of cognitive impairment, depression, and low HRQoL—would decrease 15.0% to 21.4%. In addition, this study also suggests that cognitive and functional decline and greater depressive symptomatology may be part of the same syndromic process by which Met.S atherogenic factors might be acting.

Recognition of Met.S as a risk factor not just for cerebrovascular disease, but also for "unsuccessful" aging would encourage the identification of this multirisk-factor condition and promote lifestyle modifications that would reduce all of the Met.S risk factors simultaneously. Because Met.S is a potentially reversible syndrome, once excess weight is lost and physical activity initiated (its ultimate causes), older people with Met.S should be treated aggressively.

## CONCLUSION

Met.S was significantly and independently associated with 2.2 to 2.4 times more physical dependence in ADLs and IADLs, 2.3 times higher odds for cognitive impairment, a 2.1 times higher risk of coexisting depression, and a 1.9 times higher chance of low HRQoL. If Met.S were theoretically removed from this population, the above outcomes would be reduced 15.0% to 21.4%. Met.S might be a major determinant of functional dependence, cognitive impairment, depression, and low HRQoL in later life.

Preventing and treating Met.S may be an important step in "preventing senility" and promoting successful aging.

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organisation, supporting the notion that stroke units offer stroke patients a real advantage over conventional care.

In Italy, many of the stroke units identified by the PROSIT survey are neurological and, as elsewhere, the team manager for stroke is a neurologist trained in stroke and neurovascular medicine. We agree with Sacco and Carolei that, where possible, the neurologist should have a higher-profile role in the management of hyperacute stroke in the emergency department. However, it is clear that the model of hospital organisation in which well defined stroke care is provided in a stroke unit setting should be preserved, because this is the setting in which, in recent years, the most impressive results in the acute treatment of stroke patients have been obtained.

The stroke unit setting, constituting the basic approach to the acute care of stroke patients, is the *sine qua non* for other pharmacological or neurovascular procedures that could be implemented in these patients. Confounding messages about other desirable (but debatable) models of organisation and professional figures that might be involved should be avoided if we are to guarantee an adequate and systematic approach to standardised care which is now known to be provided even by basically organised stroke units. Of course, the internal pathway linking stroke unit care with the emergency department should be developed according to the organisational model adopted by the individual hospital.

We declare that we have no conflict of interest.

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## Trends in diabetes

Lorraine Lipscombe and Janet Hux's assessment of diabetes prevalence in Ontario, Canada (March 3, p 750),[1] especially among new immigrants from south Asia, is disquieting.

About 77% of newly arrived Canadians come from high-risk developing nations.[2] Lipscombe and Hux state this fact as being one of the chief contributors to the diabetes burden in Canada. However, they do not mention the increased likelihood (three to five times) and earlier age of onset of type 2 diabetes in First Nations populations compared with other Canadians. According to the 1991 Aboriginal Peoples Survey,[2] the prevalence of diabetes is 8·5% among First Nations living on-reserve or in Aboriginal communities, 5·3% among First Nations living off-reserve, 5·5% among Metis, and 1·9% among Inuit people. We agree with Lipscombe and Hux that there is a need to address sociodemographic aspects to better contain the diabetes epidemic.

Of particular concern is the rise in childhood obesity and youth inactivity. The proportion of children and adolescents in Canada who are overweight has tripled in the past 30 years.[2] It will be interesting to evaluate the increasing burden of type 2 diabetes in those younger than 20 years to see whether it further splays the estimates proposed by the current study.

The updated WHO estimates of mortality and global burden of diseases address[3] the earlier underestimated rates for diabetes for the year 2030. They use a separate projection model taking into account the projected trends for body mass index, overweight, and obesity for the same duration. This WHO report corroborates Lipscombe and Hux's claim that previously reported projections for diabetes in 2030 were underestimates.[4]

NRP is an immigrant Canadian citizen from south Asia. VG has no conflict of interest.

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Lorraine Lipscombe and Janet Hux[1] show once again that diabetes is a major public health burden among multi-ethnic populations in Ontario, Canada. What is most worrying is the increasing rate of diabetes among the younger generation. One of the possible explanations for this increasing prevalence is the high rate of immigration from regions with more susceptible populations such as south Asia, although Lipscombe and Hux did not assess ethnic difference.

Indeed, evidence clearly shows that minority populations, especially those of south Asian descent, develop diabetes earlier and have more diabetes-related complications than their European white counterparts.[2,3] The reasons for this higher prevalence remain unclear, however.

This Canadian database provides a great opportunity to follow up newly arrived south Asian immigrants over time to gain more insight into how diabetes develops among these populations. Such information will be invaluable for devising effective measures in prevention, improving services, and, inevitably, raising standards of care for all populations in western countries.

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In view of the Article by Lorraine Lipscombe and Janet Hux,[1] and of the need to identify populations susceptible to diabetes mellitus type 2, we would like to draw attention to patients with schizophrenia and bipolar disorder. The prevalence of type 2 diabetes in these patients can be two to three times higher than in the general population, which results in increased morbidity and mortality from related disorders.[2,3] Many cases of diabetes might not be identified,[2,3] and, of those that are, up to 30% remain untreated.[4]

People with these disorders are more likely than the general population to smoke, to have a sedentary lifestyle, to present with a higher body-mass index, to consume large quantities of fatty foods, and to take certain drugs (mood stabilisers, anticonvulsants, and antipsychotics), which have been linked to adverse metabolic events.[2,3]

There is a great need for intensive baseline screening, follow-up, and treatment of diabetes in patients with bipolar disorder and schizophrenia.[2,3] The implementation of low glycaemic index diets,[5] promotion of active and healthy lifestyles,[2,3] and collaboration of all parties involved with patients' care (physicians, mental health professionals, caregivers, family members, and the patients themselves) might actually contribute to the prevention of diabetes in this particularly vulnerable psychiatric population.

We declare that we have no conflict of interest.

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The close investigation of population-based trends in diabetes in Canada reported by Lorraine Lipscombe and Janet Hux[1] deeply impressed us. In their epidemiologically strict analysis, they studied hospital-based, confirmed diabetes; however, early detection of patients with suspected diabetes or impaired glucose tolerance in the community is also important from a preventive public-health standpoint.

In 2006, we did a community-based survey of 373 community-dwelling elderly people (aged 65 years and older) to detect early diabetes or impaired glucose tolerance. There were 162 men and 211 women, the mean age was 74·5 years (SD 6·5), and all were living in Tosa town, Kochi prefecture, Japan. None had ever been diagnosed with or treated for diabetes. We assessed fasting blood sugar as well as blood sugar levels 2 h after a 75 g oral glucose tolerance test (BS-2h). We defined diabetes as a fasting blood sugar level of at least 7·00 mmol/L or a BS-2h of at least 11·11 mmol/L, and impaired glucose tolerance as a fasting blood sugar level of 6·11–6·99 mmol/L or a BS-2h of 7·77–11·10 mmol/L, on the basis of WHO criteria.

47 individuals (13%; 24 men, 23 women) were found to have diabetes, and 119 (32%; 48 men, 71 women) impaired glucose tolerance, and this was in a country where regular screening examinations and treatments for diabetes are widespread.[2] The diabetes prevalence reported by Lipscombe and Hux might therefore be an underestimate. We recommend oral glucose tolerance testing in the community setting as well as the clinical setting, if possible, to reduce the global burden of diabetes.[3]

We declare that we have no conflict of interest.

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## Hydroxychloroquine in systemic lupus erythematosus

In their Seminar on systemic lupus erythematosus (SLE; Feb 17, p 587),[1] David D'Cruz and colleagues make little mention of hydroxychloroquine as a treatment option.

Increasing evidence suggests that hydroxychloroquine is an essential medication in SLE. First, its effectiveness in preventing and alleviating not only cutaneous and articular manifestations, but also severe consequences, has been shown.[2] Second, although D'Cruz and colleagues emphasise the close relation between damage and increased risk of morbidity and mortality, they do not mention that hydroxychloroquine

mixed population of multimorbid patients on an acute geriatric treatment unit, there were a variety of accompanying factors with reciprocal influence on erythrocyte volume, such as iron deficiency. Alternatively, it is supposed that serum cobalamin might be of limited value as a marker of cobalamin deficiency.[6] Serum methyl-malonic acid and serum homocysteine, as well as holotranscobalamin, are presumed to give a superior reflection of true cobalamin and folate status,[7] but there was only a minor correlation between erythrocyte volume and serum homocysteine in another study,[8] which also confirms the finding of this study.

## CONCLUSION

The sensitivity and predictive value of macrocytosis for cobalamin and folate deficiency are low. Therefore, we recommend cobalamin and folate screening in elderly people based on clinical indications such as unexplained anemia, cognitive impairment, and other neuropsychiatric disorders, independent of hematological findings such as erythrocyte volume.

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## THE CLOSE ASSOCIATION BETWEEN LOW ECONOMIC STATUS AND GLUCOSE INTOLERANCE IN ELDERLY SUBJECTS IN A RURAL AREA IN LAOS

*To the Editor:* The incidence of diabetes mellitus (DM) is increasing fast, especially in developing countries, with economic globalization.[1] In developing countries, the nutrition transition paradox also has emerged with the phenomenon of the development of underweight and obesity in poor people.[2] Once thought of as a disorder of affluent people, DM is set to join malaria as a disease of poverty.[3] Nevertheless, there has been no report on the association between economic status, obesity, and DM diagnosed according to the oral glucose tolerance test (OGTT) in community-dwelling older people. In this study, the close association between low economic status and glucose intolerance was shown, notwithstanding the low prevalence of obesity in people of low economic status.

OGTT was performed in 235 Laotians aged 60 and older (male:female 96:139, mean age 69.9) (64.7% of all eligible subjects) living in the rural village of Lahanam (total population 4,233, population aged $\geq$ 60 363) in Savannakhet Province in Laos in 2005.[4] According to the criteria of the World Health Organization, DM (fasting blood sugar (FBS) $\geq$ 126 mg/dL or 2-hour plasma glucose (PG) $\geq$ 200 mg/dL), impaired glucose tolerance (IGT) (FBS 110–125 mg/dL or 2-hour PG 140–199 mg/dL), and normal glucose tolerance (NGT) (FBS $<$110 mg/dL and 2-hour PG $<$140 mg/dL) were defined using OGTT. Household economic status was classified according to a wealth ranking, divided by local authorities, into three groups (low (n = 43), moderate (n = 168) and high (n = 24)) according to possessions (e.g., house style, size of field, domestic animals).[5]

The prevalence of DM or IGT was 51.2% (DM 27.9%; IGT 23.3%), 28.0% (DM 14.9%, IGT 13.1%), and 37.5% (DM 20.8%, IGT 16.7%) for people of low, moderate, and high economic status, respectively (Figure 1). The low economic group had a higher prevalence of DM/IGT (51.2%) than the moderate economic group (28.0%) (chi-square test, $P = .004$) and a higher prevalence of DM (27.9%) than the moderate economic group (14.9%) ($P = .045$). There was no difference in the prevalence between the high and moderate economic groups.

All subjects with DM/IGT had a significantly higher prevalence (24.4%) of obesity (body mass index (BMI) $\geq$ 25.0) than those with NGT (14.0%) ($P = .049$). The prevalence of obesity was 4.9%, 19.5%, and 25.0% in the low, moderate, and high economic status groups, respectively. The prevalence of DM/IGT combined with obesity was 2.3%, 9.5%, and 8.3% in subjects of low, moderate, and high economic status, respectively. The prevalence of obesity was much lower (4.5%) in subjects with DM/IGT of low economic status than in those of moderate economic status (34.0%) (Figure 1).

To clarify the association between economic status, obesity, and DM/IGT, we calculated the odds ratio of economic status for DM/IGT using the confounding factor of obesity with adjustment for age and sex using multiple logistic regression analysis. Compared with the moderate economic group, the odds ratio of the low economic group for DM/IGT was 3.2 ($P = .001$) and that of the high

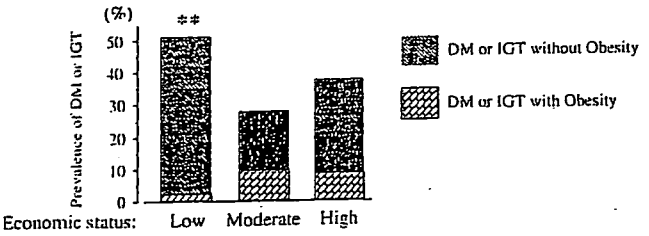


Figure 1. Prevalence of diabetes mellitus (DM) or impaired glucose tolerance (IGT) with and without obesity according to economic status in elderly subjects in a rural area in Laos (diagnosed according to 75 g oral glucose tolerance test according to World Health Organization criteria). $^{**}P = .004$, prevalence of DM/IGT according to the chi-square test (reference group: moderate economic status). Obesity: body mass index (BMI) ≥25.0.

economic group was 1.1. The odds ratio of obesity for DM/IGT was 2.5 ($P = .01$) compared with nonobesity. According to the above results, low economic status and obesity were independent factors associated with DM/IGT.

DM/IGT was common, but obesity was rare in the group with low economic status in this rural area. The elderly of low economic itself may have a high risk for suffering DM/IGT because of their lifestyle; some hypotheses for this are suggested. The first is the unbalanced diet of sticky rice, which has more calories than ordinary rice, with cheo (local pepper sauce) and a paucity of other foods. The second is the hypothesis of "fetal origins of disease," which postulates that early undernutrition causes an irreversible differentiation of the metabolic system, which may, in turn, increase the risk of DM in adulthood or old age.[2] Poor old people in rural areas may be vulnerable to IGT/DM because of those causes and others.

Recently, energy-dense foods with more sugar and fats are available near this rural area. Obesity was associated with DM/IGT especially in people of moderate or high economic status in this study. The area may be under siege from nutritional transition with economic globalization. For the prevention of obesity and DM/IGT in vulnerable people, especially those of low economic status, it is important to recognize that, not only high, but also low economic status may be a risk factor for DM, and the causes in each of them should be pursued to prevent DM and its complications.

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## ALTERED BLOOD PRESSURE HOMEOSTASIS IN THE OLDEST OLD AND SURVIVAL

*To the Editor:* We read with interest the paper by Oates et al.,[1] which demonstrated that, in veterans aged 80 and older with hypertension and controlled blood pressure (BP), defined as systolic BP less than 140 mmHg and diastolic BP less than 90 mmHg, lower BP was associated with lower 5-year survival. This observation confirms previous reports that, in the oldest old, higher BP is associated with better survival.[2] Other studies in older people show a nonlinear U- or J-shaped relationship between BP and cardiovascular and total mortality.[3]

Overall, the existing data suggest that active antihypertensive therapy significantly reduces the risk of stroke, heart failure, and major cardiovascular events in subjects aged 80 and older[4,5] to a similar extent as in younger subjects,[5] but this benefit is associated with a 6% to 23% increase in total mortality.[4] Oates et al.[1] are right to say that "clinicians should use caution in their approach to BP lowering in this age group." On this important and still controversial topic, we would like to comment on two further matters.

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松林公蔵

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