Association of trajectory of body mass index with knee pain risk in Japanese middle-aged women in a prospective cohort study: The Japan Nurses' Health Study

Ayumi Ito[1], Kunihiko Hayashi[1], Shosuke Suzuki[2], Yuki Ideno[3], Takumi Kurabayashi[4], Toru Ogata[5], Atsushi Seichi[6], Masami Akai[7], Tsutomu Iwaya[8]

Authors' affiliations

[1] Unit of International and Community Health Sciences, Graduate School of Health Sciences, Gunma University, Gunma, Japan

[2] Faculty of Medicine, Gunma University and Eco-Health Research Group, Gunma Japan

[3] Gunma University Center for Mathematics and Data Science, Gunma, Japan

[4] Department of Obstetrics and Gynecology, Niigata City General Hospital, Niigata, Japan

[5] National Rehabilitation Center for Persons with Disabilities, Saitama, Japan

[6] Mitsui Memorial Hospital, Tokyo, Japan

[7] International University of Health and Welfare, Tokyo, Japan

[8] Nagano University of Health and Medicine, Nagano, Japan

Correspondence: Kunihiko Hayashi, khayashi@gunma-u.ac.jp, +81-27-220-8974

Unit of International and Community Health Sciences, Graduate School of Health Sciences, Gunma University, 3-39-22 Showa-machi, Maebashi, Gunma 371-8514, JAPAN

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Abstract

Objectives

To investigate whether body mass index (BMI) trajectory, lifestyle, and reproductive factors are associated with knee pain risk among middle-aged women.

Design

Prospective study of the Japan Nurses' Health Study (JNHS).

Setting

The JNHS investigates the health of female nurses in Japan. Biennial follow-up questionnaires are mailed to the participants.

Participants

The 7,434 women aged over 40 who responded to the 10-year self-administered follow-up questionnaire.

Primary outcome measure

Self-reported knee pain at the 10-year follow-up was the primary outcome. We analysed BMI (normal or overweight) trajectory data from a baseline survey to the 10-year follow-up survey using group based trajectory modelling. Exposure measurements were BMI trajectory, BMI at age 18, lifestyle variables and reproductive history.

Results

BMI trajectories from baseline to the 10-year follow-up were divided into four groups: remained normal, remained overweight, gained weight or lost weight. At the 10-year follow-up, 1,281 women (17.2%) reported knee pain. Multivariable logistic regression analysis

revealed that compared with the remained normal group, multivariable-adjusted odds ratios (95%CI) of knee pain were 1.93 (1.60-2.33) for the remained overweight group, 1.60 (1.23-2.08) for the gained weight group and 1.40 (0.88-2.21) for the lost weight group. The attributable risk percent (95% CI) of the remained overweight group was 48.1% (37.3–57.0) compared with the reference group of remained normal. Alcohol intake at baseline was significantly associated with knee pain.

Conclusions

The lost weight group had a lower risk than the remained overweight group and the gained weight group, and did not carry statistically significant risks for knee pain. Weight reduction and maintaining a normal BMI in middle age was important for preventing knee pain in women.

Article Summary

Strengths and limitations of this study

- The longitudinal cohort study design provides data regarding 10–year trajectory in body mass index.
- The Japan Nurses' Health Study, a large-cohort study of female nurses, enabled comprehensive analysis, drawing on rich and accurate information regarding health care, reproductive health, and lifestyle.
- We selected knee pain as the primary outcome, whereas many studies have investigated risk factors for knee osteoarthritis and insufficiently examined risk factors

for knee pain.

- Participants were asked to provide their height and weight via self-assessment; we calculated body mass index on the basis of this information.
- We were unable to obtain information regarding the severity or duration of knee pain, or the presence of knee pain at baseline; we therefore excluded women who had been diagnosed with knee osteoarthritis prior to the baseline survey.

INTRODUCTION

Knee pain, along with lower back pain, is one of the most problematic musculoskeletal disorders, and impedes function and affects movement and daily life.[1-4] Knee pain is caused by the age-related weakness of the knee joint, or excessive load on a knee joint, as with knee osteoarthritis (KOA).[5, 6] An example of excessive load on a knee joint is one's own body weight. Furthermore, the load of long-term body weight has a great influence on a knee.[7] Although it is necessary to evaluate changes in body weight over time, when we think of knee pain, few studies have investigated the association of the trajectory of body weight and knee pain. There is a sex difference in the prevalence of knee pain; more women experience knee pain than men.[4, 7] Considering this sex difference in the prevalence of knee pain, it is important to examine associations of knee pain with reproductive and lifestyle factors among women. Moreover, several female reproductive factors were associated with BMI in a prior study,[8] so the association between BMI trajectory and knee pain merits investigation.

KOA is a disease that is typically accompanied by severe knee pain. Many publications have reported risk factors for KOA. Aging and high BMI are well-known factors; other lifestyle (e.g., smoking, alcohol drinking habits and sleep duration) and female reproductive factors are also thought to be associated with KOA.[9-15] Some studies have reported that menopausal status, parity and age at menarche are associated with KOA.[15] However, a systematic review reported no significant associations between female hormonal characteristics and KOA.[16] Risk factors for knee pain in male and female working populations were found to be similar to risk factors for KOA in those same populations.[17]

It has been reported that KOA appears after chronic knee symptoms.[18] We examined knee pain as a primary outcome, because knee pain helps to identify early stage KOA, and pain may appear before the diagnosis of musculoskeletal diseases. We conducted a prospective cohort study on the association between BMI trajectory in middle age, lifestyle, reproductive history and knee pain in middle-aged women.

METHODS

Study population

The Japan Nurses' Health Study (JNHS), which started in 2001, is a prospective cohort study to investigate the effects of lifestyle and health care practices on the health of female nurses in Japan. Participants were female public health nurses, midwives, registered nurses and assistant nurses aged 25 years or older at the time of registration. The JNHS continues through follow-up surveys conducted once every two years by a postal self-administered

questionnaire.[19, 20] The subjects of the current study included 10,667 women over the age of 40 at the 10-year follow-up who responded to the 10-year follow-up surveys. We excluded 142 women who had diagnosed KOA on the baseline survey, 575 women who became pregnant at least once during the 10-year follow-up period, and 2,516 women who had not provided their body weight or height for the calculation of BMI between the baseline survey to the 10 years. The remaining 7,434 women were analysed (Figure 1).

Outcomes and covariates

Knee pain on the 10-year follow-up surveys was the primary outcome. Participants were asked if they were currently experiencing knee pain, to which they responded yes or no. We also collected data regarding age, female reproductive factors and menopausal status, and parity on the 10-year follow-up questionnaire.

The other covariate data used from the baseline survey were lifestyle factors including smoking status, alcohol intake and sleep duration, and female reproductive factor including age at menarche and body weight at age 18 (included as BMI at age 18). To identify the BMI trajectory, weight and height from the baseline survey to the 10-year follow up survey were used. The participants were listed as either never-smokers or ever-smokers (including former smokers and current smokers). Alcohol intake was defined by intake frequency: non-drinkers were those who never drank or drank one to two times per month, light drinkers were those who drank one to two times per week, moderate drinkers were those who drank three to six times per week, and heavy drinkers were those who drank every

day. The participants were divided into three groups based on average sleep duration, regardless of shift pattern: short (< 6 hours per night), moderate (6 to < 7 hours per night) and long (≥ 7 hours per night). For menopausal status, women were classified as premenopausal or postmenopausal; notably, postmenopausal included those who were undetermined (i.e., those undergoing hormone replacement therapy, and those in whom it could not be determined whether they were postmenopausal due to a transitional period). Age at menarche was categorized by tertiles as early (≤ 11 years old), moderate (12 years old) or late (≥ 13 years old). We calculated BMI using the women's self-reported height and weight at age 18 and between the baseline survey and the 10-year follow-up survey. We converted the continuous BMI variable into either normal or overweight prior to drawing the BMI trajectories. BMI <25 kg/m^2 was regarded as normal, and BMI ≥25 was regarded as overweight for all time points. We defined BMI trajectory as the change in BMI from the baseline survey to the 10-year follow-up survey.

Statistical analysis

Data analyses were performed using SAS statistical software, Version 9.4 (SAS Institute Inc., Cary, NC, USA). Group-based trajectory modelling was used to analyse BMI trajectory for indicating the longitudinal changes using PROC TRAJ in SAS.[21, 22, 23] This method is one of finite mixture modelling, where some groups are made around an individual BMI trace.

To examine differences between subjects with and without knee pain, Chi-square tests

were used for nominal variables, and Mann-Whitney U-tests were used for ordinal variables. A logistic regression analysis was conducted to explore the associations between knee pain and BMI trajectory, lifestyle and reproductive factors. We selected all variables for logistic regression analysis (full model) regardless of univariate relationships. We calculated multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs), adjusting for age at the 10-year follow-up survey, and for BMI trajectory, smoking, alcohol intake, sleep duration, menopausal status, parity, age at menarche and BMI at age 18. The attributable risk percent of the remained overweight group was estimated using multivariable-adjusted OR for BMI trajectory, when the reference group was the other groups.

For sensitivity analyses, the analysis excluded women who had self-reported having cancer due to the possible influence on BMI, and the analysis with multiple imputation for the missing BMI data from the 2-year to 8-year follow-up survey were conducted to confirm the results of primary analyses.[24]

The results were regarded as statistically significant when two-tailed p-values were less than 0.05.

Ethical Consideration

Participants were informed of the purpose and procedures of the JNHS. All participants signed consent sheets when they completed the baseline survey. The JNHS study protocol was approved by the institutional review board of Gunma University (Approval No. 101, study protocol = JNHS0101, main JNHS protocol).

Patient and Public Involvement

Patients and the public were not involved this study. The results will not be presented at conferences. The announcement of the publication is expected to be sufficient. We send annual newsletters to all study participants; these newsletters include information regarding JNHS papers that were published in the previous year.

RESULTS

Characteristics of the study population

The characteristics of the study population are shown in Table 1. The mean (SD) age was 53.5 (7.7) years. The mean BMI at age 18 was 21.1 (2.3), and the mean BMI at the baseline survey was 21.8 (2.8). The percentage of those who were overweight based on BMI at the baseline survey was 11.9%, while 88.1% had a normal BMI. At the 10-year follow-up survey, the mean BMI was 22.2 (3.2), overweight BMI was 16.0%, normal BMI was 84.0%. Regarding the four BMI trajectory groups, there were 6,123 (82.3%) women in the remained normal group, 785 (10.6%) in the remained overweight group, 401 (5.4%) in the gained weight group and 125 (1.7%) in the lost weight group (Figure 2). The mean (SD) sleep duration was 6.5 (0.9) hours per night. The mean (SD) age at menarche was 12.6 (1.3) years. The population included 2,673 (36.0%) premenopausal women and 4,761 (64.0%) postmenopausal women.

Prevalence of knee pain and musculoskeletal diseases

A total of 1,281 (17.2%) women with knee pain at the 10-year follow-up survey were identified in the study population (Table 2). Table 2 shows p-values from the chi-square tests for nominal variables and from Mann-Whitney U-tests for ordinal variables to examine the differences between respondents with and without knee pain.

Factors associated with knee pain

Table 2 also shows the associations between knee pain and potential risk factors from multivariable logistic regression. Age at the time of the 10-year follow-up survey was significantly associated with risk of knee pain. Multivariable-adjusted ORs (95% CIs) were 1.29 (1.03–1.61) and 1.57 (1.21–2.04) for women between the age of 50-59 years and age 60 or older, respectively, compared with women between 40 and 49 years old. Multivariable-adjusted ORs were 1.93 (1.60-2.33), 1.60 (1.23-2.08) and 1.40 (0.88-2.21) for remained overweight, gained weight, and lost weight groups, respectively, compared with women in the remained normal group. The attributable risk percent, that is, excess risk fraction, (95% CI) of the remained overweight group was 48.1% (37.3–57.0), 27.5% (-17.0 – 55.1) and 16.8% (-12.3 – 38.4) compared with the reference groups of remained normal, lost weight and gained weight groups, respectively. The association between BMI at age 18 and knee pain was not statistically significant (multivariable-adjusted OR=1.28, 95% CI: 0.98–1.68).

The multivariable-adjusted OR for experiencing knee pain was 1.37 (1.06-1.77) for

heavy drinker compared with non-drinker. There were no statistically significant associations between knee pain and smoking, sleep duration, menopausal status, parity or age at menarche.

We conducted sensitivity analyses, multivariable-adjusted ORs excluded women who had self-reported having cancer were 2.09 (1.70-2.56), 1.62 (1.22-2.15) and 1.40 (0.83-2.37) for the remained overweight, gained weight and lost weight groups, respectively, compared with women in the remained normal group. In another sensitivity analysis, the multiple imputation for the missing BMI data from the 2-year to 8-year follow-up survey showed that multivariable-adjusted ORs were 2.11 (1.78-2.49), 1.62 (1.27-2. 06), and 1.23 (0.93-1.62) for the remained overweight, gained weight, and lost weight groups, respectively, compared with women in the remained normal group.

According to these sensitivity analyses, we confirmed there were no significant differences in the other resulting odds ratios of BMI trajectory using logistic regression.

DISCUSSION

We found that BMI trajectory was a predictive factor for knee pain. Remaining overweight increased the risk of knee pain. It is known that high BMI is associated with knee pain or KOA,[9] and our results were partially in agreement with prior studies. We found that remaining overweight was associated with a 1.9 times increased risk compared with those who remained at a normal weight. The risk of knee pain was increased approximately 1.6 times when the women who were a normal weight became overweight.

232 It cannot be said that there is not knee pain 10 years later if the women were a normal BMI
233 10 years prior. However, if overweight women reduced their weight over 10 years, they were
234 able to decrease the risk of knee pain by 27.5%. Furthermore, remaining overweight group
235 and gained weight group carried statistically significant risks for knee pain, on the other
236 hand, lost weight group did not. This BMI trajectory showed the need to reduce the weight
237 and maintain a normal BMI to help prevent knee pain. There are some studies that have
238 described weight change and its influence on knee pain.[9, 25, 26] Our study showed that a
239 dynamic BMI change was related to knee pain. We found that there was no statistically
240 significant association between BMI at age 18 and knee pain in middle age, and BMI
241 trajectory in middle age was a much stronger predictor of knee pain compared with BMI at
242 age 18, although these results were different from a prior study in men.[27] This
243 phenomenon of knee pain may be caused by loading on the knee joint. The mechanisms of
244 the association between obesity and knee pain constitute a combination of mechanical,
245 structural, metabolic and behavioural changes.[28] Obesity leads to a loss of muscle mass
246 and strength, as well as the accumulation of fat tissue; these factors together contribute to
247 knee joint compression.[29] Conversely, weight loss may improve physical activity level,
248 increase muscle strength, and reduce knee pain-related disability.[30] Our findings suggest
249 that major weight gain or the presence of an overweight status for a long period in middle
250 age are probable risk factors for knee pain. In addition, weight loss and maintenance of
251 normal weight may prevent the development of knee pain. Musculoskeletal pain might
252 impact health-related quality of life.[31] Therefore, the continuous control of body weight

253 in middle age may be effective not only to prevent knee pain, but also to maintain quality
254 of life.

255 The present study had several strengths. First, the present study was a longitudinal
256 cohort study, such that a 10–year trajectory in BMI could be examined. Second, because the
257 JNHS comprises a large cohort study of female nurses, we were able to conduct a
258 comprehensive analysis, drawing on rich and accurate information regarding health care,
259 reproductive health and lifestyle. Third, we selected knee pain as the primary outcome,
260 whereas many studies have investigated risk factors for KOA and insufficiently examined risk
261 factors for knee pain. Knee pain is a prodromal symptom of KOA, it helps us to identify the
262 risk of KOA. However, the present study had two limitations. First, participants were asked
263 to provide their height and weight, which was a self-assessment. We calculated BMI on the
264 basis of this information. Second, we were unable to obtain information regarding the
265 severity or duration of knee pain, or the presence of knee pain at baseline; if we had this
266 information, we could assess the incidence of knee pain from baseline among Japanese
267 female nurses in middle age. However, we excluded women who had been diagnosed with
268 KOA prior to the baseline survey.

269 The prevalence of knee pain in the present study among Japanese nurses (17.2%) was
270 higher than the prevalence of extremity joint pain previously found among the general
271 population of Japanese women (7.0%).[32] In previous studies involving nurses, the
272 prevalence of knee symptoms (including ache, pain and discomfort) ranged from 10.6% to
273 24.7% in the United States, Australia, Korea and Estonia.[33-36] Nurses worldwide are

clearly in at-risk settings for knee symptoms, and consideration must be given to nurses' knee pain. One of the limitations of the present study was the composition of the study population. Nurses may be exposed to different risk factors, such as manually handling patients, hard physical work and high mental pressure because of their working circumstances.[37] Therefore, our findings regarding prevalence may not be generalizable to the general population. However, there is no reason to suspect that the general population of women would differ in the association between the risk of knee pain and BMI trajectory.

Heavy drinkers had a risk for 10-years later knee pain than non-drinkers in this study and the association between alcohol intake and KOA also had shown.[10] There is no convincing explanation about the mechanism of the association between alcohol drinking habit and knee pain.

In conclusion, the lost weight group had a lower risk than the remained overweight group and the gained weight group. From our longitudinal observational study of the 10–year trajectory in BMI, we found that weight reduction and maintaining a normal BMI in middle age was important for preventing knee pain in women. Further studies are needed to indicate the effectiveness of losing weight and maintaining a normal BMI in the prevention of knee pain.

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Authors' contributions

AI analysed the data and drafted the report. KH designed and initiated the study. AI, KH, SS, and YI contributed to the interpretation and discussion of the data and writing of the manuscript. AI, KH, SS, YI, TK, TO, AS, MA, and TI approved the final draft to be published and have agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests

All authors declare that they have no competing interests.

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Data sharing statement

All data relevant to the study are included in the article.

Patient consent

316 Patient consent was obtained.

317

318 **Ethical approval**

319 The JNHS study protocol was approved by the institutional review board of the Gunma
320 University (Approval No. 101, study protocol = JNHS0101, main JNHS protocol; and Approval
321 No. 25-54, study protocol = JNHS0401, detailed study of knee pain).

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Table 1. Age, BMI trajectories, lifestyle variables and reproductive variables for the population of 7,434 women

	N	percentage		N	percentage
Age at the 10-year follow-up			**Menopausal status**		
40s	2,521	33.9	Premenopausal	2,673	36.0
50s	3,166	42.6	Postmenopausal/undetermined	4,761	64.0
≥ 60s	1,747	23.5			
			Parity		
BMI trajectory			0	1,605	21.6
Remained normal	6,123	82.3	1	907	12.2
Remained overweight	785	10.6	2	2,907	39.1
Gained weight	401	5.4	3-8	1,947	26.2
Lost weight	125	1.7	Missing	68	0.9
Smoking			**Age at menarche**		
Never smoker	5,445	73.3	Early (≤ 11 years)	1,598	21.5
Ever smoker	1,936	26.0	Moderate (12 years)	2,148	28.9
Missing	53	0.7	Late (≥ 13 years)	3,641	49.0
			Missing	47	0.6
Alcohol intake					
Non-drinker	4,244	57.1	**BMI at age 18**		
Light drinker	1,143	15.4	Normal (< 25)	6,874	92.4
Moderate drinker	1,311	17.6	Overweight (≥ 25)	363	4.9
Heavy drinker	439	5.9	Missing	197	2.7
Missing	297	4.0			
Sleep duration					
Short	1,093	14.7			
Moderate	3,213	43.2			
Long	2,898	39.0			
Missing	230	3.1			

BMI: body mass index

BMI trajectory: BMI from the baseline to the 10-year follow-up survey

Table 2. Prevalence and multivariate-adjusted odds ratios for knee pain on the 10-year follow-up survey

	Knee pain N = 1,281 N (prevalence %)[*1]	No knee pain N = 6,153 N	p-value	Multivariate-adjustedORs (95% CI)
Age				
40s	316 (12.5)	2,205		reference
50s	580 (18.3)	2,586	**< 0.0001[*2]**	**1.29 (1.03-1.61)**
≥ 60s	385 (22.0)	1,362		**1.57 (1.21-2.04)**
BMI trajectory				
Remained normal	939 (15.3)	5,184		reference
Remained overweight	224 (28.5)	561	**< 0.0001[*3]**	**1.93 (1.60-2.33)**
Gained weight	89 (22.2)	312		**1.60 (1.23-2.08)**
Lost weight	29 (23.2)	96		1.40 (0.88-2.21)
Smoking				
Never smoker	902 (16.6)	4,543	**0.0138[*3]**	reference
Ever smoker	369 (19.1)	1,567		1.14 (0.99-1.32)
Missing	10	43		
Alcohol intake				
Non-drinker	719 (16.9)	3,525		reference
Light drinker	192 (16.8)	951	0.4671[*2]	1.02 (0.85-1.23)
Moderate drinker	212 (16.2)	1,099		0.93 (0.77-1.10)
Heavy drinker	95 (21.6)	344		**1.37 (1.06-1.77)**
Missing	63	234		
Sleep duration				
Short	217 (19.9)	876		1.12 (0.93-1.34)
Moderate	553 (17.2)	2,660	**0.0068[*2]**	reference
Long	463 (16.0)	2,435		0.92 (0.79-1.06)
Missing	48	182		
Menopausal status				
Premenopausal	337 (12.6)	2,336	**< 0.0001[*3]**	reference
Postmenopausal/undetermined	944 (19.8)	3,817		1.24 (0.99-1.54)
Parity				
0	263 (16.4)	1,342		reference
1	145 (16.0)	762	**0.0475[*2]**	0.96 (0.76-1.22)
2	494 (17.0)	2,413		0.90 (0.75-1.07)
3-8	363 (18.6)	1,584		0.99 (0.82-1.20)
Missing	16	52		

Age at menarche				
Early (≤ 11 years)	276 (17.3)	1,322		1.04 (0.86–1.25)
Moderate (12 years)	369 (17.2)	1,779	0.9477*2	reference
Late (≥ 13 years)	630 (17.3)	3,011		1.01 (0.87–1.18)
Missing	6	41		
BMI at age 18				
Normal (< 25)	1,158 (16.9)	5,716	< 0.0001*3	reference
Overweight (≥ 25)	91 (25.1)	272		1.28 (0.98–1.68)
Missing	32	165		

multivariate-adjusted odds ratio (95% confidence interval), adjusted for age at the 10-year survey, BMI trajectory, smoking, alcohol intake, sleep duration, menopausal status, parity, age at menarche, and BMI at age 18

*1: Prevalence of knee pain (%)

*2: Mann-Whitney U-test

*3: Chi-square test

BMI: body mass index

BMI trajectory: BMI from baseline to the 10-year follow-up survey

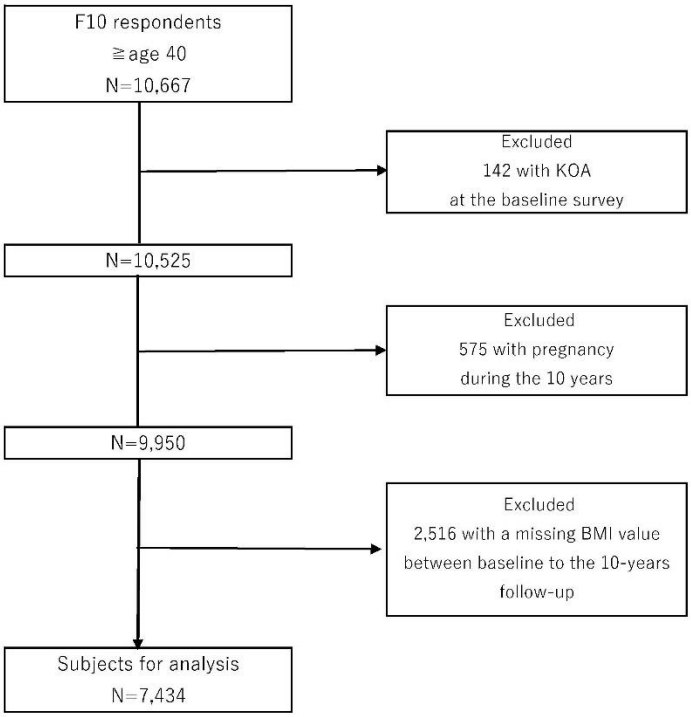

Figure 1. Selection of subjects for our analysis from the Japan Nurses' Health Study. Of the 10,667 women over forty years old who responded to the 10-year follow-up (F10) survey, a total of 7,434 were included in our analysis.

BMI: Body Mass Index

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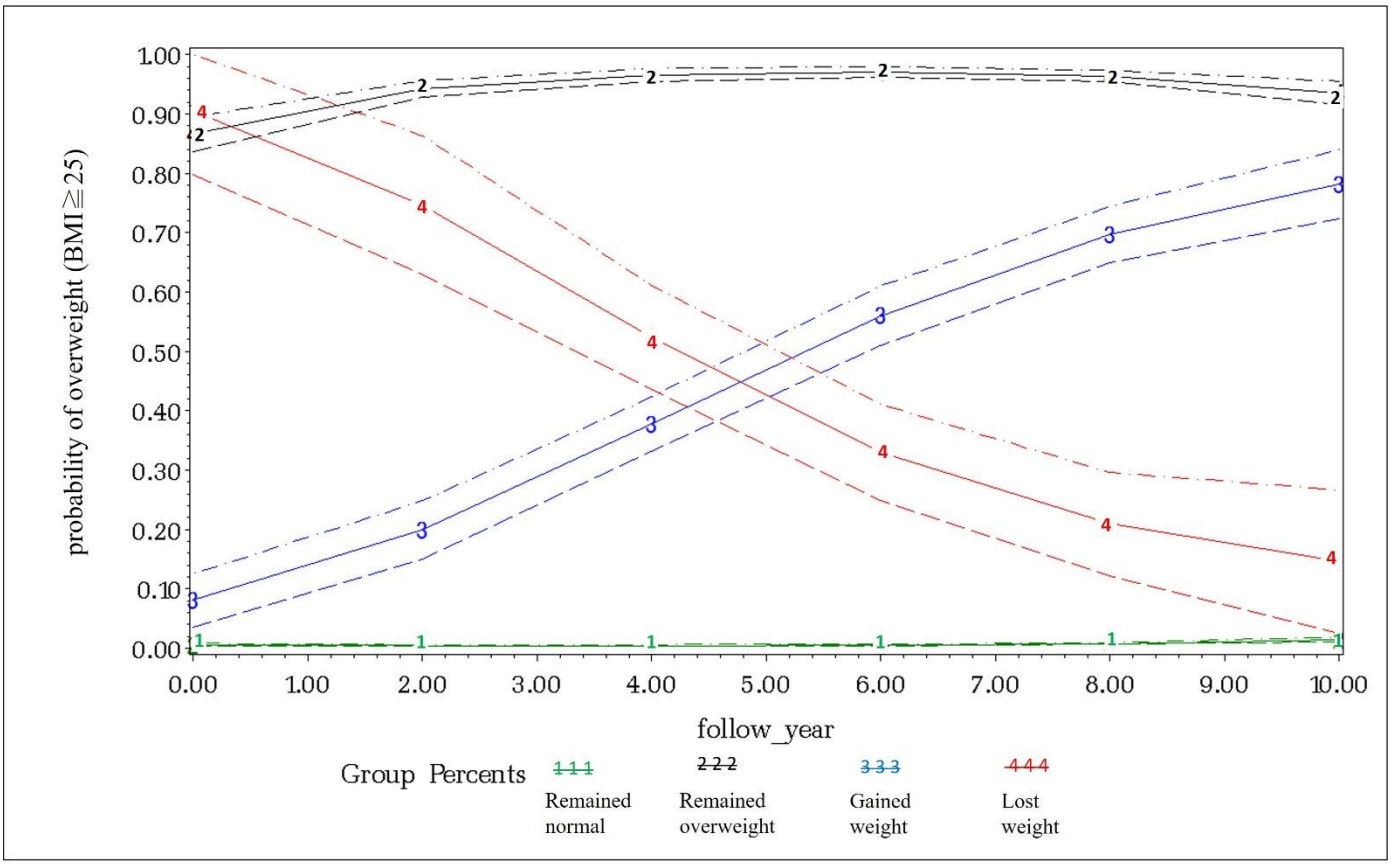

Figure 2. Trajectories of body mass index (BMI) changes.
BMI was converted to binary data - BMI ≥ 25 as overweight was 1.0, and BMI <25 as normal was 0.0.
95% confidence intervals are shown as a dashed line. Overall, 82.3% remained normal weight; 10.6% remained overweight; 5.4% gained weight; 1.7% lost weight.

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