

# Body mass trajectories, diabetes mellitus, and mortality in a large cohort of Austrian adults

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## Abstract

There are only few studies on latent trajectories of body mass index (BMI) and their association with diabetes incidence and mortality in adults.

We used data of the Vorarlberg Health Monitoring & Prevention Program and included individuals (N=24,875) with BMI measurements over a 12-year period. Trajectory classes were identified using growth mixture modeling for predefined age groups (<50, 50–65, >65 years of age) and men, women separately. Poisson models were applied to estimate incidence and prevalence of diabetes for each trajectory class. Relative all-cause mortality and diabetes-related mortality was estimated using Cox proportional hazard regression.

We identified 4 trajectory classes for the age groups <50 years and 50 to 65 years, and 3 for age groups >65 years. For all age groups, a stable BMI trajectory class was the largest, with about 90% of men and 70% to 80% of women. For the low stable BMI classes, the corresponding fasting glucose levels were the lowest. The highest diabetes prevalences were observed for decreasing trajectories. During subsequent follow-up of mean 8.1 (SD 2.0) years, 2741 individuals died. For men <50 years, highest mortality was observed for steady weight gainers. For all other age-sex groups, mortality was the highest for decreasing trajectories.

We found considerably heterogeneity in BMI trajectories by sex and age. Stable weight, however, was the largest class over all age and sex groups, and was associated with the lowest diabetes incidence and mortality suggesting that maintaining weight at a moderate level is an important public health goal.

**Abbreviations:** BIC = Bayesian Information Criterion, BMI = body mass index, CI = confidence interval, FG = fasting plasma glucose, GMM = growth mixture modeling, SD = standard deviation, T2DM = type 2 diabetes mellitus, VHM&PP = Vorarlberg Health Monitoring & Prevention Program.

**Keywords:** body mass index, diabetes, GMM, mortality, trajectories

## 1. Introduction

Health consequences of obesity usually defined by a body mass index (BMI)  $>30\text{kgm}^{-2}$  have been well established. Obesity substantially increases the risk for hypertension,<sup>[1]</sup> type 2 diabetes mellitus (T2DM),<sup>[2]</sup> distorted lipid metabolism, and consequentially of cardiovascular events and mortality.<sup>[3,4]</sup> Whereas low body

mass might be the result of previous weight loss due to disease and is associated with increased mortality,<sup>[5]</sup> especially in older individuals.<sup>[6]</sup> Furthermore, there may be not 1 BMI value where mortality is lowest, but the BMI associated with lowest mortality may change with age.<sup>[7,8]</sup> Studies on weight change and mortality found weight stability to be associated with lowest mortality.<sup>[9,10]</sup> Obesity affects survival besides other mechanisms through disturbed glucose metabolism. Weight gain is associated with T2DM in middle aged adults (40–59 years of age),<sup>[11]</sup> and with impaired fasting glucose (a pre-diabetic state) in young adults (20–39 years of age).<sup>[12]</sup> On the contrary, weight loss may also be associated with T2DM risk,<sup>[13,14]</sup> which, however, might depend on the individuals' baseline BMI.

So far most studies rely on arbitrary chosen categories of weight change<sup>[15]</sup> and may not be able to give a clear picture of underlying trajectories. There are only few studies on latent trajectories and their association with diabetes incidence and mortality in adults.<sup>[16–18]</sup> One reason might be the need for multiple measurements in adequate time distance and a sufficiently long follow-up. By identification of different BMI trajectories, our understanding of underlying etiological processes over life time can be increased.

Thus, it might be a more sensible approach to identify individuals following an unfavorable BMI trajectory instead of stratifying individuals based on their current BMI or short-term weight changes into risk groups. The objectives of our study were to identify long-term BMI trajectories and to appraise them in different age groups regarding their impact on glucose impairment, diabetes related, and overall mortality.

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## 2. Methods

### 2.1. Study population and design

The Vorarlberg Health Monitoring & Prevention Program (VHM&PP) is a population-based risk factor surveillance program in Vorarlberg, the westernmost province of Austria. The program is administered by the Agency of Social and Preventive Medicine. All adults (aged  $\geq 19$  years) within the province were invited by letter, newspaper, radio, and television to participate. Enrolment is voluntary and costs for 1 examination per year are covered by the participant's compulsory health insurance. Between January 1985 and June 2005, 185,316 adult Vorarlberg residents (53.9% female) were enrolled in the VHM&PP study cohort after signing informed consent. Participants were mainly Caucasians. Pregnant women have not been included in the program. Most of the participants have 2 or more registered visits with varying time interval between them.

The program includes a physical examination with measuring of systolic and diastolic blood pressure, height, and weight. The screening examinations take place in the clinics of local physicians according to a standard protocol. Anthropometric measures were carried out by medical staff with participants wearing light indoor clothes and no shoes. Smoking status got documented. Blood samples were taken in fasting state since January 1988. Details of the program and characteristics of the study population have been described previously.<sup>[19,20]</sup>

We included participants of the VHM&PP (1988–2005) for this study in case they provided height and weight measurements within at least 5 consecutive 3-year age-intervals. If 2 measurements for 1 person were available within one 3-year age interval, the measurement closest to the center of the interval was chosen. Of 177,299 participants, 38,193 provided 5 or more measurements, of which 24,875 fitted in the five 3-year interval structure.

Death information was provided by the Vorarlberg Death Registry and was linked to the VHM&PP data. All deaths were identified from death certificates and were confirmed by trained physicians. Follow-up time for mortality started at the date of a participant's last measurement and was censored by December 31, 2009.

Ethical approval was obtained by the Vorarlberg ethic commission (EK-Nr. 2006–6/2).

### 2.2. Statistical methods

**2.2.1. Identification of trajectory classes.** Trajectory classes were identified using growth mixture modeling (GMM).<sup>[21,22]</sup> GMM assumes that there are different subgroups within the population characterized by different patterns of growth, and estimates their trajectory coefficients (intercept, slope). Unlike latent class approaches where individuals belonging to a class have identical trajectories, GMM allows for within-class variation. Each individual is assigned to the latent trajectory class with the highest probability of describing the subject's trajectory.<sup>[23]</sup>

We considered linear and quadratic terms in the GMM to allow for curved BMI trajectories. Furthermore, variances for the intercepts are set free to account for the broad range of BMIs at the first measurement point, whereas the variances for the slopes and the quadratic coefficients have been fixed to be equal across classes for better estimation of the model parameters. The decision on the optimal number of latent trajectory classes was based on the Bayesian Information Criterion (BIC), an often used selection criterion.<sup>[21]</sup> The lowest BIC value indicates the most parsimonious model, that is, the one with a high log likelihood estimate (goodness

of fit) along with a low number of parameters. Other indices such as the AIC and the CAIC were additionally used to check for the best-fitting model, as well as interpretability of the model and not too small class sizes.<sup>[24,25]</sup> All solutions were rerun with many starting values, to confirm stable solutions and avoid local maxima.

We expected trajectories to differ between different periods of adulthood and possibly by sex. Therefore, trajectories were modeled separately for men and women, and for age groups (<50, 50–65, and >65 years), resulting in 6 separate analyses. These age groups were chosen as 50 years is commonly used as cutoff for pre/post-menopausal and 65 years of age to define populations of older individuals. The number of deaths per age-sex group was also part of the consideration, in order to achieve adequate power for the survival analysis. Trajectory classes were ordered by their size within each age-sex group. The biggest class is presented in green, the next largest in yellow, followed by orange and red. We defined trajectories as stable, if the absolute change from one to the following measurement did not exceed  $1 \text{ kg m}^{-2}$  for any of the measurement intervals. This equals about 3 kg weight gain or loss within the 3 years from one measurement to the next for a 1.75 cm tall individual.

**2.2.2. Prevalence and incidence of diabetes.** Diabetes was defined as fasting plasma glucose (FG)  $> 6.9 \text{ mmol L}^{-1}$  ( $125 \text{ mg dL}^{-1}$ ). Poisson models were applied to estimate incidence and prevalence of diabetes at the last (fifth) measurement for each trajectory. Robust variance estimation was used to attain nominal coverage of confidence intervals (95%).<sup>[26]</sup> For the calculation of diabetes incidence, participants with FG  $\geq 5.6 \text{ mmol L}^{-1}$  ( $100 \text{ mg dL}^{-1}$ ) at the first measurement were excluded, as glucose metabolism in these individuals is already impaired.

**2.2.3. Survival analysis.** Relative all-cause mortality and diabetes related mortality by trajectory class was estimated using Cox proportional hazard regression. Models were adjusted for smoking and calculated separately for each age-sex group. Age was used as underlying time scale for all Cox models. Using age as time scale in Cox models effectively controls for age.<sup>[27]</sup> Proportionality of hazards over age was assessed graphically using scaled Schoenfeld residuals. There was no evident violation of the proportional hazard assumption for any of the models.

Diabetes-related mortality included the following underlying causes of death (ICD-10): diabetes (E10–E14, O24), myocardial infarction (I21–I22), ischemic heart disease (I20, I24, I25), stroke or sequelae of stroke (I60–I64, I69.0–I69.4), heart failure (I50), sudden death (I46), peripheral vascular disease (I70–I74), kidney disease (N00–N28), hyperglycemia (R73), hypoglycemia (E16.1–E16.2).

In sensitivity analyses, we modeled the trajectory all-cause mortality association after exclusion of the first 5 years of follow-up and the exclusion of ever-smokers.

GMM were calculated using Mplus version 7 (Muthén & Muthén, Los Angeles, CA). Descriptive and survival analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC).

## 3. Results

Characteristics of the study population can be found in Table 1. Most participants, but also the lowest number of deaths, could be found in the age group <50 years. Mean age in the lowest age group was about 37 years at first measurement and about 49 years at start of mortality follow-up. Mortality follow-up of the highest age group started at 81 years of age and 61% died during subsequent follow-up. Overall, baseline BMI was higher in men than in women.

**Table 1**  
**Characteristics of the study population.**

|  | Men        |                | Women      |               |
|--|------------|----------------|------------|---------------|
|  | M1         | M5             | M1         | M5            |
| <b>&lt; 50 years of age, birth-years: 1938–1973</b>  |            |                |            |               |
| N  |            | 6160           |            | 9164          |
| Subsequent deaths, N, %                              |            | 217 (3.5)      |            | 210 (2.3)     |
| Subsequent follow-up, y, mean, SD                    |            | 8.0 (1.9)      |            | 8.2 (1.8)     |
| Age, y, mean, SD                                     | 37.7 (8.1) | 49.4 (8.1)     | 37.2 (8.4) | 49.0 (8.4)    |
| BMI, kg m <sup>-2</sup> , mean, SD                   | 25.0 (3.1) | 26.2 (3.4)     | 23.4 (4.0) | 25.0 (4.6)    |
| Insurance status, %*                                 |            |                |            |               |
| Blue collar/white collar/other                       |            | 66.0/23.9/10.2 |            | 61.6/31.0/7.4 |
| Smoking, %   |            |                |            |               |
| Current/former                                       | 28.1/12.7  | 22.7/26.3      | 24.4/6.4   | 21.7/15.0     |
| <b>50–65 years of age (birth-years: 1923–1943)</b>   |            |                |            |               |
| N  |            | 3221           |            | 4593          |
| Subsequent deaths, N, %                              |            | 735 (22.8)     |            | 630 (13.7)    |
| Subsequent follow-up, years, mean, SD                |            | 7.8 (2.3)      |            | 8.3 (2.0)     |
| Age, y, mean, SD                                     | 56.9 (4.2) | 68.6 (4.2)     | 57.0 (4.3) | 68.7 (4.2)    |
| BMI, kg m <sup>-2</sup> , mean, SD                   | 26.2 (3.1) | 26.8 (3.6)     | 25.9 (3.9) | 26.8 (4.3)    |
| Insurance status, %                                  |            |                |            |               |
| Blue collar/white collar/other                       |            | 61.4/33.2/7.4  |            | 51.0/46.1/3.0 |
| Smoking, %   |            |                |            |               |
| Current/former                                       | 17.9/20.0  | 12.7/34.3      | 9.3/4.1    | 7.3/8.2       |
| <b>&gt; 65 years of age (birth-years: 1902–1928)</b> |            |                |            |               |
| N  |            | 600            |            | 954           |
| Subsequent deaths, N, %                              |            | 407 (67.8)     |            | 542 (56.8)    |
| Subsequent follow-up, y, mean, SD                    |            | 6.6 (3.1)      |            | 7.4 (2.7)     |
| Age, y, mean, SD                                     | 69.5 (3.6) | 81.1 (3.6)     | 69.2 (3.3) | 80.8 (3.2)    |
| BMI, kg m <sup>-2</sup> , mean, SD                   | 25.9 (3.0) | 25.8 (3.2)     | 25.6 (3.9) | 25.6 (4.2)    |
| Insurance status, %                                  |            |                |            |               |
| Blue collar/white collar/other                       |            | 61.1/35.1/3.9  |            | 48.4/49.5/2.2 |
| Smoking, %   |            |                |            |               |
| Current/former                                       | 13.3/24.0  | 8.8/39.8       | 4.4/2.6    | 3.6/4.7       |

M1 = first measurement, M5 = fifth measurement, SD = standard deviation.

\* Assessed at the last contact with the Agency of Social and Preventive Medicine. Housewives were classified according to their husband's job.

### 3.1. BMI trajectory classes

We identified 4 trajectory classes in men (Fig. 1) and women (Fig. 2) for the age groups <50 years and 50 to 65 years, and 3 for age groups >65 years.

For all age groups a stable trajectory class included the majority of individuals, with about 90% of men and 70% to 80% of women. This trajectory class started in the normal weight (18.5–25.0 kg m<sup>-2</sup>) or lower half of the overweight (25.0–27.5 kg m<sup>-2</sup>) range and remained relatively stable with slight increases over time. In women, we also found a relatively large (10 to 19% of women) stable class with high BMI values around 30 kg m<sup>-2</sup> for each age group. Such a class was not present in men.

The remaining classes started at higher BMI (>27.0 kg m<sup>-2</sup>), showed more pronounced changes and differed in form and size between age groups. However, at least 1 class with weight decrease at some point was present in all age groups of both sexes. Classes with weight increase were observed for all, but the age groups >65 years at baseline.

### 3.2. Fasting glucose levels and diabetes incidence

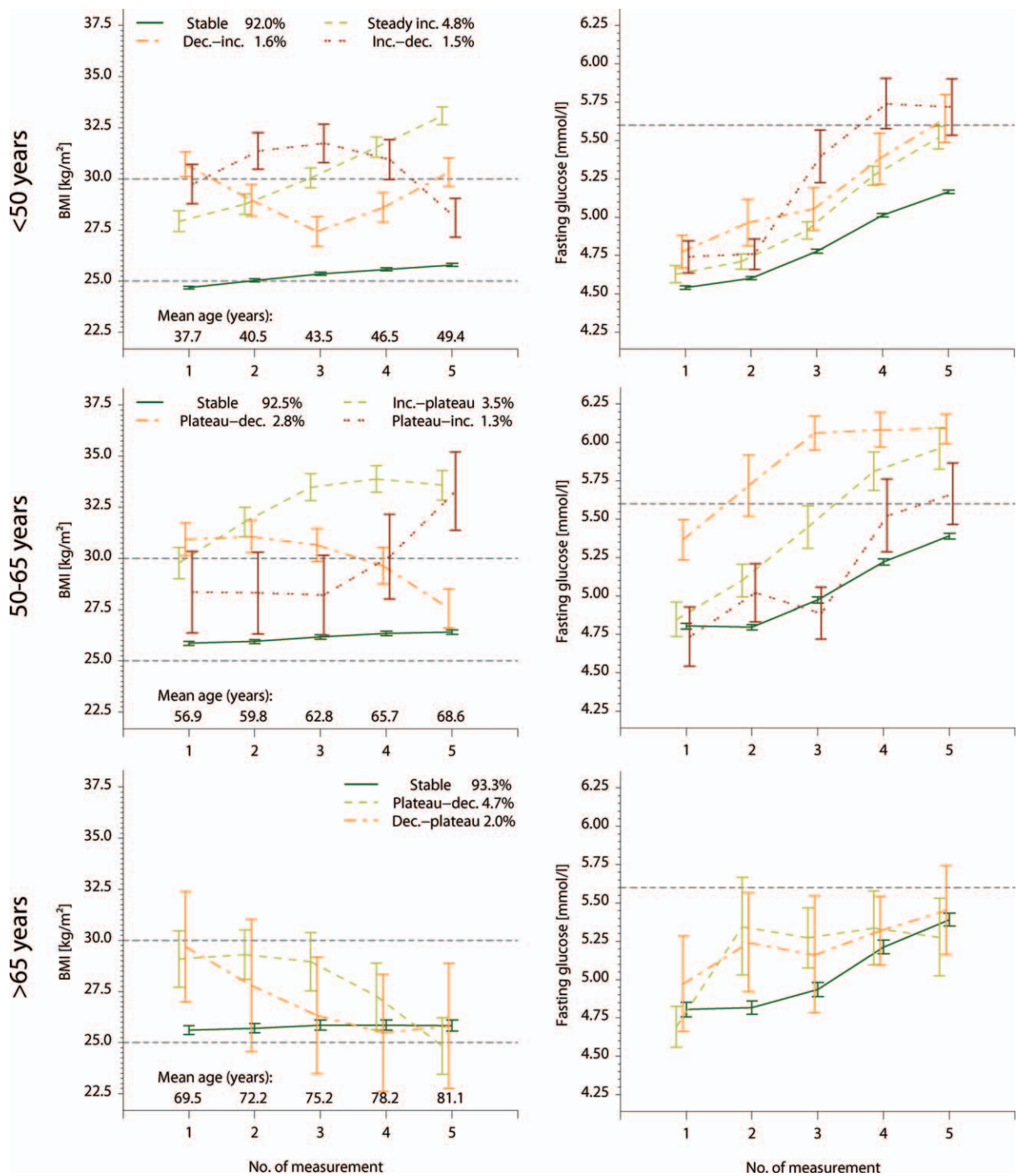
For all classes fasting glucose levels increased with age from measurement 1 to 5. For the low stable BMI class, the corresponding fasting glucose levels were generally the lowest.

Differences in glucose levels of other classes were small for age groups <50 years in men and women, and in men >65 years of age, but clearly differentiated glucose trajectories for men and women in the age group 50 to 65 years and women >65 years of age. For men and women in these age groups, the plateau-decrease class was associated with the highest glucose values, which were on average clearly above the current cut-point for impaired fasting glucose.

Accordingly, the prevalence and incidence of diabetes was lowest in the stable BMI class for each age group in both women and men (Table 2). Also consisted over age groups, the highest diabetes prevalences were observed for classes with BMI decrease during their course (decrease-increase, increase-decrease, and plateau-decrease classes). Differences in diabetes incidence were less pronounced than differences in prevalence between the nonstable classes.

### 3.3. Mortality

During the subsequent follow-up of mean 8.1 (SD 2.0) years, 2741 individuals died, 884 due to diabetes-related diseases. All-cause mortality generally was lowest for the stable BMI class (Table 3). For men in the age group <50 years, the highest mortality was observed for the steady increase class (HR = 2.23, 95% CI: 1.35 – 3.69). In all other groups, mortality was highest for classes with BMI decrease at some point (increase-decrease



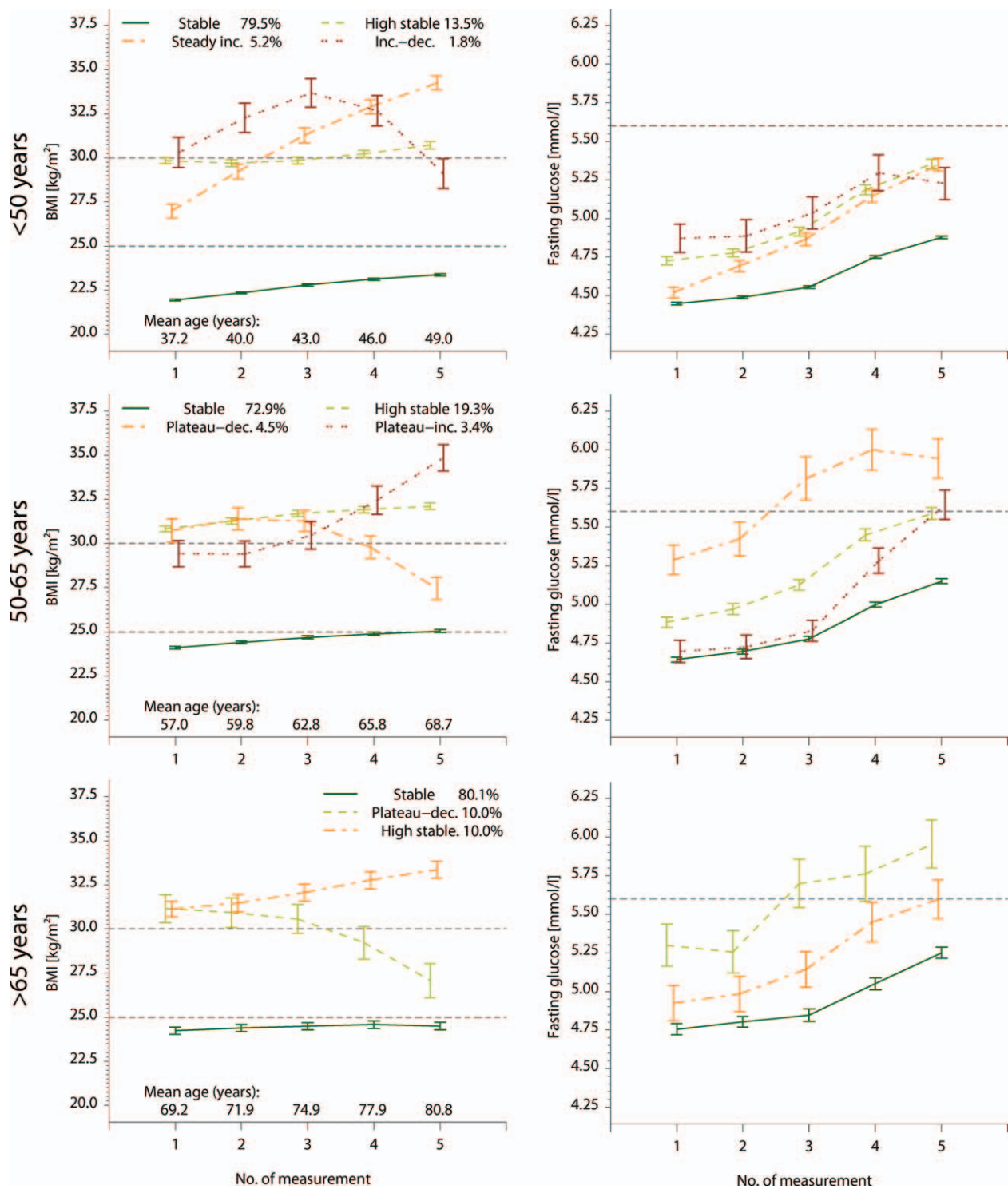
**Figure 1.** Identified BMI trajectory classes (mean BMI values and 95% — confidence limits for the mean) and corresponding geometric mean fasting glucose values by the age group in men. BMI = body mass index.

and plateau-decrease classes). Sensitivity analyses excluding the first 5 years of follow-up or excluding ever-smokers revealed similar associations of BMI trajectories with all-cause mortality (see Tables S1 and S2, Supplemental Content, <http://links.lww.com/MD/B443>).

With regard to diabetes-related mortality, we also observed highest risk for classes with BMI decrease.

#### 4. Discussion

In our large population-based cohort study, we identified 4 distinct trajectories of BMI in a middle-aged population and 3 in an older population. For persons with stable weight, we found the lowest prevalence and incidence of diabetes. However, with increasing age the rates increased. The highest



**Figure 2.** Identified BMI trajectory classes (mean BMI values and 95%—confidence limits for the mean) and corresponding geometric mean fasting glucose values by the age group in women. BMI = body mass index.

prevalence and incidence of diabetes were observed for trajectory classes characterized by BMI decline after a plateau. Concerning diabetes mortality, the highest relative hazards were in men and women under 50 years with increasing and then decreasing BMI. In older age, the class characterized by a plateau or increase followed by a decrease of BMI is associated with increased overall and diabetes mortality.

The analyses revealed sex differences, showing lower initial BMI in men than in women. This observation is in line with other findings concerning trajectories,<sup>[28,29]</sup> but also differences in baseline BMI.<sup>[9]</sup> Men in the stable BMI class were characterized by only little weight gain over time, whereas women in the corresponding class gained more weight over time. Among women below 65 years, we observed a class of persistent obesity

**Table 2** Prevalence and incidence of diabetes at the last (fifth) measurement by sex, age group, and trajectory class.

| Pattern            | Men                                  |                    |                                      |                   | Women                                |                    |                                      |                   |
|--------------------|--------------------------------------|--------------------|--------------------------------------|-------------------|--------------------------------------|--------------------|--------------------------------------|-------------------|
|                    | Prevalence                           |                    | Incidence <sup>a</sup>               |                   | Prevalence                           |                    | Incidence <sup>a</sup>               |                   |
|                    | N <sub>Diab./N<sub>Total</sub></sub> | % (95%-CI)         | N <sub>Diab./N<sub>Total</sub></sub> | % (95%-CI)        | N <sub>Diab./N<sub>Total</sub></sub> | % (95%-CI)         | N <sub>Diab./N<sub>Total</sub></sub> | % (95%-CI)        |
| < 50 years of age  |                                      |                    |                                      |                   |                                      |                    |                                      |                   |
| Stable             | 173/5667                             | 1.5 (1.2 – 1.9)    | 117/5092                             | 1.1 (0.9 – 1.5)   | 68/7287                              | 0.5 (0.4 – 0.7)    | 47/6765                              | 0.4 (0.2 – 0.5)   |
| Steady increase    | 24/297                               | 4.2 (2.7 – 6.5)    | 18/264                               | 3.6 (2.2 – 6.1)   | 94/1239                              | 3.3 (2.4 – 4.6)    | 55/1049                              | 2.0 (1.3 – 3.0)   |
| Decrease–increase  | 18/101                               | 7.6 (4.8 – 12.0)   | 6/82                                 | 3.3 (1.5 – 7.3)   | 23/476                               | 2.6 (1.7 – 4.1)    | 16/440                               | 1.7 (1.0 – 3.0)   |
| Increase–decrease  | 12/95                                | 5.6 (3.2 – 9.8)    | 7/74                                 | 4.4 (2.1 – 9.3)   | 13/162                               | 3.9 (2.3 – 6.9)    | 5/131                                | 1.7 (0.6 – 4.2)   |
| 50–65 years of age |                                      |                    |                                      |                   |                                      |                    |                                      |                   |
| Stable             | 229/2980                             | 7.4 (6.0 – 9.0)    | 109/2467                             | 3.9 (2.8 – 5.3)   | 135/3349                             | 3.0 (2.5 – 3.9)    | 72/2924                              | 1.9 (1.4 – 2.6)   |
| Increase–plateau   | 21/111                               | 18.2 (12.1 – 27.3) | 11/82                                | 12.0 (6.7 – 21.3) | 99/884                               | 8.6 (6.6 – 11.1)   | 51/688                               | 5.7 (4.9 – 8.2)   |
| Plateau–decrease   | 22/89                                | 23.4 (15.5 – 35.3) | 8/53                                 | 12.8 (6.3 – 26.2) | 52/206                               | 18.9 (13.9 – 25.6) | 21/142                               | 11.1 (6.8 – 18.2) |
| Plateau–increase   | 7/41                                 | 16.3 (8.1 – 33.0)  | 4/31                                 | 11.3 (4.3 – 29.6) | 23/154                               | 11.9 (7.9 – 18.0)  | 18/134                               | 10.7 (6.6 – 17.5) |
| > 65 years of age  |                                      |                    |                                      |                   |                                      |                    |                                      |                   |
| Stable             | 45/560                               | 6.4 (4.0 – 10.3)   | 22/456                               | 3.5 (1.8 – 6.5)   | 51/764                               | 6.9 (4.3 – 11.0)   | 62/636                               | 4.9 (2.6 – 9.5)   |
| Plateau–decrease   | 3/28                                 | 8.1 (2.3 – 28.4)   | 2/27                                 | 4.9 (0.9 – 25.8)  | 17/95                                | 18.5 (9.6 – 35.8)  | 9/67                                 | 16.6 (6.6 – 42.0) |
| Decrease–plateau   | 0/12                                 | 0                  | 0/9                                  | 0                 | 13/95                                | 14.0 (7.6 – 26.0)  | 7/76                                 | 10.8 (4.7 – 24.8) |

CI=confidence interval.  
<sup>a</sup>At the last (fifth) measurement.

**Table 3** All-cause and diabetes-related mortality relative to the stable class, by sex and age group.

| Pattern            | Men   |                       |   |                       | Women   |                       |   |                       |
|--------------------|---|-----------------------|---|-----------------------|---|-----------------------|---|-----------------------|
|                    | Prevalence                                      |                       | Incidence <sup>a</sup>                          |                       | Prevalence                                      |                       | Incidence <sup>a</sup>                          |                       |
|                    | N <sub>Death</sub> (N <sub>Diab. rel.</sub> /N) | HR (95%-CI) for death | N <sub>Death</sub> (N <sub>Diab. rel.</sub> /N) | HR (95%-CI) for death | N <sub>Death</sub> (N <sub>Diab. rel.</sub> /N) | HR (95%-CI) for death | N <sub>Death</sub> (N <sub>Diab. rel.</sub> /N) | HR (95%-CI) for death |
| < 50 years of age  |   |                       |   |                       |   |                       |   |                       |
| Stable             | 186 (35)/5667                                   | (ref.) 1.00           | 141 (15)/7287                                   | (ref.) 1.00           | 141 (15)/7287                                   | (ref.) 1.00           | 47 (6)/6765                                     | (ref.) 1.00           |
| Steady increase    | 17 (4)/297                                      | 2.23 (1.35 – 3.69)    | 45 (6)/1239                                     | 2.76 (0.97 – 7.84)    | 45 (6)/1239                                     | 1.22 (0.87 – 1.72)    | 55 (10)/1049                                    | 1.28 (0.49 – 3.35)    |
| Decrease–increase  | 6 (3)/101                                       | 1.68 (0.74 – 3.79)    | 15 (2)/476                                      | 4.51 (1.38 – 14.76)   | 15 (2)/476                                      | 1.52 (0.89 – 2.60)    | 16 (4)/440                                      | 2.03 (0.46 – 9.01)    |
| Increase–decrease  | 8 (4)/95  | 1.53 (0.73 – 3.20)    | 9 (3)/162                                       | 5.06 (1.77 – 14.50)   | 9 (3)/162                                       | 2.26 (1.14 – 4.46)    | 5 (1)/131                                       | 6.60 (1.80 – 24.16)   |
| 50–65 years of age |   |                       |   |                       |   |                       |   |                       |
| Stable             | 640 (190)/2980                                  | (ref.) 1.00           | 420 (129)/3349                                  | (ref.) 1.00           | 420 (129)/3349                                  | (ref.) 1.00           | 72 (22)/2924                                    | (ref.) 1.00           |
| Increase–plateau   | 29 (6)/111                                      | 1.17 (0.80 – 1.70)    | 131 (36)/884                                    | 0.77 (0.34 – 1.76)    | 131 (36)/884                                    | 1.10 (0.91 – 1.34)    | 51 (16)/688                                     | 0.98 (0.68 – 1.42)    |
| Plateau–decrease   | 51 (14)/89                                      | 2.86 (2.15 – 3.81)    | 56 (26)/206                                     | 2.59 (1.50 – 4.46)    | 56 (26)/206                                     | 2.04 (1.54 – 2.69)    | 21 (10)/142                                     | 3.03 (1.98 – 4.62)    |
| Plateau–increase   | 15 (5)/41                                       | 1.68 (1.00 – 2.80)    | 23 (7)/154                                      | 1.97 (0.81 – 4.79)    | 23 (7)/154                                      | 1.54 (1.01 – 2.36)    | 18 (8)/134                                      | 1.83 (0.85 – 3.93)    |
| > 65 years of age  |   |                       |   |                       |   |                       |   |                       |
| Stable             | 371 (155)/560                                   | (ref.) 1.00           | 420 (180)/764                                   | (ref.) 1.00           | 420 (180)/764                                   | (ref.) 1.00           | 62 (26)/636                                     | (ref.) 1.00           |
| Plateau–decrease   | 28 (12)/28                                      | 2.72 (1.84 – 4.01)    | 75 (32)/95                                      | 2.88 (1.59 – 5.22)    | 75 (32)/95                                      | 1.70 (1.33 – 2.17)    | 9 (6)/76  | 1.72 (1.18 – 2.50)    |
| Decrease–plateau   | 8 (4)/12  | 1.28 (0.62 – 2.60)    | 47 (16)/95                                      | 1.49 (0.54 – 4.12)    | 47 (16)/95                                      | 1.28 (0.94 – 1.73)    | 7 (7)/76  | 1.09 (0.65 – 1.83)    |

CI=confidence interval.

(<50 years 13.5% and 50–65 years 19.2%), whereas in men no such group has been identified.

Our observation that stable weight is the largest group is consistent with the literature.<sup>[16,17]</sup> In a 16-year survey of adults aged 51 to 61 years at baseline, 3 classes were identified of which the largest was characterized by stable weight.<sup>[16,30]</sup> Vistisen et al<sup>[17]</sup> followed about 6700 middle aged for a median of 14 years and identified 3 groups, of which the stable overweight group was the largest. In consistency with previous studies, we found a group of progressive weight gainers among participants aged up to 65 years (in men 4.8% and in women 5.2%).<sup>[17]</sup>

Tirosh et al<sup>[31]</sup> investigated the association between BMI from adolescents to adulthood and diabetes risk. They found that diabetes risk is mainly associated with increased BMI close to the diagnosis of diabetes. Dahl et al<sup>[29]</sup> found higher mean BMI and a steeper increase in BMI until the age of 65 years to be strongly associated with T2DM.

Our observation that in age up to 50 years a steady increase of BMI is associated with increased mortality is consistent with the finding by Hirko et al<sup>[32]</sup> They investigated the association between adolescent BMI and mortality in a cohort with average age about 52 years and BMI at baseline around 30 kg m<sup>-2</sup>. In their study, risk of premature death later in life that was driven largely by a higher risk of death from cardiovascular disease and other noncancer diseases.<sup>[32]</sup> Song et al<sup>[33]</sup> studied body shape trajectories from age 5 to 50 years and found that individuals maintaining a stable lean body shape had the lowest mortality. In line with previous observations, we found that in the age over 50 years, patterns with a final decrease of BMI are associated with increased mortality.<sup>[10,16,18,28]</sup> There is evidence that participants losing weight may have experienced substantial poorer health at baseline.<sup>[16,34]</sup> Dahl et al<sup>[29]</sup> found that women with T2DM had a steeper decline in BMI.<sup>[29]</sup> However, the observed associations with all-cause mortality remained stable when excluding the first 5 years of follow-up or when restricting the analysis to never-smokers.

Our study has some limitations. Our study population is likely to be healthier than the general population, as it only includes individuals living long enough to attend at least 5 consecutive measurements. We were unable to distinct between type 1 and type 2 diabetes. The high diabetes related mortality among participants aged 50 year or younger could be due to type 1 diabetes. Time between the measurements was on average about 3 years, limiting information about changes in between. Our definition of diabetes-related mortality was less strict than other proposed definitions,<sup>[35]</sup> as only data on underlying cause but not contributing causes of death were available. Investigating life-course trajectories is methodologically challenging. Analyzing deaths directly caused by diabetes (ICD-10: E10–E14, O24) was also not possible due to low numbers per age-sex group (n=2 to 21).

We applied growth mixture models to identify distinct BMI classes, which have several strengths, in particular allowing for latent nonlinear growth curves and within-class variation. To explore BMI trajectories different statistical methods such as hierarchical clustering,<sup>[36]</sup> linear spline models,<sup>[30]</sup> semiparametric mixture models,<sup>[28]</sup> linear mixed-effects model have been used,<sup>[17]</sup> which may have influenced the observed patterns and number of classes. Zheng et al<sup>[18]</sup> identified 6 latent BMI trajectories in a US study including 9,538 adults aged 51 to 77 years. Botosaneanu et al. identified 5 subgroups in 10,314 adults in the mean age of 56 years.<sup>[28]</sup>

A strength of our study is that we were able to explore BMI trajectories by sex in different age groups in 1 cohort.

Interestingly, except for the stable class, the trajectories differed by sex and age groups. Another strength of the VHM&PP study is that measured instead of self-reported height and weight was used to calculate BMI. In addition, the follow-up of the cohort was about 8 years from the last measurement and 19.8 years from the first measurement.

In conclusion, we found considerably heterogeneity in BMI trajectories by sex and age. Stable weight, however, was the largest class over all age and sex groups, and was associated with the lowest risk for incident diabetes and death suggesting that maintaining weight at a moderate level is an important public health goal.

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