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学位論文

Gait speed, daily walking and all-cause mortality in the younger-elderly Japanese: a cohort study

（日本の前期高齢者における歩行速度、日常的な歩行習慣とその後の死亡：コホート研究から）

2015 年 9 月

北海道大学

趙文静

WENJING ZHAO

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List of publications and presentations at academic conference

I. List of publications

(1) Wenjing Zhao, Shigekazu Ukawa, Kazuyo Tsushita, Takashi Kawamura, Kenji Wakai, Masahiko Ando, Akiko Tamakoshi. Association of gait speed with mortality among the younger elderly in the New Integrated Suburban Seniority Investigation Project: a prospective cohort study, Age Ageing. 2015 Jan;44(1):153-7. doi: 10.1093/ageing/afu121. Epub 2014 Sep 18.

(2) Wenjing Zhao, Shigekazu Ukawa, Takashi Kawamura, Kenji Wakai, Masahiko Ando, Kazuyo Tsushita, and Akiko Tamakoshi. Health benefits of daily walking on mortality among younger-elderly men with or without major critical diseases in the New Integrated Suburban Seniority Investigation Project: A prospective cohort study, J Epidemiol. 2015 Jul 4. [Epub ahead of print]

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(2) Wenjing Zhao, Shigekazu Ukawa, Kazuyo Tsushita, Takashi Kawamura, Kenji Wakai, Masahiko Ando, Satoe Okabayashi, Madoka Matsushita, Junko Oikawa, Reiji Kojima, Akiko Tamakoshi. The impact of gait speed on mortality among Japanese elderly in a New Integrated Suburban Seniority Investigation Project: A prospective cohort study, the 20th International Epidemiology Association World Congress of Epidemiology, Alaska, USA, August, 2014.

(3) Shigekazu Ukawa, Akiko Tamakoshi, Kazuyo Tsushita, Kenji Wakai, Masahiko Ando, Hideki Ohira, Satoe Okabayashi, Madoka Matsushita, Wenjing Zhao, Junko Oikawa, Takashi Kawamura. Body mass index is a predictor for developing hypertension among the younger Japanese elderly: Findings from the New Integrated Suburban Seniority Investigation project Cardiovascular Disease, Epidemiology and Prevention/Nutrition, Physical Activity and Metabolism 2014 Scientific Sessions, San Francisco, U.S.A., March, 2014.

Introduction

1) Global aging population

During the 20th century, life expectancy at birth (LE) increased greatly in many developed countries, such as USA, Canada, Australia, New Zealand, Japan, Spain, and Italy. Particularly since 1950, these countries obtained almost the same increment in LE due to declining fertility and mortality[1]. LE continues to rise linearly, with no sign of deceleration, especially in more developed countries, where it was estimated to increase to 78 years by 2015, and 83 years between 2045 and 2050. Continued medical developments result in longer LE, which in turn contributes to an ageing society regionally, nationally and globally[2].

2) Japan's aging society

Japan, as one of the world's leading aging societies, has the highest proportion of elderly citizens, and has been aging for more than five decades: it ranked as an aging society early in 1970 (aging population proportion: 7%) based on the definition of aged population from the United Nation (aged 65 and older), an aged society in 1994 (14%), and a super-aged society in 2007 (21%) (Figure 1). Significant increase in both numbers and proportion of elderly citizens can be expected. Although the growth of the old population slowed down after 2007, the number of citizens aged 65 years and older in 2013 has increased to 31.9 million (Male, 13.7 million; female, 18.2 million), 25.0% of the total population. By 2035, the proportion will be 33.4% and by 2060, one in every 2.5 persons will be 65 years or older, and a quarter will be aged 75 years or older. The older-elderly (75-84 years) is increasing more rapidly than their younger counterpart (65-74 years) (Figure 1). According to these estimations, the proportion of older-elderly is projected to double during the next 5 decades from 2010 to 2060 while the younger-elderly will be staggered at approximately 12%. This means that the rapid increase of older-elderly will give rise to societal and economic burden for the super-aged society.

Over the past 6 decades, the LE in Japan had been increasing linearly, though the latter estimated trend after 2010 is slower than before (Figure 2). The longest LE record has been held by Japanese females since 1986 (80.93 years)[3,4] and Japanese female LE (86 years) in 2007[5] surpassed the ideal average life span (85 years) proposed by Fries in 1980[6], which made Japan the top runner of global aging. According to the latest information from the Ministry of Health, Labour and Welfare, the LE is 81.21 years for males and 86.61 years for females in 2013, showing that male life expectancy has exceeded 80 years for the first time and female maintains the world record, even after the Great Eastern Japan Earthquake in 2011. Based on estimates, LE will further increase to 84.19 years for males and 90.93 years for females in 2060 (Figure 2). The continued increased growth of LE is contributing to the sharp increases of remaining life expectancy at the age of 65 years[3]. The remaining life expectancy in 2010 for Japanese men aged 65 years was 18.74 years and 23.80 years for women. It is expected to rise to 22.33 and 27.72 years for men and women, respectively, in 2060.

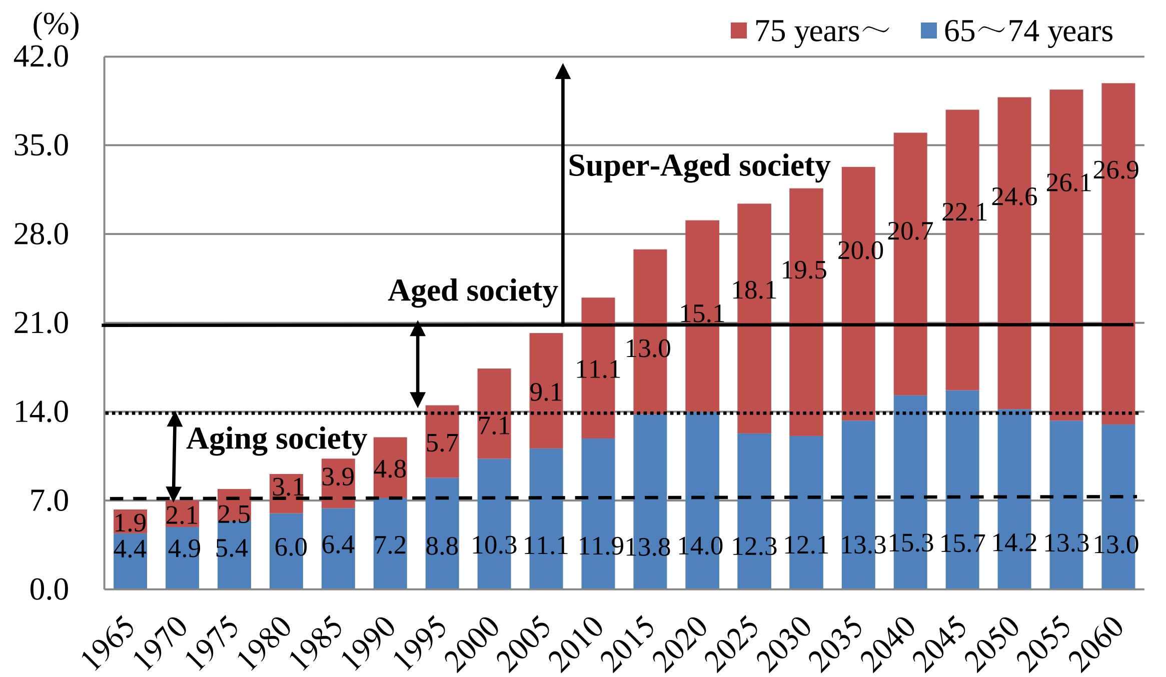

Figure 1. The percentage change of the old population in Japan from 1965-2060

(Data from National Institute of Population and Social Security Research, Japan; Data after 2010 was according to the estamation in 2012)

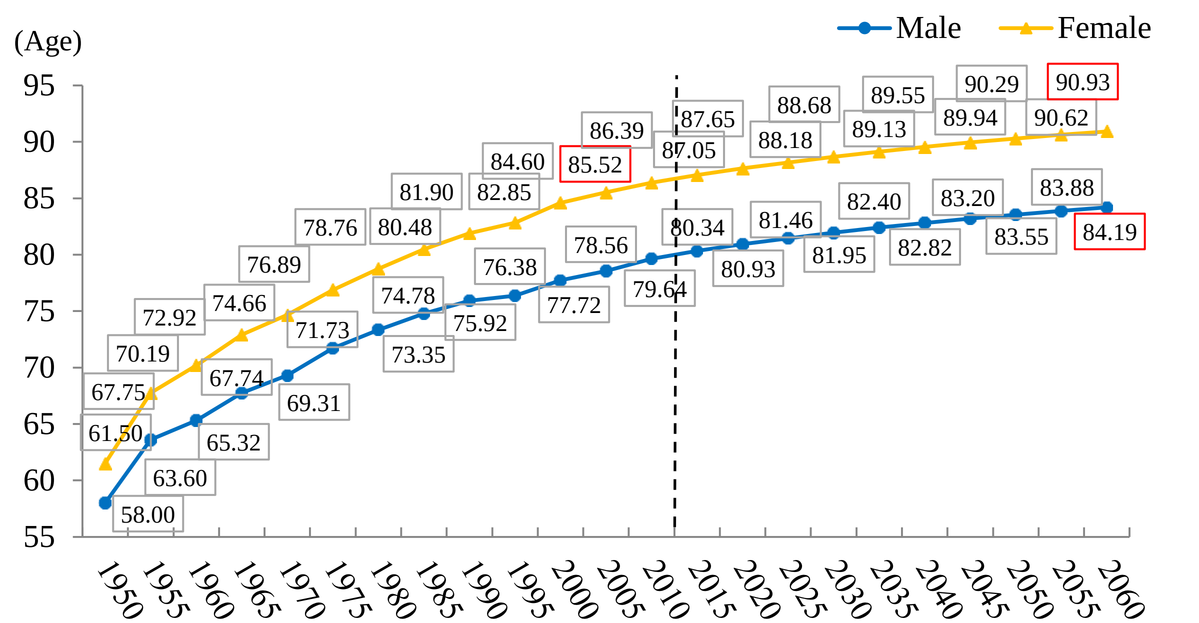

Figure 2. The change of life expectancy at birth in Japan from 1950-2060
(Data from National Institute of Population and Social Security Research; data after 2010 came from the estimation in 2010)

In the context of an increasing aging population and the concurrent longer remaining life expectancy at the age of 65 years, along with the unprecedented mortality reduction, Japan's society will be further challenged by coexisting and intertwined problems, such as the prevention of leading risk factors for non-communicable diseases, the prevention of disabilities caused by accumulative non-communicable diseases, the maintenance or postponement of aged-related physical and psychological function, the adequate and equal provision of medical care and long-term care, as well as the societal and economic capacity for an aging population's health.

3) The prevalence of functional decline in Japan

With advanced aging, whether the Japanese old populations are living longer but accompanied with good health is in debate[7]. Age has been showed to be one of the crucial risk factors for functional decline for older Japanese community residents[8,9]. Although global and national evidence has shown substantial reductions in disability among aging population[1,10-12], functional decline was prevalent along with diminished mortality and increased LE, particularly in Japan, the country with the oldest population in the world. The study by Schoeni et al. summarized the trend of old-age functioning during 1993 and 2002 that functional limitation were common for

Japanese aged ≥66[10]. It was reported that the prevalence of light or moderate levels of disability has increased in Japan over the last decade[13,14], and moderate functional decline is more prevalent than severe functional decline[14]. One report from the Cabinet Office also provided us with a new picture of functional capacity for an elderly Japanese population.

First, healthy life expectancy (HALE) increased more slowly than did life expectancy. HALE has been defined by World Health Organization (WHO) into a summary index of health states that average of number of years that a person can expect to live in full health by taking into account years lived in less than full health due to disease and/or injury, which could summarize the average level of population's health whether a person is able to live longer with high quality of life. The change of comparison between HALE and LE could reflect the compression or expansion of morbidity in a population, or the extent to which the increase of LE is going hand in hand with good or poor health[15]. HALE in Japan increased in 2010 (to 70.42 years for males, 73.62 years for females) compared with the data in 2001 (69.40 and 72.65 years for males and females, respectively). Namely, Japan, during these 10 years, has obtained about 1 year in HALE for both sexes, but 2-year gain in LE (Figure 2). The gap between HALE and LE in both sexes during the past decade implies that mortality reduction may be accompanied with expansion of morbidity.

Second, the number of elderly persons reporting subjective symptoms is increasing. It is reported that nearly half of the elderly population reported the subjective symptoms in 2010, which impacted 20% of their daily life. With advanced age, there were more elderly women reporting difficulties in activities of daily living (ADL) than men after the age of 70 years. The prevalence of ADL and Instrumental Activities of Daily Living (IADL) disability and the incidence of functional decline increased with age[16].

Third, the frequency of medical care utility for those aged 65 years and older (Inpatients 3136/100,000; outpatients 11414/100,000 in 2011) was higher than that of young Japanese, and higher than that of Korea, America, Germany and Switzerland. The high use of medical care is mainly attributable to cerebrovascular diseases and cancer for elderly men and women. Such conditions are reported to be the main chronic conditions leading to functional decline or disability[14] and the main risk factors that hampered recovery from functional decline[17].

Forth, long-term care need certification is growing. One survey in 2012 showed that the number of elderly who need long-term care certification is increasing rapidly, especially those aged 75 and older, 23.0% of whom obtained the certification of long-term care needs, more than seven times that of elderly persons aged 65-74 (3%). Cerebrovascular diseases, cognitive dysfunction, frailty, arthritis were reported to be the leading reasons for issuing of the certificate among the six categories of long-term care, which included strict physical and mental status test to determine service eligibility[18]. The higher the certification is, the more degenerative the functional capacity is. Functional decline and the consequent informal or formal long-term care will lead to substantial social and economic consequences on elderly individuals, their families, pension, the health insurance system, the health care system and long-term care system[11].

4) Physical and psychological function decline, one of the challenges posed by an aging society

Aging is natural and inevitable. It is accompanied with loss of physical and psychological function, prevalence of chronic conditions and physically inactive lifestyle, the latter of which will exacerbate the functional declines and thus contribute to dependence on daily living activity. Functional declines are commonly defined as difficulties with ADL or lower or upper extremity function[19,20]. Functional decline is not only impacted by multifarious risk factor profiles from biological, psychological, functional, social, and environmental aspects[20], but also related to mortality rate growth, medical service utility, institutionalization, and increased high family, social and economic burden. Functional decline is undoubtedly becoming one of the major challenges posed by an aging population because the maintenance of physical and psychological functioning is the foundation of keeping the elderly people independently carrying out the activities of daily living.

5) The screening and assessment of functional decline

The evaluation of functional decline involves a wide aspect of functioning. A range of common instruments are applied to screening for functional decline, including self-reported measures such as the Tokyo Metropolitan Institute of Gerontology Index of Competence (TMIG)[21], ADL (bathing, dressing, transferring from the bed to a chair, toileting)[22], Basic Activities of Daily Living (bathing, dressing, getting around the house, toileting, feeding, grooming)[23], and IADL (shopping, housekeeping, preparing meals, taking medications, handling finances, using public transportation)[24,25], and performance-based measurement such as Performance-based Physical Function test (PPT)[26], and the Short Physical Performance Battery (SPPB)[27]. It was reported that the performance-based measurements were moderately correlated with self-reported measurements[28,29], and both of them might reflect a similar assessment of functions[29]. Of the available instruments, SPPB was recommended most highly to be used in older community-dwelling residents due to its validity, reliability and responsiveness[30]. There have been previous studies which demonstrated that gait speed was as sensitive as composite score SPPB, and lower or upper extremity performance (e.g. gait speed, repeated chair stands, balance tests, and hand-grip strength and so on) to discriminate the functional status of elderly men and women[31-33]. One study in Japan also showed the predictive power of usual gait speed on a wide range of functional status in elderly women, which performed as well as other composite scores, such as lower or upper extremity performance or overall scores[34]. The reason for gait speed attracting more attention may be because it has been regarded as the six vital sign[35] and reflects the integrated dysfunction systems of the central nervous system, perceptual system, peripheral nervous system, muscles, bone/joints, and energy production/delivery[36]. It is the reflection of simultaneous functioning of such organs that make gait speed available to estimate the overall burden of preclinical diseases or diseases hard to diagnosis, and predict diverse health related-outcomes[37].

6) Interventional strategies for functional decline or the subsequent adverse outcomes

In the face of an aging society coming and staying, healthy and active aging has been championed[38]. One of the priorities of successful aging is the identification of people at high risk of functional decline, and then applying appropriate and targeted strategies to maximize the physiological and psychological functions which influence the capacity to be mobile and live independently until late on in life[30]. However, how to identify subjects with the onset of or progressive functional decline, and develop strategies for interventions will contribute to structure the healthy and active aging society and mitigate the consequence caused by aging society.

It was reported that early stage functional decline in community-dwelling elderly persons can be prevented through effective screening, postponed or reversed by favorable interventions[19] and the recovery of early declines is less costly, while the recovery of severe disability is less likely and more costly[17,39]. Regular physical activity has been reported to be one of suggestive intervention strategies to maintain functional independence or enhance functional capacity and decrease the adverse outcomes precipitated by functional decline[40-42].

Consequently, the current study includes two chapters. Chapter 1 attempts to demonstrate the association between the indicator of functional decline—gait speed, and all-cause mortality among the younger–elderly (aged 65-74 years) Japanese, and determine whether the most popular physical activity domain—daily walking, could modify this association. Based on the results obtained in the chapter 1, the following chapter, chapter 2 will explore the association between daily walking and all-cause mortality among the younger elderly with or without major critical diseases. These two chapters will provide practical guidelines or interventional strategies for an aging society, not only adding years to life in the elderly but also adding life to years.

List of abbreviations

ADL	Activity of Daily Living
ACSM&AHA	American College of Sport Medicine and the American Heart Association
BMI	Body Mass Index
CI	Confidence Interval
GDS-15	Short-form Geriatric Depression Scale
GOF Testing approach	The Goodness of Fit Testing Approach
HALE	Healthy Life Expectancy
HR	Hazard Ratio
IADL	Instrumental Activity of Daily Living
JDS	Japan Diabetes Society
LE	Life Expectancy at birth
NGSP	National Glycohemoglobin Standardization Program
NISSIN Project	New Integrated Suburban Seniority Investigation Project
SPPB	Short Physical Performance Battery
TMIG	Tokyo Metropolitan Institute of Gerontology Index of Competence
WHO	World Health Organization

Chapter 1 The association of gait speed and all-cause mortality and its modifier factor—daily walking

1. Background

⑴ The predictive value of gait speed

With the number and proportion of older populations increasing worldwide, nationally and regionally, functional decline is widely prevalent in older populations. Maintenance of high physical performance has been recognized as one of the essential components of successful aging[43]. Of various assessment instruments for physical performance, gait speed has been demonstrated as a powerful and reliable indicator of functional decline to identify frail or vulnerable elderly persons living in the community[31-33] and may have a screening role in identifying the elderly people at high risk of functional decline or subsequent adverse outcomes. Gait speed, underlies the ability to mobilize, is the basis of independent daily living, and slow gait speed may reflect the effect of chronic conditions, coexisting conditions and physiologic decline which have not yet been diagnosed or caused disability[44].

⑵ Gait speed and health-related outcomes

Gait speed has been reported to be associated with a wide array of adverse health-related outcomes, including disability, cognitive impairment, institutionalization, falls, or/and mortality[44]. Previous studies have shown the predictive value of gait speed that gait speed alone could do as well as a comprehensive summary of physical performance (e.g. SPPB) in predicting the subsequent mortality (Table 1–1)[45-48]. This identifying role of gait speed has encouraged researchers to determine that association among well-functioning elderly toward recognizing the risk of early mortality (Table 1–1)[47-50]. However, the association between gait speed and mortality was well-demonstrated towards different ages of elderly populations in the United States and Europe. To our knowledge, no study in this regard has been conducted among the younger elderly in Japan.

⑶ The modifiable factor for gait speed and all-cause mortality

Over recent decades, greater priority has been placed on preventing or postponing disability and reducing early mortality in the aging population[43]; many modifiable behavioral factors have been reported in conjunction with disability or early mortality, such as physical activity[43,51-53]. Physical activity has been commonly acknowledged to contribute to individuals' health. However, when researchers have adopted gait speed in mortality prediction most previous studies have neglected the modifiable factor of physical activity with only a few cohorts considering the adjustment for physical activity (Table 1–1).

⑷ The aim of the current part

Based on the limitations of these previous studies, the current study is designed to investigate the influence of gait speed on mortality among younger-elderly Japanese; another aim of this study is to determine whether daily walking modifies that association considering that daily walking, which is a popular moderate-intensity physical activity, is easy to implement among the elderly, helps to promote or maintain physical function[54] and decrease mortality[41].

Table 1–1 Gait speed and mortality among the community dwelling old population in previous cohort studies

Authors/ country/ year	Study	Subjects	Predictors	Confounders	Follow up	Outcomes / Results
Cesari et al./ USA/ 2005[49]	Health ABC	3047 well-functioning elderly aged 70-79	gait speed (6m walking test)	age, sex, race, site, smoking, BMI, MMSE, PA, DM, hypertension, cerebrovascular disease	Mean 4.9 yrs	Mortality, <1.0 vs. ≥1.0 m/s:1.64, (1.14, 2.37) Hospitalization; Persistent lower extremity limitation
Rolland et al. /France / 2006[45]	EPIDOS	7,250 non-disabled women aged ≥75	SPPB: walking speed, repeated chair stands, balance tests; handgrip strength	Smoking, physical function, Anthropometric measurements, cognitive performance, sensory status, HD, PA, MU, subjective SAH	Mean 3.8 yrs	Mortality, ≥0.78 vs. ≤ 0.61-0.77m/s: 1.11 (0.89, 1.38); ≥0.78 vs. 0.44-0.60 m/s: 1.52 (1.13, 2.03); ≥0.78 vs. ≤ 0.43m/s: 1.50 (0.97, 2.33); ≥0.78 vs. 0 m/s: 4.15 (1.87, 9.19)
Ostir et al. /USA/ 2007[46]	H-EPESE	1630 Mexican-Americans aged ≥65 yrs	SPPB: standing balance, a short walk, five repetitive chair stands	age, sex, marital status, education, smoking, health status, BMI, depression, cognition	7 yrs	Mortality, ≤ 3.9 vs. 0 s/8feet: 1.82, (1.10, 3.01); ≤ 3.9 vs. ≥9 s/8feet: 1.63, (1.12, 2.39); ≤ 3.9 vs. ≥ 6.0-8.9 s/8feet: 1.29, (0.87, 1.91); ≤ 3.9 vs. ≥ 4.0-5.9 s/8feet:1.28, (0.87, 1.87)
Rosano et al. / USA/ 2008[47]	CHS	3156 well-functioning persons, mean age 70.4 yrs,	the Digit Symbol Substitution Test, gait speed (15-foot course)	age, sex, race, education, cardiovascular disease, brain magnetic resonance imaging abnormalities	≥ 8 yrs	Mortality, <1.0 vs. >1.0 m/s: 0.90, (0.80, 1.00); Disability incidence
Cesari et al./USA/ 2009[48]	Health ABC	3024 well-functioning elderly aged 70-79	Timed gait, repeated chair stands, balance	age, sex, race, site, smoking, drinking, education, BMI, MMSE, PA, HD	Mean 4.9 yrs	Mortality, <1.0 vs. >1.0 m/s:1.49, (1.23, 1.80) Hospitalization; Persistent lower extremity limitation

EPIDOS, the Epide´miologie de l'oste´oporose study; H-EPESE, the Hispanic Established Populations for Epidemiologic Studies of the Elderly; CHS, Cardiovascular Health Study; Health ABC, Health, Aging and Body Composition Study; SAH, self-assessment health status; MMSE, Mini Mental State Examination Score; PA, physical activity, DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; HD, history of diseases; MU, medication use; Results in the outcomes were shown HR/RR(CI).

Table 1–1 Gait speed and mortality among the community dwelling old population in previous cohort studies (continue)

Authors/ country/ year	Study	Subjects	Predictors	Confounders	Follow up	Outcomes/Results
Cesari et al. /USA/2009[55]	H-EPESE	2,139 Mexican-Americans aged ≥65 yrs	gait speed (8-ft walk test), SAH	age, gender, smoking, BMI, MMSE, CES-D, cancer, diabetes, heart attack, stroke, hypertension, ADLs, IADLs	Mean 5.8 yrs	Mortality, ≥0.81 vs. 0.54-0.80 m/s: 1.21, (0.92, 1.60); ≥0.81 vs. 0.29-0.53m/s: 1.40, (1.10, 1.79); ≥0.81 vs. <0.29 m/s: 1.71, (1.29, 2.26)
Dumurgier et al. /France/2009[50]	The Three-City (3C) study	3208 well-functioning persons aged ≥65 yrs,	gait speed (6m walking test)	age, sex, BMI, height, PA, DM, education, MMSE, MU, alcohol, smoking, HD, IADL, Hypertension, depressive symptoms, homocysteine concentration	Mean 5.1 yrs	CVD mortality, Lower vs. upper third: 2.92 (1.46,5.84); All cause-, 1.44 (1.03,1.99); Cancer -, 1.03 (0.65,1.70); Other cause-, 1.41(0.74,2.67)
Studenski et al. /USA/2011[56]	9 pooled cohort studies	34485 persons aged ≥67 yrs	gait speed (8m-6m walking test)	age, height, sex, race, BMI, smoking, SBP, diseases, prior hospitalization, SAH	6-21 yrs	Survival rates, 0.88/0.1m/s (0.87,0.90)
Toots et al. /Sweden, Finland /2013[57]	The Umea 85+ / GERDA study	772 persons aged ≥85 yrs	Gait speed (over 2.4m walking test)	age, sex, care facility resident, lives alone, education, MMSE, depression, HD, hip fracture, MU, number of prescribed drugs, SBP, DBP, vision, or hearing impairment, BMI	5 yrs	Mortality, ≥0.64 vs. 0.50-0.63 m/s: 1.11 (0.76,1.62); ≥0.64 vs. 0.37-0.49 m/s: 1.99 (1.38,2.85); ≥0.64 vs. ≤ 0.36 m/s: 1.97 (1.34,2.88); ≥0.64 vs. unable: 2.27 (1.44,3.59)

EPIDOS, the Epide´miologie de l’oste´oporose study; H-EPESE, the Hispanic Established Populations for Epidemiologic Studies of the Elderly; CHS, Cardiovascular Health Study; Health ABC, Health, Aging and Body Composition Study; SAH, self-assessment health status; MMSE, Mini Mental State Examination Score; PA, physical activity, DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; HD, history of diseases; MU, medication use; Results in the outcomes were shown HR/RR(CI).

2. Methods

2.1 Study population

The present study extracted data from the New Integrated Suburban Seniority Investigation Project (the NISSIN Project) — an ongoing age-specific prospective cohort study. This ongoing age-specific cohort study aimed to provide evidence on early changes in health and related factors in terms of longevity. The community-dwelling elderly residents who were 64 years old at the beginning of the given survey year in a city in central Japan were all invited via letter to take part in a free comprehensive medical checkup and complete a self-administrated questionnaire in June each year from 1996 through 2005. The individual list was obtained from the basic resident registry, and 3073 people (response rate, 43.9%) agreed to register as cohort members. The self-administrated questionnaire included items on demographic and lifestyle characteristics, physical function and quality of life. The medical check-up included height and weight, systolic and diastolic blood pressure, dipstick urinalyses, fecal occult blood, laboratory blood testing, and other clinical tests. All clinical tests were performed at a single laboratory. Physical fitness tests were also conducted, such as the test of gait speed, walking pace, grip strength and so on (Figure 1–2–1.).

The current study attempts to determine the impact of gait speed at the age of 64/65 years on mortality over the subsequent 10 years. The exclusion criteria include those subjects who entered the study after 2003 (617 people) because 10-year follow-up was not complete, those who reported a history of heart disease, cerebrovascular disease, or cancer (437 people) because such diseases may impact gait speed and it is also difficult to regard such subjects as well-functioning younger elderly, and those lacking data on gait speed (four people). Finally, 2105 participants (990 men and 1025 women) were used in the final analyses (Figure 1–2–2).

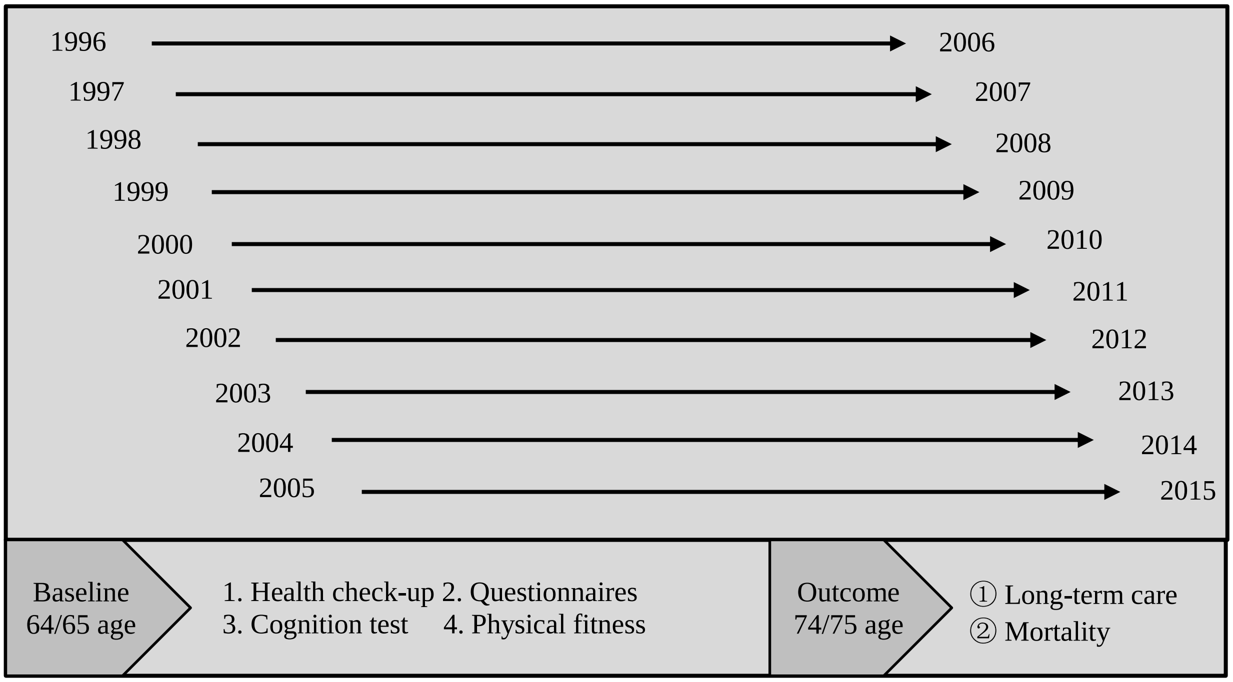

Figure 1–2–1. The flow chart of study design for the current study from the NISSIN Project

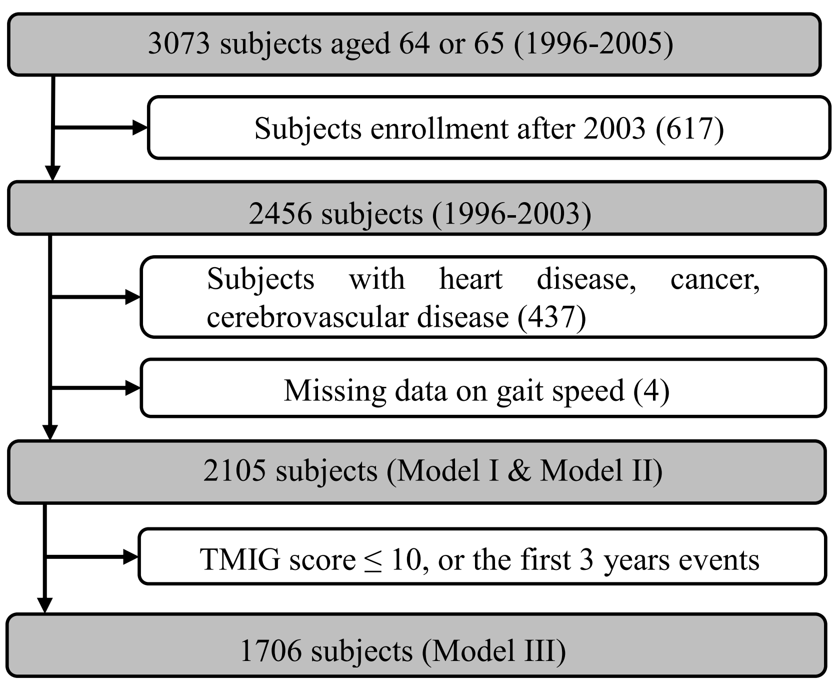

Figure 1–2–2. The flow chart of study population in Chapter 1

2.2 Ethical issues

For the questionnaire survey, oral consent was obtained using an opt-out approach up to 2001; thereafter, written consent was acquired through an opt-in approach. The study protocol was approved by the Ethics Committee of Nagoya University Graduate School of Medicine, the National Center for Geriatrics and Gerontology of Japan, the Aichi Medical University School of Medicine, and Hokkaido University Graduate School of Medicine.

2.3 Baseline assessment

The baseline data were obtained through self-administered questionnaires and objective measurement in the comprehensive health checkup.

2.3.1 Gait speed and daily walking time

Gait speed was assessed with the question "How fast have you walked over the past year?" the response was categorized into three groups—slow, normal, and fast. Daily walking was determined using the question "How many hours a day do you walk?" the options were <30 min/day, 30 min to 1 hour/day, 1–2 hours/day (h/d), and ≥2 h/d. The time spent walking included not only walking as exercise but also time spent working or doing household, social, or other activities.

2.3.2 Covariates

Social and demographic factors included marital status (married, divorce, widow, single, or other), education (up to elementary school, junior high school, high school, junior college, university, or other), and working status (working or not working). Lifestyle factors included smoking status (never, past, or current) and drinking status (never or current). Body mass index (BMI) was calculated by the measured weight divided by the height squared and was categorized into three groups (<18.5, 18.5–24.9, or ≥25 kg/m^2). Medical status included hypertension, hyperlipidemia, and diabetes mellitus. Hypertension was defined as measured systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, self-reported hypertension, or the use of antihypertensive medication. Hyperlipidemia was defined as total cholesterol level ≥220 mg/dl or self-reported hyperlipidemia. Diabetes mellitus was defined as hemoglobin A1C ≥6.5% (NGSP), fasting plasma glucose ≥126 mg/dl, or self-reported diabetes mellitus. In the NISSIN Project, hemoglobin A1c was measured according to Japan Diabetes Society (JDS). We transformed it to

National Glycohemoglobin Standardization Program values (NGSP) based on the conversion formula: NGSP (%) = 1.02 * JDS (%) + 0.25%[58]. Intellectual, physical, and social function capacity was evaluated through the Tokyo Metropolitan Institute of Gerontology Index of Competence, which is a multidimensional scale composed of 13 items: five concerning instrumental independence, four concerning intellectual activity, and four concerning social score; the total possible score ranges from 0 to 13, and a higher score indicates a greater competence level[21]. This index of competence has been adapted and validated in Japan community residents[59].

2.4 Follow-up

The outcome in this study was all-cause mortality. Data relating to the date of death and relocation out of the city were obtained from the basic resident register. All participants were followed until death, relocation, or the last day of the year when they reached the age of 75 years —whichever came first.

2.5 Statistical analysis

Descriptive statistics were used to describe the baseline characteristics of the participants by gender and gait speed. Cox proportional-hazard regression was applied to estimate the hazard ratios (HRs) for all-cause mortality and 95% confidence intervals (CIs) by gender. The proportional hazard assumption was tested with the Goodness of Fit (GOF) Testing approach by calculating the Schoenfeld residuals of gait speed (P=0.670, SAS for 9.4 Microsoft Windows). In multivariate analysis, we created three models to adjust for the potential confounders. Model I adjusted for the survey year; model II adjusted for the confounder in model I plus marital status, working status, education, smoking and drinking status, BMI, and medical status; model III adjusted for all the confounders in model II in the restricted sample (1706 participants) by excluding the participants who had low functional capacity (TMIG scores ≤10) or who died or were otherwise censored within the first 3 years. Analyses were also repeated with regard to stratified daily walking (<1 h/d and ≥1 h/d).

Two-tailed p values were used, and $p<0.05$ was considered to be statistically significant. All the statistical analyses were conducted using JMP Pro 10.0.0 for Microsoft Windows (SAS Institute Inc., Cary, NC, USA).

3. Results

1) The baseline characteristics of the participants

During the total 21,192 person-year follow-up, 188 participants (140 men and 48 women) died. Table 1–3–1 summarizes the baseline characteristics of the subjects in terms of gender and gait speed. Compared with male and female participants with normal gait speed, those with slow gait speed had lower functional capacity. Men with slow gait speed were more likely to smoke, have a greater BMI, have a higher prevalence of diabetes mellitus, and spend little time on daily walking, while women with slow gait speed were characterized by a lower education, were less likely to drink than those with normal gait speed.

2) The association between gait speed and all-cause mortality by gender

The hazard ratio of gait speed for mortality and 95% CI by gender is shown in Table 1–3–2. Slow gait speed was significantly associated with increased all-cause mortality among men after adjustment for survey year (HR, 2.02; 95% CI, 1.30–3.05) (model I). After adjusting for all the confounding factors, survey year, marital status, work status, education, smoking and drinking status, BMI, and medical status (model II), the HR for slow gait speed decreased about 30% and still remained significant (HR, 1.72; 95% CI, 1.08–2.63). In the restricted sample, this association was not substantially altered (HR, 1.81; 95% CI, 1.00–3.09). Among women, slow gait speed tended to be associated with increased mortality risk in both the full (HR, 2.01; 95% CI, 0.98–3.86) and restricted samples (HR, 2.38; 95% CI, 0.96–5.35); fast gait tended to decrease the risk of death in the full (HR, 0.19; 95% CI, 0.01–0.88) and restricted samples (HR, 0.24; 95% CI, 0.01–1.17), although only one case of death occurred.

Table 1–3–1 Gender-specific characteristics of the participants at baseline by gait speed (n=2015)

	Men (n=990)			Women (n=1025)		
	Slow	Normal	Fast	Slow	Normal	Fast
Marital status						
Married	105(92.9)	703(94.9)	127(93.4)	110(75.9)	627(83.0)	101(80.8)
Other	7(6.2)	38(5.1)	9(6.6)	35(24.1)	126(16.7)	23(18.4)
Working status						
Not working	54(47.8)	293(39.5)	57(41.9)	102(70.3)	556(73.6)	91(72.8)
Working	59(52.2)	442(59.6)	77(56.6)	43(29.7)	195(25.8)	34(27.2)
Education						
Junior high school or less	38(33.6)	244(32.9)	26(19.1)	67(46.2)	297(39.3)	30(24.0)
High school	36(31.9)	279(37.7)	55(40.4)	63(43.4)	357(47.3)	72(57.6)
College or more	39(34.5)	217(29.3)	55(40.4)	15(10.3)	101(13.4)	23(18.4)
Smoking						
Never	22(19.5)	142(19.2)	29(21.3)	134(92.4)	687(91.0)	113(90.4)
Past	44(38.9)	331(44.7)	72(52.9)	5(3.4)	35(4.6)	9(7.2)
Current	46(40.7)	268(36.2)	35(25.7)	6(4.1)	33(4.4)	3(2.4)
Drinking						
Never	35(31.0)	237(32.0)	31(22.8)	133(91.7)	608(80.5)	86(68.8)
Current	78(69.0)	504(68.0)	105(77.2)	12(8.3)	147(19.5)	39(31.2)
BMI (kg/m²)						
<18.5	5(4.4)	35(4.7)	5(3.7)	6(4.1)	29(3.8)	7(5.6)
18.5-25	72(63.7)	544(73.4)	109(80.1)	104(71.7)	573(75.9)	105(84.0)
≥25	36(31.9)	162(21.9)	22(16.2)	35(24.1)	153(20.3)	13(10.4)
Medical history						
Hypertension	59(52.2)	393(53.0)	65(47.8)	61(42.1)	312(41.3)	53(42.4)
Hyperlipidemia	29(25.7)	259(35.0)	54(39.7)	83(57.2)	461(61.1)	81(64.8)
Diabetes mellitus	26(23.2)	100(13.5)	25(18.4)	17(11.7)	53(7.0)	9(7.2)
TMIG scores						
≤ 10	29(25.7)	95(12.8)	14(10.3)	22(15.2)	63(8.3)	8(6.4)
> 10	84(74.3)	645(87.2)	122(89.7)	123(84.8)	692(91.7)	117(93.6)
Time spent walking						
< 1 h/d	77(68.1)	375(50.6)	67(49.3)	52(35.9)	259(34.3)	35(28.0)
≥ 1 h/d	36(31.9)	361(48.7)	69(50.7)	92(63.4)	491(65.0)	89(71.2)

Note: the proportions of variables do not equal 100% because of missing data. Values are shown as numbers (%). BMI, body mass index; TMIG, Tokyo Metropolitan Institute of Gerontology Index of Competence. h/d, hours/day.

Table 1–3–2 Association of gait speed and mortality according to gender

	Men			Women		
	Slow	Normal	Fast	Slow	Normal	Fast
Person-years	1109	7710	1412	1537	8082	1341
Death cases	28	94	18	12	35	1
Model I	2.02(1.30,3.05)*	1.00	1.07(0.63,1.73)	1.86(0.92,3.50)	1.00	0.18(0.01,0.82)*
Model II	1.72(1.08,2.63)*	1.00	1.19(0.69,1.95)	2.01(0.98,3.86)	1.00	0.19(0.01,0.88)*
Model III	1.81(1.00,3.09)*	1.00	1.20(0.62,2.15)	2.38(0.96,5.35)	1.00	0.24(0.01,1.17)

HR, hazard ratio. CI, confidence interval. * P< 0.05.

Model I adjusted for survey year;

Model II adjusted for the confounder in Model I and marital status, work status, education, smoking and drinking status, BMI, medical status;

Model III excluded the participants who had low functional capacity, died or were otherwise censored within the first 3 years and adjusted for all the confounders in Model II.

3) The association between gait speed and mortality stratified by daily walking time

Table 1–3–3 presents the HR of gait speed for mortality and 95% CI stratified by the time spent daily walking. For men, participants with slow gait speed and walking less than 1 h/d had significantly increased risk for all-cause mortality compared with subjects with normal or fast gait speed and walking more than 1 h/d after full adjustment (HR, 2.41; 95% CI, 1.40–4.01) (model II). This association remained significant in the restricted sample (HR, 2.68; 95% CI, 1.34–5.10). The association disappeared when men with slow gait speed walked more than 1 h/d (HR, 2.41 vs. 0.98). Among women, however, slow gait speed yielded a threefold greater risk of mortality before and after adjustment for all the covariates when women walked more than 1 h/d compared with the normal- or fast-gait group (HR, 3.04; 95% CI, 1.34–6.49), and this association persisted in the restricted sample (HR, 3.58; 95% CI, 1.31–8.95). Slow gait speed did not cause substantial mortality risk for women walking < h/d compared with the reference group (HR, 1.02; 95% CI, 0.16–3.57).

4) The validity of self-reported gait speed

We examined the validity of self-reported gait speed by analyzing the relationship between self-reported and objective gait speed among 924 of the 2105 subjects (data using the comfortable and usual 10-meter walking test). The mean of the objective gait speed according to self-reported gait speed (slow, normal, and fast) was, respectively, 1.33, 1.39, and 1.52 m/s for men, and 1.28, 1.39, and 1.50 m/s for women. Self-reported gait speed was significantly related to objective gait speed (p<0.0001, one-way analysis of variance).

Table 1–3–3 Association between gait speed and mortality according to gender and the time spent on walking

		Men		Women	
		<1 h/d	≥1 h/d	<1 h/d	≥1 h/d
Person-year	Slow	738	371	548	978
	Normal/fast	4605	4468	3164	6190
Death cases	Slow	23	5	2	10
	Normal/fast	60	51	14	22
Model I	Slow	2.65(1.58,4.30)*	1.09(0.38,2.49)	1.10(0.18,3.77)	2.94(1.32,6.09)*
	Normal/fast	1.10(0.76,1.60)	1.00	1.24(0.62,2.40)	1.00
Model II	Slow	2.41(1.40,4.01)*	0.98(0.34,2.25)	1.02(0.16,3.57)	3.04(1.34,6.49)*
	Normal/fast	1.24(0.85,1.82)	1.00	1.07(0.52,2.12)	1.00
Model III	Slow	2.68(1.34,5.10)*	1.24(0.30,3.52)	0.95(0.05,4.85)	3.58(1.31,8.95)*
	Normal/fast	1.51(0.96,2.40)	1.00	1.01(0.41,2.33)	1.00

HR, hazard ratio. CI, confidence interval. * P< 0.05.

Model I adjusted for survey year;

Model II adjusted for the confounder in Model I and marital status, work status, education, smoking and drinking status, BMI, medical status;

Model III excluded the participants who had low functional capacity, died or were otherwise censored within the first 3 years and adjusted for all the confounders in Model II.

4. Discussion

In this cohort study, it is found that slow gait speed at baseline increased the risk of all-cause mortality among the younger-elderly participants. This association was greater among men who walked less than 1 h/d and disappeared when the men walked more than 1 h/d, though it was greater among women who walked more than 1 h/d.

This is the first age-specific cohort study in Japan to elucidate the effect of gait speed on all-cause mortality among the younger-elderly persons. The main findings are consistent with a number of other studies, which have demonstrated the association between slow gait speed and mortality among elderly subjects living in communities[45,46,50,55,56,60]. In those studies, the participants were aged ≥65[46,50,55,56], ≥75[45], and even ≥ 85 years[57]. With age advancing, gait speed decreases by 12.4% per decade among women and by 16.1% for men[61]. Slow gait speed in different age stage is likely to reflect different functional capacity, therefore the present study adds to the body of evidence about the younger elderly, and we can regard slow gait speed as an indication of aging.

There is as yet no agreement as to whether gait speed among the well-functioning population is associated with mortality. Some studies have found that gait speed could successfully predict subsequent all-cause mortality[45,47] and cardiovascular mortality[50] in the well-functioning elderly; however, another study failed to detect a significant effect of gait speed on mortality among healthy elderly women without disabilities[45]. The well-functioning subgroup with slow gait speed (restricted to those with higher function capacity, no life-threatening diseases, and not excluded by death or being otherwise censored in the first 3 years of the cohort) was indeed at an increased risk of death; however, this association did not reach significance owing to the small sample size. This finding leads us to generalize the identified role of gait speed to the general aging population and encourages us to identify the high risk of mortality in the younger-elderly people to improve longevity. Various possible explanations for this association have been proposed in a number of studies. Walking consumes energy, and it requires movement control, coordination, and the support of multiple organ systems, such as the brain, heart, and lungs, and the circulatory, nervous, and musculoskeletal systems[37,56,62]. When such organ systems are not functioning properly, gait speed becomes slow[37]. Diminished gait speed has been found to be an integrated indicator of organ impairment[44,57]. From a biological perspective, the inflammatory response is correlated with age-related decline in physical performance[63-66] and increasing mortality in the elderly[67]. Furthermore, age-related white matter[68] and gray matter volume of the brain[69], pulmonary function[70], and cognitive functions[71,72] have all been demonstrated as being associated with slow gait speed.

The stratified analyses further highlight the value of intervention strategies based on daily walking. The simultaneous condition of inactivity (walking <1h/d) and slow gait speed produced an approximately threefold increase in mortality risk for younger-elderly men, whereas the risk of slow gait speed on mortality almost disappeared when men walked more than 1 h/d. Although in the present study it was difficult to explain the causal pathway between slow gait speed and inactivity owing to both variables being measured simultaneously at baseline, it was observed that inactivity did indeed strengthen the association between slow gait speed and mortality and physically activity, on the contrary, diluted this association. Poor physical performance (slow gait speed) was more likely to induce a vicious cycle of sedentary behavior[48], and low physical activity partly accounted for mortality[65]. On the other hand, keeping physically active was more possible to improve gait speed, and then decrease subsequent mortality. At the same time, there is mounting evidence to support the direct effect of daily walking on mortality[73-75]. It is suggested that daily walking could be considered an effective modifiable factor in the association between gait speed and mortality among men.

Among women, a different pattern from men was detected. Slower women who walked more than 1 h/d had a threefold higher death risk than those with normal or fast gait speed. This finding adds support to other studies, which have found that elderly women once disabled are more unlikely to recover from disability or frailty than men[76,77]. It is also necessary to consider the definition of daily walking used in the present study. Walking for women included not only walking as exercise but also household activities, which are likely to involve a good deal of their daily time[78]. Household activity has been reported to an important activity which was spent more time on by women and produced energy expenditure for them[79]. One survey on household-related time in Japan found that women spent almost 4 h/day on housework[80]. It may be that the long time spent walking, especially with household activities, may be too vigorous, and represent a risk among women with slow gait speed.

5. Strengths and Limitations

One of the main strengths of this age-specific cohort study was that it completely eliminated age-derived bias[81] because the age of the participants has been reported to be a significant determinant of gait speed changed among the elderly[61]. The present study has the advantage of a long follow-up period from 64- or 65-year-olds to 75-year-olds, which covers the early stage of late life. Moreover, the restricted sample with higher functional capacity and without life-threatening illnesses allowed us to avoid the reverse causal relationship between gait speed and mortality.

There are several important limitations to take into account. First, self-reported gait speed could be the main limitation of the present study. To examine the reliability of self-reported gait speed, the relationship between self-reported gait speed and objective gait speed (using physical fitness test data for 924 of the 2105 participants) was analyzed. We obtained a significant positive association between self-reported gait speed and objective gait speed. Thus, the self-reported gait speed used in this study would appear to be reliable. Second, the small number of deaths after follow-up to age 75 as a result of the average long life expectancy of Japanese limited the powerful, significant association between gait speed and mortality among women. Third, due to our study was observational study other than random clinical trial study, the causal relationship between gait speed and mortality cannot be inferred.

In summary, slow gait speed was associated with an increase in all-cause mortality among the younger-elderly Japanese, and daily walking could modify this association. This study improves our understanding related to establishing an evaluation and screening system for screening younger-elderly people at high risk of functional decline, and encouraging the elderly population to incorporate daily walking to decrease mortality caused by functional declines.

Chapter 2 The health benefits of daily walking on all-cause mortality among the younger-elderly Japanese men

1. Background

⑴ The epidemiology of physical activity

There is mounting evidence that regular physical activity is a good indicator of health-related outcomes later in life[41]. Regular physical activity has been reported to positively contribute to primary and secondary prevention of cardiovascular diseases, cancer, hypertension, diabetes and other chronic disease events[82]. However, age-related declines in physical activity are common[83], especially for elderly people with heart diseases, which restricts their physical activity[82]. The Global Recommendations on Physical activity for Health[84] and Physical Activity Guidelines for Americans (2008)[85] respectively by WHO and U.S. Department of Health and Human Services (USDHH) issued, suggested that the adults at all ages should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or at least 75 minutes vigorous-intensity aerobic physical activity, or the equivalent combination per week; the old adults should keep as physically active as possible based on their chronic conditions and physical abilities if they cannot meet the recommendations. However, about half of adults cannot attain the recommendations in the USA[86], let alone the elderly adults or those with chronic conditions. The U.S. national data showed that only 34% and 16% adults with coronary heart diseases aged 60-69 met the moderate-intensity (duration & frequency, ≥30 minutes/day on ≥5 days/week) and vigorous-intensity (≥20 minutes/day on ≥3 days/week) physical activity recommendations, respectively[87]. Data from the Japan National Health and Nutrition Survey in 2003 and 2012 showed that sedentary lifestyle was extremely common for the elderly, and there was an increasing trend in prevalence of light or moderate intensity physical activity for the elderly population (Figure 2–1).

⑵ The importance of walking

With aging, the elderly are inclined to do moderate-intensity activities (such as walking) instead of high intensity[41,88]. Walking, a preferred moderate physical activity for the elderly because of its relative ease and accessibility, has been paid attention to in the USA since 1990s, when the Centers for Disease Control and the American College of Sports Medicine shifted their emphasis to moderate intensity physical activity[89]. Walking has been encouraged to be incorporated into the daily routines of aging populations to help maintain a physically active lifestyle[90,91], and has even been recommended for patients with existing diseases who are less likely to practice moderate-to-vigorous physical activity[74,92].

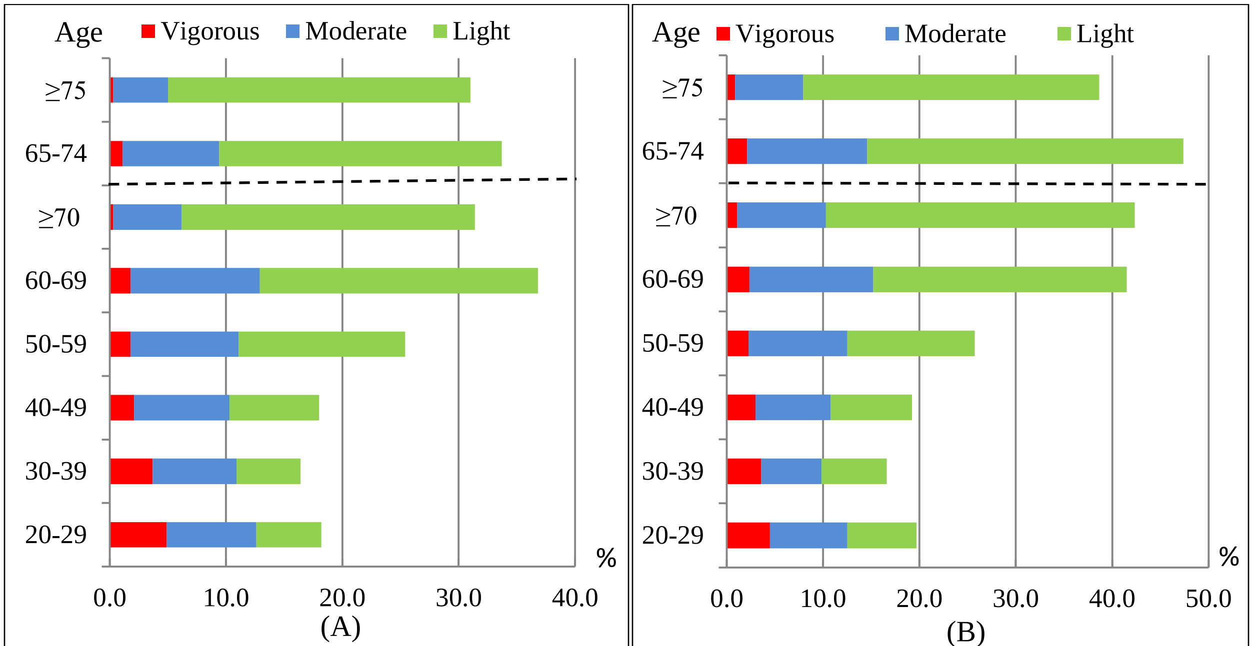

Figure 2–1. The distribution of physical activity intensity according to age in 2003(A) and 2012 (B); data from National Health and Nutrition Survey in 2003 and 2012, Ministry of Health, Labour and Welfare, Japan.

⑶ The limitations of the previous studies in terms of walking

Several reviews and meta-analyses have elucidated an inverse association between walking and cardiovascular disease events among the general population[75,93,94]. The effect of these benefits on all-cause or cardiovascular mortality in elderly population have also been previously demonstrated[73,95,96,97], but some researchers did not specially focus on the elderly populations, for example, in the Harvard Alumni Study, the Health Professional's Follow-up Study, and JACC Study (Table 2–1–1); looking at a broad spectrum of ages might fail to clarify the beneficial effects of walking on health-related issues among the elderly. It is therefore, unreasonable to apply the results observed among younger or middle-aged adults to an older population[98] as pre-existing illnesses in part of the study population might enhance the bias in terms of health outcomes[93]. The studies that took elderly populations as subjects have applied various walking measurements including walking time, distance, frequency and energy expenditure. However, these different indicators may lead to different effects on health-related outcomes (Table 2–1–1). Moreover, although some previous studies have suggested that patients are more likely to obtain health benefits through regular walking[94], data on secondary prevention is still lacking (Table 2–1–2). Examination of these issues can improve our understanding of the role walking may play in the presence or absence of established chronic conditions in an elderly population.

⑷ The objectives of the current part are as follows:

Chapter one concluded that daily walking could modify the association between gait speed and mortality among men rather than women. Therefore, the current study was designed to investigate the health benefits of daily walking on mortality among younger-elderly (aged 65-74 years) men with or without major critical diseases (heart diseases, cerebrovascular diseases, or cancer) to elucidate how walking could aid in successful aging and longevity.

Table 2–1–1 Walking and primary prevention among the community-dwelling old population in the previous studies

Author/ Country/Year	Study	Subjects	Predictors	Confounders	Follow up	Outcomes/Results
Lacroix et al. / USA/ 1996[98]	GHC Study	1645 men and women aged ≥65yrs	Walking time: <1 (ref.), 1-4, >4 h/wk	Age, sex, functional status, smoking status, BMI, AU, chronic disease score, SAH,	Mean 4.2 yrs	Mortality, 1-4: 0.83 (0.53, 1.29); >4: 0.91 (0.58, 1.42); CVD hospitalizations
Wannamethee et al./ UK/ 1998[99]	British Regional Heart Study	4311 men aged 52-73 yrs	Walking time: 0 (ref.), ≤20, 21-40, 41-60, >60 min/day	Age, smoking, BMI, social class, SAH, other types of activity	3 yrs	Mortality, ≤20: 1.15 (0.73, 1.79); 21-40: 1.06 (0.75, 1.50); 41-60: 0.97 (0.65, 1.46); >60: 0.62(0.37, 1.05)
Hakim et al. / USA/ 1998[100]	Honolulu Heart Study	707 nonsmoking retired men aged 61-81 yrs	Walking distance: <0.9, 1.0-2.0, 2.1-8.0 miles/day	Age, HDL-C, DM, AU, hypertension, the overall PA index, preference for a Japanese diet	12 yrs	CHD Mortality, 1.0-2.0 vs. 0-0.9: 1.1(0.4, 2.5); 2.1-8.0 vs. 0-0.9: 2.6 (0.7, 10.3); 2.1-8.0 vs. 1.0-2.0: 2.5 (0.7, 8.6) Cancer-, 2.4 (1.1, 5.4); 1.5 (0.9, 2.7); 1.6 (0.8, 3.4); All cause-, 1.8 (1.2, 2.7); 1.5 (1.1, 2.1); 1.1 (0.8, 1.7)
Hakim et al. / USA/ 1999[101]	Honolulu Heart Study	2678 physical capable elderly men aged 71-93 yrs	Walking distance: <0.25, 0.25-1.5, >1.5 miles/day	Age, TC, HDL-C, Hypertension, DM, AU, performance physical function score, number of years lived in Japan during childhood.	4 yrs	CHD morbidity/ mortality, <0.25 vs. >1.5: 2.3 (1.3, 4.1); 0.25-1.5 vs. >1.5: 2.1 (1.2, 3.6); <0.25 vs. 0.25-1.5: 1.1 (0.7, 1.7)
Sesso et al. / USA/ 2000[96]	The Harvard Alumni Study	12516 men aged 39-88 yrs	Km/wk (block walked): <5, 5-<10, 10-<20, ≥20	Age, other components of PA, BMI, AU, hypertension, DM, smoking status, early parental death (<65 years)	17 yrs	CHD occurrence, not report

GHC, Group Health Cooperative of Puget Sound; HPS, The health professionals' follow-up study; SOF, Study of Osteoporotic Fractures; the Jerusalem Study, the Jerusalem 70-year-olds Longitudinal Study; HDL-C, HDL-cholesterol; DM, diabetes mellitus; AU, alcohol use; TC, total cholesterol; SBP, systolic blood pressure; SAH, self-assessment health status; SES, socioeconomic status; HD, history of diseases; MU, medication use; CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; CRP, C reactive protein.

Table 2–1–1 Walking and primary prevention among the community-dwelling old population in the previous studies (continue 1)

Author/ Country/Year	Study	Subjects	Predictors	Confounders	Follow up	Outcomes/Results
Stessman et al./Israel/ 2000[102]	the Jerusalem Study	456 men and women aged 70 yrs	Walking time: <4 (ref.), around 4 h/wk, ≥1h/d	Gender, smoking, subjective economic hardship, hypertension, DM, coronary artery, cerebrovascular, rental, respiratory diseases, anemia, malignancy	6 yrs	Mortality, around 4: 0.41 (0.19, 0.91); ≥1: 0.14 (0.04, 0.50)
Tanasescu et al./USA/2002[97]	HPS	44452 men aged 40-75 yrs	Walking expenditure: 0-1.19 (ref.), 1.20-3.49, 3.50-6.99, 7.00-14.74, ≥14.75 MET-h/wk	AU, smoking, family history of MI, nutrient intake, DM, high cholesterol levels, hypertension, walking volume, walking pace	2 yrs	Fatal CHD/ nofatal MI occurrence, 1.20-3.49: 1.03(0.85, 1.25); 3.50-6.99: 0.96 (0.78, 1.17); 7.00-14.74: 1.10 (0.90, 1.34); , ≥14.75: 0.90 (0.73, 1.10)
Gregg et al./ USA/2003[103]	SOF	9518 women aged ≥65yrs	Kcal/wk: <70 (ref.), 70-186, 187-419, 420-897, ≥898	Age, smoking, BMI, stroke, DM, SAH, hypertension	12.5 yrs	CVD mortality, 70-186: 0.88(0.73, 1.06); 187-419: 0.66 (0.53, 0.82); 420-897: 0.68 (0.55, 0.84); ≥898: 0.61(0.49, 0.78); Cancer-, 1.08 (0.85, 1.36); 0.89 (0.69, 1.15); 0.90 (0.70, 1.16); 0.85 (0.65, 1.10); All cause-, 0.91 (0.81, 1.02); 0.78 (0.68, 0.88); 0.71 (0.63, 0.82); 0.71 (0.62, 0.82)

GHC, Group Health Cooperative of Puget Sound; HPS, The health professionals' follow-up study; SOF, Study of Osteoporotic Fractures; the Jerusalem Study, the Jerusalem 70-year-olds Longitudinal Study; HDL-C, HDL-cholesterol; DM, diabetes mellitus; AU, alcohol use; TC, total cholesterol; SBP, systolic blood pressure; SAH, self-assessment health status; SES, socioeconomic status; HD, history of diseases; MU, medication use; CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; CRP, C reactive protein.

Table 2–1–1 Walking and primary prevention among the community-dwelling old population in the previous studies (continue 2)

Author/ Country/Year	Study	Subjects	Predictors	Confounders	Follow up	Outcomes/Results
Noda et al./ Japan/2005[73]	JACC Study	73265 men and women aged 40-79 yrs	Walking time: <0.5, 0.5 (ref.), 0.6-0.9, ≥1.0 h/day	Age, gender, sports time, cardiovascular risk factors	Mean 9.7 yrs	CHD mortality, <0.5: 1.34 (0.96, 1.89); 0.6-0.9: 0.89 (0.65, 1.21); ≥1.0: 0.84 (0.64, 1.09); Stroke-,<0.5: 1.37 (1.10, 1.72); 0.6-0.9: 0.80 (0.65, 0.99); ≥1.0: 0.88 (0.74, 1.05)
Smith et al./ USA/2007[95]	the Rancho Bernardo Study	1317 men and women aged 50-90yrs without DM	Walking distance: non (ref.), < 1mile, ≥1 mile walker	Gender, age, smoking, BMI, average drinking/day, exercise, hypertension, triglycerides, HDL-C, history of CHD	10 yrs	Non-CHD CVD mortality, <1: 0.77(0.48, 1.21); ≥1: 0.55(0.32, 0.96); CHD-, 1.14(0.67, 1.94); 1.29 (0.73, 2.28); All cause-, 0.98(0.76, 1.25); 0.89 (0.67, 1.18)
Ueshima et al./ Japan/2010[104]	Shizuoka study	11671 men and women aged 65-84 yrs	walking for transportation: none (ref.), 1-2, 3-4, ≥5 d/wk	BMI, smoking, AU, SES, mental health, SAH, stroke treatment, hypertension, heart disease, cancer, DM, fracture, gastrointestinal/ lung/joint/other diseases	6 yrs	CVD mortality, 1-2: 0.75 (0.59, 1.22); 3-4: 0.59 (0.37, 0.92); 0.68 (0.47, 0.99) Cancer-, 1.00(0.72, 1.40); 0.89 (0.61, 1.31); 0.83 (0.59, 1.15) All cause-, 0.77 (0.63, 0.95); 0.66(0.52, 0.84); 0.68 (0.55, 0.83)

GHC, Group Health Cooperative of Puget Sound; HPS, The health professionals' follow-up study; SOF, Study of Osteoporotic Fractures; the Jerusalem Study, the Jerusalem 70-year-olds Longitudinal Study; HDL-C, HDL-cholesterol; DM, diabetes mellitus; AU, alcohol use; TC, total cholesterol; SBP, systolic blood pressure; SAH, self-assessment health status; SES, socioeconomic status; HD, history of diseases; MU, medication use; CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; CRP, C reactive protein.

Table 2–1–1 Walking and primary prevention among the community-dwelling old population in the previous studies (continue 3)

Author/ Country/Year	Study	Subjects	Predictors	Confounders	Follow up	Outcomes/Results
Jefferis et al./ UK/2014[105]	the British Regional Heart Study	3435 men aged 60-79 yrs	Walking time: 0-3 (ref.), 4-7, 8-14, 15-21, ≥22 h/wk; Walking distance: 0-3(ref.), 4-7, 8-14, >15 miles/wk; Walking pace: slow, ≥ steady average	Age, region, AU, vigorous recreational/ sporting activity, smoking history, social class, TC, HDL-C, triglycerides, SBP, blood pressure MU, BMI, atrial fibrillation, left ventricular hypertrophy, FEV_1, CRP, D-dimer, NT-proBNP	Median 10.9 yrs	First fatal / nonfatal stroke Distance, 4-7: 0.89 (0.60, 1.33); 8-14:1.08 (0.73, 1.59); >15: 0.70 (0.43, 1.15); Time, 4-7: 0.90 (0.61, 1.33); 8-14: 0.66 (0.42, 1.04); 15-21: 0.70 (0.36, 1.36); ≥22: 0.35 (0.14, 0.88);

GHC, Group Health Cooperative of Puget Sound; HPS, The health professionals' follow-up study; SOF, Study of Osteoporotic Fractures; the Jerusalem Study, the Jerusalem 70-year-olds Longitudinal Study; HDL-C, HDL-cholesterol; DM, diabetes mellitus; AU, alcohol use; TC, total cholesterol; SBP, systolic blood pressure; SAH, self-assessment health status; SES, socioeconomic status; HD, history of diseases; MU, medication use; CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; CRP, C reactive protein.

Table 2–1–2 Walking and secondary prevention among the community-dwelling old population in the previous studies

Author/Country /Year	Study	Subjects	Predictors	Confounders	Follow up	Outcomes
Wannamethee et al./UK/ 2000[108]	British Regional Heart Study	772 men aged 52-73yrs with CHD	Walking time: none (ref.), 1-40, or > 40 min/d	Age, smoking, social class, obesity, SAH, history of MI, stroke, DM	5 yrs	CVD mortality: 1-40 min/d, 0.73(0.49,1.09); >40 min/d, 0.48(0.30,0.77); All cause-mortality: 1-40 min/d, 0.77 (0.49,1.22); >40 min/d, 0.39(0.22,0.70);
Smith et al./ USA/2007[95]	the Rancho Bernardo Study	347 men and women aged 50-90yrs DM	Walking distance: non (ref.), < 1miles, ≥1 miles walker	Gender, age, smoking, BMI, average drinking/day, exercise, hypertension, triglycerides, HDL-C, history of CHD	10 yrs	Non-CHD CVD mortality: <1 mile, 1.08 (0.51, 2.30); ≥ 1 mile, 0.19(0.04, 0.86); CHD-mortality: 1.07(0.55, 2.07); 1.05 (0.48, 2.31); All cause-mortality: 1.02(0.70, 1.43); 0.54 (0.33, 0.88)
Hamer et al./ UK/2008[106]	the Scottish Health Survey	837 men and women aged 64.0±9.9 yrs with CVD	Walking: none (ref.), any	Age, sex, social economic group, marital status, BMI, smoking, AU, survey year, mutual adjustment for different types of activity	Mean 5.6 yrs	CVD mortality: Any, 0.63 (0.38,1.05); All cause-mortality : 0.74 (0.53,1.04)

CHD, coronary heart disease; CVD, cardiovascular disease; AU, alcohol use; DM, diabetes mellitus; MI, myocardial infarction; SAH, self-assessment health status; CRP, C reactive protein.

Table 2–1–2 Walking and secondary prevention among the community-dwelling old population in the previous studies (continue)

Author/Country /Year	Study	Subjects	Predictors	Confounders	Follow up	Outcomes
Landi et al./ Italy/2008[74]	Italy/the iISIRENTE Study	248 men and women aged ≥80yrs, frail, very old, without impairment	Walking time: no walk (ref.), walking for 0.5, 1, >1h	Age, gender, functional and cognitive disability, congestive heart failure, hypertension, osteoarthritis, depression, number of medications, BMI, cholesterol, CRP	1yrs	Mortality: 30 min, 0.33(0.07, 1.57); 1h, 0.16(0.04, 0.79); >1h, 0.11(0.02, 0.95)
Ueshima et al./ Japan/2010[104]	Shizuoka Study	men and women aged 65-84 with at least one pre-existing disease: stroke, hypertension, heart disease, cancer, DM, fracture, gastrointestinal / lung/ join/other disease (sample unclear)	Walking for transportation: none (ref.), 1-2, 3-4, ≥5 d/wk	BMI, smoking status, AU, socioeconomic status, mental health, SAH	6 yrs	CVD mortality: 1-2 d/w, 0.48 (0.30, 0.79); 3-4 d/w, 0.76 (0.49, 1.19); ≥5 d/w, 0.71 (0.46, 1.09) Cancer-mortality: 1-2 d/w, 1.02 (0.70, 1.49); 3-4 d/w, 1.11 (0.75, 1.64); ≥5 d/w, 0.77 (0.51, 1.15) All cause-mortality: 1-2 d/w, 0.69 (0.54, 0.88); 3-4 d/w, 0.76(0.59, 0.98); ≥5 d/w, 0.67 (0.52, 0.85)

CHD, coronary heart disease; CVD, cardiovascular disease; AU, alcohol use; DM, diabetes mellitus; MI, myocardial infarction; SAH, self-assessment health status; , CRP, C reactive protein.

2. Methods

2.1 Study population

Data were derived from the NISSIN Project, an on-going age-specific prospective cohort study. Briefly, based on the basic resident registry, community-dwelling elderly who were 64 years old at the beginning of the given survey year in a city in central Japan were invited via letter to take part in a free comprehensive medical examination and complete a self-administrated questionnaire each June from 1996 through 2005. A total of 3073 participants (1548 men, 1525 women) agreed to register as cohort members. (For other background to the research, please refer to chapter 1.) In the present study, only men were chosen because there were few women suffering from critical diseases or dying after 10 years follow-up; 1239 men were selected as the study sample after excluding those who entered the study after 2003 (304 subjects) because their 10-year follow-up had not been completed, and men with missing data on daily walking (5 subjects).

2.2 Ethical issues

Please refer to Ethical issues in chapter one.

2.3 Baseline variables

2.3.1 Daily walking measurement

Walking duration was assessed based on self-reported time spent daily walking by asking “How many hours a day do you walk?” The available options included <30 minutes/day, 30 minutes to 1 hour/day, 1–2 hours/day and ≥2 hours/day. Time spent on daily walking was clearly defined in the questionnaire that included walking for exercise, working, and household, social or other activities. According to the physical activity recommendation from the Ministry of Health, Labour and Welfare of Japan, at least 40 minutes per daily living activity was recommended for the elderly (age 65 or above), regardless of intensity[107]. And the Global Recommendations of Physical Activity for Health suggested that the persons aged 65 or above should do at least 150 minutes of moderate intensity aerobic physical activity throughout the week or increase it to 300 minutes to obtain additional health benefits [84]. Based on the above-mentioned physical activity guidelines, the four categories of daily walking were combined into three categories (<1 hour/day, 1–2 hours/day and ≥2 hours/day).

2.3.2 The definition of major critical diseases

The term "major critical diseases" was defined as any one of the following: heart disease, cerebrovascular disease, or cancer (the three leading causes of death in Japan), which account for more than 50% of the mortality of the elderly aged 65[108]. Information on these diseases was also obtained from the questionnaire where subjects recorded their current treatment situation for existing diseases and the age when the physician diagnosed them with these diseases.

2.3.3 Socio-demographic and lifestyle factors

Socio-demographic and lifestyle factors included marital status, education, work status, smoking status, drinking status (please refer to the categories in chapter 1 for above variables), regular exercise (never, <once/week, ≥once/week), participation in regular sports (yes or no) and sleeping time (<7, 7–8, or ≥8 hours/day).

2.3.4 General health examination

Body mass index (BMI) was calculated and categorized into three groups (<18.5, 18.5–24.9 or ≥25kg/m^2). Medical status included hypertension, hyperlipidaemia, and diabetes mellitus. (With regard to the definition of hypertension, hyperlipidaemia and diabetes mellitus, please refer to chapter 1.) History of disease included self-reported history of clinically recognized chronic bronchitis, neuralgia/osphyalgia, and/or arthritis, and/or medication for these diseases.

2.3.5 Functional capacity

The short-form Geriatric Depression Scale (GDS-15), a self-rating depression-screening tool for the elderly, was used to evaluate the depressive symptom and a total score of 6 or higher was treated as significant depressive tendency[109-111]. For the application of TMIG scores, please refer to chapter 1. Gait speed was used to assess physical function as in previous studies, where it has been applied to evaluate the physical function of elderly populations with intellectual disability[112] and community–dwelling populations[113]. It was categorized into three groups (slow, normal, and fast) by asking "How fast have you walked over the past year?" Although our data were self-reported gait speed rather than objective gait speed, we checked the validity of self-reported gait speed in our previous study[114].

2.4 Follow-up

Dates for death and relocation out of the city were obtained from the basic resident registry. All participants were followed until death from any cause, relocation, or the last day of the year when they reached 75 years of age, whichever occurred first.

2.5 Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics of participants according to time spent daily walking and the morbidity of major critical diseases. If the data were continuous, they were categorized according to standard clinical reference values. A Cox proportional hazard model was applied to estimate the hazard ratios (HRs) for all-cause mortality and 95% confidence intervals (CIs) based on time spent walking for men with or without major critical diseases. The proportional hazard assumption was tested with the GOF Testing approach by calculating the Schoenfeld residuals of daily walking ($P=0.828$, SAS 9.4 for Microsoft Windows). The interaction between daily walking and exercise, or daily walking and sports participation was examined by the likelihood-ratio test. In multivariate analysis, three models were created by adjusting for potential confounders. Model I was adjusted for survey year; Model II included survey year, socio-demographic and lifestyle factors (marital status, working status, education, smoking and drinking status, exercise habits, regular exercise, regular sports, and sleeping time) and BMI; Model III was adjusted for all the confounders in Model II as well as medical status (hypertension, hyperlipidaemia, and diabetes mellitus), history of disease (chronic bronchitis, neuralgia/osphyalgia, and/or arthritis), and functional capacity (gait speed, GDS-15 and TMIG scores). Sensitivity analyses were conducted by excluding subjects who died or that dropped out of the study for any reason (e.g. relocation, refused follow-up) within the first three years (Model IV), or by excluding subjects who were diagnosed with heart diseases, cerebrovascular diseases, or cancer at age 63, 64, or 65 (Model V). The linear trends in the categories of time spent walking was also tested in the Cox proportional hazard models.

All P values were based on two-tailed tests of significance; $P<0.05$ was taken to be statistically significant. All statistical analyses were performed using JMP Clinical 5 for Microsoft Windows (SAS Institute Inc., Cary, NC, USA).

3. Results

1) The baseline characteristics of the participants

During the total 12,829 person-year follow-up, 175 men died. Table 2–3–1 presents the baseline characteristics of the participants according to time spent daily walking and absence or presence of major critical diseases. Of all the1239 men, 253 reported a history of heart diseases (161 events), cerebrovascular diseases (67 events) or cancer (42 events). For men without major critical diseases, those walking ≥2 hours/day were less likely to be married, more likely to smoke, had a lower education level and fewer depressive symptoms compared with men walking <1 hour/day. For men with major critical diseases, those who walked 1–2 hours/day had a higher education level, attended more exercise activities per week and regular sports, had a lower prevalence of diabetes mellitus, walked faster and had fewer depressive symptoms than men in other walking groups.

Table 2–3–1 Baseline characteristics of participants according to daily walking and morbidity of major critical diseases (n=1239)

	Without major critical diseases (n=986)			With major critical disease (n=253)		
	<1 h/d (520)	1-2 h/d (245)	≥2 h/d (221)	<1 h/d (156)	1-2 h/d (54)	≥2 h/d (43)
Marital status						
Married	499(96.0)	228(93.1)	204(92.3)	152(97.4)	54(100.0)	42(97.7)
Other	20(3.8)	17(6.9)	17(7.7)	4(2.6)	-	1(2.3)
Working status						
Not working	222(42.7)	116(47.3)	64(29.0)	78(50.0)	28(51.9)	14(32.6)
Working	295(56.7)	128(52.2)	153(69.2)	74(47.4)	26(48.1)	28(65.1)
Education						
Junior school or less	133(25.6)	69(28.2)	103(46.6)	30(19.2)	15(27.8)	15(34.9)
High school	203(39.0)	84(34.3)	81(36.7)	68(43.6)	16(29.6)	18(41.9)
College or more	184(35.4)	91(37.1)	37(16.7)	58(37.2)	23(42.6)	10(23.3)
Smoking status						
Never	99(19.0)	47(19.2)	48(21.7)	30(19.2)	8(14.8)	6(14.0)
Past	256(49.2)	104(42.4)	85(38.5)	84(53.8)	31(57.4)	25(58.1)
Current	165(31.7)	93(38.0)	88(39.8)	42(26.9)	15(27.8)	12(27.9)
Drinking status						
Never	167(32.1)	71(29.0)	65(29.4)	51(32.7)	19(35.2)	17(39.5)
Current	353(67.9)	174(71.0)	156(70.6)	105(67.3)	35(64.8)	25(58.1)
BMI (kg/m²)						
<18.5	22(4.2)	13(5.3)	10(4.5)	7(5.6)	2(3.7)	1(2.3)
18.5-25	376(72.3)	184(75.1)	162(73.3)	103(66.0)	40(74.1)	29(67.4)
≥ 25	122(23.5)	48(19.6)	49(22.2)	46(29.5)	12(22.2)	13(30.2)

Note: All values shown are in n (%). The proportion of each variable does not always add up to 100% owing to missing data. With or without diseases: heart disease, cerebrovascular disease, or cancer. h/d, hours/day. History of disease: suffering one or more of chronic bronchitis, neuralagia/osphyalgia or arthritis. TMIG: Tokyo Metropolitan Institute of Gerontology Index of Competence. GDS-15: short-form Geriatric Depression Scale.

Table 2–3–1 Baseline characteristics of participants according to daily walking and morbidity of major critical diseases (n=1239) (continue)

	Without major critical diseases (n=986)			With major critical disease (n=253)		
	<1 h/d (520)	1-2 h/d (245)	≥2 h/d (221)	<1 h/d (156)	1-2 h/d (54)	≥2 h/d (43)
Exercise						
Never	214(41.2)	78(31.8)	109(49.3)	67(42.9)	13(24.1)	19(44.2)
<1/week	62(11.9)	22(9.0)	21(9.5)	11(7.1)	2(3.7)	5(11.6)
≥1/week	242(46.7)	145(59.2)	91(41.2)	78(50.0)	39(72.2)	19(44.2)
Regular sports						
No	233(45.1)	98(40.0)	129(58.4)	81(51.9)	19(35.2)	21(48.8)
Yes	281(54.6)	144(58.8)	90(40.7)	74(47.4)	35(64.8)	22(51.2)
Sleeping time						
< 7h/d	243(46.7)	101(41.2)	101(45.7)	64(41.0)	19(35.2)	15(34.9)
7-8h/d	209(41.2)	113(46.1)	89(40.3)	68(43.6)	29(53.7)	23(53.5)
≥ 8h/d	67(12.9)	31(12.7)	31(14.0)	23(14.7)	6(11.1)	5(11.6)
Medical status						
Hypertension	270(51.9)	134(54.7)	110(49.8)	85(54.5)	30(55.6)	23(53.5)
Hyperlipidaemia	182(35.1)	91(37.1)	68(30.8)	46(29.5)	19(35.2)	14(33.3)
Diabetes Mellitus	79(15.3)	50(20.4)	21(9.5)	33(21.2)	12(22.2)	5(11.9)
History of disease	69(13.3)	28(11.4)	25(11.3)	23(14.7)	3(5.6)	5(11.6)
Gait speed						
Slow	77(14.8)	16(6.5)	20(9.1)	29(18.6)	10(18.5)	3(7.0)
Normal	375(72.1)	193(78.8)	168(76.0)	115(73.7)	38(70.4)	34(79.1)
Fast	67(12.9)	36(14.7)	33(14.9)	11(7.0)	6(11.1)	6(14.0)
GDS-15 scores						
<6	415(79.8)	197(80.4)	182(82.4)	113(72.4)	46(85.2)	34(79.1)
≥6	105(20.2)	47(19.2)	35(15.8)	42(26.9)	8(14.8)	9(20.9)
TMIG scores						
≤10	75(14.4)	34(13.9)	27(12.2)	23(9.0)	6(11.1)	9(20.9)
>10	445(85.6)	211(86.1)	193(87.3)	132(84.6)	48(88.9)	34(79.1)

Note: All values shown are in n (%). The proportion of each variable does not always add up to 100% owing to missing data. With or without diseases: heart disease, cerebrovascular disease, or cancer. h/d, hours/day. History of disease: suffering one or more of chronic bronchitis, neuralagia/osphyalgia or arthritis. TMIG: Tokyo Metropolitan Institute of Gerontology Index of Competence. GDS-15: short form Geriatric Depression Scale.

2) The association between daily walking and mortality among men without major critical diseases

Table 2–3–2 summarizes the HRs of daily walking on mortality and 95% CIs for men without major critical diseases. For men without major critical diseases, the risk of death declined linearly as walking duration increased after adjustment for survey year, socio-demographic and lifestyle factors, and BMI (Model II: P for trend=0.008). Further adjustment for medical status, history of diseases, and functional capacity did not alter the initial trend (Model III: P for trend=0.009), and led to a significant association of walking ≥2 hours/day with mortality (HR: 0.49, 95% CI: 0.28－0.80).

Table 2–3–2 Association of daily walking with mortality among men without major critical diseases

	<1 h/d	1-2 h/d	≥2 h/d	P for trend
Person-year	5354	2509	2330	
Death Case	83	36	20	
Model I	1.00	0.95(0.64, 1.39)	0.56(0.34, 0.90)*	0.029*
Model II	1.00	0.89(0.58, 1.32)	0.50(0.30, 0.81)*	0.008*
Model III	1.00	0.93(0.60, 1.39)	0.49(0.28, 0.80)*	0.009*
Model IV	1.00	0.92(0.58, 1.42)	0.40(0.21, 0.69)*	0.002*
Model V[ł]	-	-	-	-

Values shown are HR (95% CI). HR: hazard ratio; CI: confidence interval; h/d: hours/day.

[ł]HR and 95% CI are not shown for men without diseases because it was equal to that in Model III. * P < 0.05

Model I adjusted for survey year;

Model II adjusted for survey year, marital status, working status, education, smoking and drinking status, BMI, regular exercise, regular sports, and sleeping time;

Model III adjusted for the confounders in Model II as well as hypertension, hyperlipidaemia, diabetes mellitus, chronic bronchitis, neuralagia/osphyalgia, arthritis, gait speed, and GDS-15 and TMIG scores;

Model IV excluded subjects who died or were censored within the first three years, and adjusted for all the confounders in Model III. Model V excluded subjects who were diagnosed with heart diseases, cerebrovascular diseases, or cancer at the age of 63, 64, or 65 years and adjusted for all the confounders in Model III.

3) The association between daily walking and mortality among men with major critical diseases

Table 2–3–3 presents the HRs of daily walking on mortality and 95% CIs for men with major critical diseases. For men with major critical diseases, walking 1–2 hours/day showed a significant protective effect on mortality after adjustment for survey year, socio-demographic and lifestyle factors and BMI (Model II; HR: 0.30, 95% CI: 0.09－0.84) compared with walking <1 hour/day. Following adjustment for medical status, history of disease, and functional capacity (Model III), walking 1–2 hours/day was still associated with decreased mortality (HR: 0.30, 95% CI: 0.08－0.91). Walking ≥2 hours/day did not show substantial benefits for mortality in men with major critical diseases after full adjustment for confounding factors (HR: 0.87, 95% CI: 0.26－2.56), and a linear trend was not observed for men with major critical diseases.

Table 2–3–3 Association of daily walking with mortality among men with major critical diseases

	<1 h/d	1-2 h/d	≥2 h/d	P for trend
Person-year	1582	592	462	
Death Case	26	4	6	
Model I	1.00	0.38(0.11, 1.01)	0.83(0.30, 1.92)	0.329
Model II	1.00	0.30(0.09, 0.84)*	0.70(0.24, 1.80)	0.180
Model III	1.00	0.30(0.08, 0.91)*	0.87(0.26, 2.56)	0.338
Model IV	1.00	0.24(0.05, 0.81)*	0.57(0.15, 1.83)	0.104
Model V	1.00	0.21(0.04, 0.91)*	0.77(0.15, 3.20)	0.376

Values shown are HR (95% CI). HR: hazard ratio; CI: confidence interval; h/d: hours/day.

* $P < 0.05$

Model I adjusted for survey year;

Model II adjusted for survey year, marital status, working status, education, smoking and drinking status, BMI, regular exercise, regular sports, and sleeping time;

Model III adjusted for the confounders in Model II as well as hypertension, hyperlipidaemia, diabetes mellitus, chronic bronchitis, neuralagia/osphyalgia, arthritis, gait speed, and GDS-15 and TMIG scores;

Model IV excluded subjects who died or were censored within the first three years, and adjusted for all the confounders in Model III;

Model V excluded subjects who were diagnosed with heart diseases, cerebrovascular diseases, or cancer at the age of 63, 64, or 65 years and adjusted for all the confounders in Model III.

4) The sensitivity analysis

In the sensitivity analyses, after excluding participants who died or were censored within the first three years, walking 2 hours/day was still inversely associated with mortality among men without major critical diseases (Table 2–3–2: Model IV; HR: 0.40, 95% CI: 0.21－0.69), and decreased mortality was observed among those with major critical diseases within the intermediate walking duration of 1–2 hours/day (Table 2–3–3: Model IV; HR: 0.24, 95% CI: 0.05－0.81). After excluding subjects who suffered from major critical diseases at the age of 63, 64, or 65, this association did not change substantially among men with major critical diseases (Table 2–3–3: Model V; HR: 0.21, 95% CI: 0.04－0.91). In addition, any significant interactions on mortality between daily walking and exercise (P=0.221) or participation in regular sports (P=0.257) was not observed.

4. Discussion

After follow-up to the age of 75, it was observed that daily walking was associated with a decreased risk of death for younger-elderly Japanese men, independent of socio-demographic and lifestyle factors, BMI, medical status, history of disease, and functional capacity. There was a linear association between daily walking and all-cause mortality among men without major critical diseases, while there was a peak in benefit at an intermediate level of daily walking for men with major critical diseases.

To our knowledge, this is the first age-specific cohort study to elucidate the effect of daily walking on mortality among younger-elderly men, separating for the presence and absence of heart disease, cerebrovascular disease, or cancer. The findings are consistent with the few existing reports that mortality from cardiovascular diseases[101,105], cancer[100], or all-causes[100,115] among older men decreases with increasing walking distance or duration. Recent evidence suggests that daily walking could protect against all-cause mortality among elderly aged ≥65 years[116]. Physically active participants have been reported to have low levels of inflammatory markers (serum high-sensitivity C-reactive protein and interleukin-6) that might be responsible for cardiovascular disease or other age-related diseases[117]. It is suggested that walking could contribute to improved cardiovascular fitness, reduced body weight and body fat, and decreased resting diastolic blood pressure, as well as influence lipid profiles, clotting factors, and other concomitant risk factors[101,118]. Moreover, circulatory insulin-like growth factor I was reported to be inversely related to time spent walking among men, which may partly account for the protective effects of physical activity against cancer at certain sites in the body[119].

The evidence is still unclear in terms of the benefits of time spent walking on mortality among the elderly with major critical diseases, although the minimum amount and type of physical activity has been advocated by the American College of Sport Medicine and the American Heart Association (ACSM&AHA) for the elderly with chronic conditions to prevent other conditions from developing and assist with therapy for the documented diseases[120]. The findings provide new evidence that an intermediate walking duration (1–2 hour/day) can decrease mortality risk by 70% in younger-elderly community-dwelling men with cardiovascular or cerebrovascular disease, or cancer, while walking for a longer duration (more than 2 hours/day) may not provide many more significant benefits in these men. In the previous studies related to old population, the largest category of daily walking was one hour/day or more and thus the threshold of walking duration in the elderly with major critical diseases might not be identified[74,75,115]. The result is consistent with physical activity recommendations from ACSM&AHA that older people with chronic diseases should tailor their activity plan according to recommendations from physicians to avoid the risk of inappropriate physical activity[120]. There are also some studies concluding the same trend as the current findings regarding the association between physical activity intensity and mortality, though there are no previous studies focusing on the association of walking duration with mortality for older populations with chronic diseases. For example, the British Regional Heart Study has demonstrated that regular light or moderate intensity physical activity such as walking is likely to be sufficient to achieve significant benefits, while sports or vigorous activities conferred no additional benefit for older men with established cardiovascular disease[121] and coronary heart disease[99]. A systematic review concerning cancer survivors showed that decreased mortality from colon cancer was associated with 6 hours of walking per week, and more vigorous exercise may not improve survival[122]. However, any precise mechanism to explain why long duration of physical activity confers no additional benefits for the elderly is still not fully understood[123]. Presumably, in the context of age-related and disease-related heterogeneity in cardiorespiratory capacity, musculoskeletal fitness, medical comorbidities, and performance in activities of daily living, an intermediate walking duration, regardless of walking intensity, might be an optimal amount of time for men with major critical diseases. This amount of time might be appropriate for their capacity to undertake physical activities, while any longer is unlikely to yield any benefits.

5. Strengths and limitations

The age-specific cohort study effectively eliminated the influence of age on mortality because age is a major risk factor for mortality and physical activity practice[41]. An extensive range of adjustments was conducted including socio-demographic and lifestyle factors, BMI, medical status, history of disease, and functional capacity, which isolated, as far as possible, an independent association between daily walking and mortality[89]. That the interaction between walking and exercise, walking and regular sports was checked, and the adjustment for these two kinds of physical activity kept the independent association between walking and all-cause mortality.

Some limitations have to be taken into account. First, as a prospective cohort study rather than a randomized clinical trial, this study has the inherent weakness of all cohort studies and is less likely to show true causality because the health status of the elderly participants might produce certain walking habits at baseline or change the level of daily walking over time, especially for participants with established major critical diseases who may have contraindications to participating in physical activities during the initial stage of disease diagnosis. However, to avoid reverse causality, two approaches were adopted to support this association. The first was to exclude participants who died or were censored within the first three years, thereby eliminating the bias caused by participants at higher risk of death. The second approach was to check the age of diagnosis for cardiovascular or cerebrovascular diseases, and cancer, and then exclude those subjects diagnosed with one or more of these diseases at the age 63, 64, or 65 years, thereby decreasing the possibility that walking duration changed in those with major critical diseases. Second, the sample size for men with major critical diseases was small compared with similar previous studies that involved physical activity in patients with established cardiovascular diseases or cancer and covered a wide range of ages in the elderly. However, the present study paid specific attention to the sub-domain of physical activity – regular walking and the younger-elderly, which as a whole limited the enrollment of subjects. Meanwhile, due to the small sample size of this subgroup, the power of the test may be low, which may lead to the high possibility of type II error. This encouraged us to conduct further studies in the future to understand this association and focus more attention on the younger-old persons with one or more chronic diseases. Third, the data on walking duration came from a self-administrated questionnaire rather than an objective measurement, and the validity of the single-item questionnaire was not conducted. The overestimation on walking duration categories might be a possibility[124]. Finally, information about walking intensity was lacking in our survey; however, this will be addressed in a future study.

In summary, the findings provide suggestion with regards to walking duration for younger-elderly men with or without major critical diseases. Walking for longer periods was associated with a decrease in all-cause mortality for men without major critical diseases, while an intermediate walking duration was beneficial to younger-elderly men with major critical diseases. These findings support the view that daily walking has the potential to contribute to primary and secondary prevention of heart diseases, cerebrovascular diseases, cancer and other diseases, and might be a promising and effective prescription medicine for elderly citizens with chronic conditions. This may also provide evidence for public health recommendations that incorporating regular walking into daily life may contribute to successful aging and longevity. Younger-elderly men with one or more chronic conditions should gradually and regular practice walking based on individual ability and fitness to improve management of existing disease and overall survival.

Conclusions

1) Summary

Chapter one found an inverse association between slow gait speed and increased mortality among the younger-elderly Japanese, and the modifier factor–daily walking. Chapter two concluded that different durations of walking time were necessary for younger-elderly men with or without heart disease, cerebrovascular disease or cancer. More importantly, this result helps us understand the pathway of how daily walking modifies the association between gait speed and mortality among younger-elderly men. All these findings are fundamental and practical for the daily life of the younger-elderly individuals, and are likely to contribute to a healthy aging society, and provide suggestive evidence for future intervention studies.

2) The significance and implications of the study

This study paid attention to the screening tool–gait speed, attempting to identify the younger-elderly people at high risk of functional decline and thus, decreasing subsequent mortality. Gait speed has been regarded as a simple, safe, and accessible screening tool to reflect the subclinical impairment in health status. These findings encouraged us to establish an effective and efficient risk evaluation system to recognize early disabled and frail elderly persons, regardless of self-reported or objective measurement. In particular, considering the rapid and continued growth in the aging population in Japan, screening and monitoring functional decline in the early stage will contribute to independent living and activities, which are the premise of participating in other activities to maintain high quality of life, especially in the period when they live to their 70 age. Living longer is not only adding years to life but also adding life to years.

Daily walking, as one of the common and preferred physical activity in the elderly, plays a crucial role in sustaining independent function and promoting survival. It is and continues to be an effective and accessible way to increase physical activity amount in order to keep an active lifestyle in older people’s late lifespan. Daily walking should be incorporated into the routine life of the older people. The current study extends the evidence and supports the hypothesis that both healthy elderly and frail elderly will obtain health benefits from daily walking. Being active as much as possible will undoubtedly contribute to a healthy aging society globally, nationally or regionally. National physical activity guideline recommendations should take into consideration the practicability of daily walking. In addition, understanding the association between daily walking and mortality is of importance for those countries faced with a forthcoming aging society and struggling to improve the populations' health.

3) Future study

To well understand the association between gait speed and mortality and its modifier factor, I will further explore whether daily walking could contribute to improvement in functional capacity or at least maintenance of functional capacity in the future. And I will find a potential method to conclude the previous evidence that whether, or to what extent physical activity is beneficial for the frail or venerable elderly suffering from different chronic conditions, for example conducting a meta-analysis. Additionally, the above studies encourage me to pay more attention to the subjects who suffered from various diseases at baseline of a cohort study, and explore the benefits they obtained from the following physical activity besides the improvement of survival, such as the promotion of quality of life.

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