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Prospective Study of Ageing Trajectories in the European DO-HEALTH Study

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Healthy ageing · Successful ageing · Ageing trajectories

Abstract

Introduction: Ageing trajectories range from delayed ageing with extended health to accelerated ageing, with an increased risk of frailty. We evaluated the prevalence and prospective change between health states among community-dwelling European older adults. ***Methods:*** This prospective study is a secondary analysis of DO-HEALTH, a randomized trial that included adults aged 70 years and older across 5 European countries. Healthy agers (HA) fulfilled the Nurses' Health Study healthy ageing criteria and accelerated agers were non-HA being at least pre-frail according to the Fried frailty criteria. We assessed the proportion of participants changing between health states over 4 assessments and evaluated the odds of changing to a more favourable category. To increase reliability and avoid regression to the mean, we averaged the first 2 years and compared them to the average of the last 2 years. ***Results:*** Of 2,157 participants, 12.4% were excluded for meeting both healthy ageing and pre-frailty criteria simultaneously. Among the remaining 1,889 participants (mean age 75.1 years, 60.9% female), 23.1% were initially HA, 44.4% were non-HA but not pre-frail, and 32.6% were pre-frail or frail. Subsequently, 65.3% remained in the same health state, 12.0% improved to a healthier state, and 22.8% progressed to a less advantageous state. After adjusting for sex, study centre, treatment, and body mass index, each year of age was associated with 6% lower odds of improving health states. Women had 35% higher odds than men of following a disadvantageous trajectory. ***Conclusion:*** We observed dynamic trajectories of ageing where transitioning to a healthier state became less likely with advancing age and among women.

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A list of the members of the DO-HEALTH research group is provided as online supplementary material 2 at www.karger.com/doi/10.1159/000523923.

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Introduction

The European population is ageing rapidly; by 2050, nearly one-third of all Europeans will be over 60 years [1]. This development presents a substantial challenge to society as one-fifth of the current global burden of disease originates from conditions developed in people over 60 years [1]. There is thus an imminent need to promote a healthy way of ageing.

As a general concept, "healthy ageing" describes the ideal status of ageing while maintaining independence and quality of life in older adults while simultaneously delaying premature ageing and incident frailty. Although the research community has still to reach consensus on a precise definition, the Nurses' Health Study (NHS) definition [2] is widely accepted. It describes "healthy ageing" as a status of no major chronic diseases (i.e., cancer – except non-melanoma skin cancer– diabetes, myocardial infarction, coronary artery bypass graft surgery, congestive heart failure, stroke, kidney failure, chronic obstructive pulmonary disease, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis), no disabilities, no cognitive impairment, and no mental health limitation. In contrast, frailty is a state of vulnerability for negative health outcomes [3]. According to Fried et al. [4], pre-frailty is defined as the presence of at least one and frailty is defined as the presence of three or more of the following symptoms: unintentional weight loss, exhaustion, low physical activity, slow walk time, and weak grip strength.

The start and progression of health deterioration varies between individuals [5]. One of the best ways to assess ageing, as a dynamic process, is by long-term trajectories of functioning [5–7]. Multiple studies reported stable or declining trajectories of ageing and physical functioning [8–12], but only a few observed trajectories improved to healthier states [13–15].

The objective of our study was to assess the trajectories between healthy ageing status and frailty, including not only the progression in health deterioration but also improvement from unhealthier to healthier states, among community-dwelling adults 70 years and older without major comorbidities over 4 years of follow-up. To address this research gap, we evaluated the transitions between healthy ageing and frailty and compared the differences between age groups and sex using data from the large and extensively phenotyped DO-HEALTH population.

Methods

Study Population

This is a secondary analysis of the multicentre, randomized clinical trial DO-HEALTH, designed to evaluate the effects of omega-3, vitamin D, and a home strength exercise programme on six primary outcomes (ClinicalTrials.gov Identifier: NCT01745263) [16]. Participants were 2,157 community-dwelling older adults 70 years and older from Switzerland (Zurich, Basel, Geneva), Austria (Innsbruck), Germany (Berlin), France (Toulouse), and Portugal (Coimbra) recruited between November 2012 and November 2014. Assessments included 4 clinical visits and 9 phone calls over 3 years. While participants with major health events (i.e., cancer, angina pectoris – stable or unstable – myocardial infarction, stroke, severe kidney or liver disease) in the previous 5 years were excluded. By design, 40% of the population had at least one prior fall; therefore, the trial aimed to include not only healthy older adults but also people who could be pre-frail. The participants were recruited through different community services, media, public events, educational programmes, and healthcare. Detailed inclusion and exclusion criteria as well as the recruitment process are described elsewhere [17]. This study was approved by the Ethics Committee of Zurich (BASEC-No. 2018-01767).

Measures

Participants completed extensive clinical visits every year including physical examinations by trained study nurses and medical doctors following standardized procedures in each study centre. Clinical and sociodemographic characteristics included body mass index (BMI), age, and the level of education. In addition, participants were asked about their regular physical activity engagement ("In an average week, how many days do you usually exercise, including brisk walking or more strenuous activity"?) [18]. We classified participants into high (≥3 times a week), medium (1–2 times a week), and low physical activity (none) to approximate the recommendations of the World Health Organization [19].

Healthy Ageing Status

We assessed healthy ageing based on the assessment of mental, physical, and cognitive function as proposed in the NHS healthy ageing definition [2]. "Healthy agers" where those participants who fulfilled all of the following conditions:

1. no major chronic diseases based on the Sangha self-administered comorbidity questionnaire [20],
2. Montreal Cognitive Assessment (MoCA) score ≥25 [21],
3. no mental health problems based on the Geriatric Depression Scale (GDS-5) score <2 [22] and no diagnosis of depression, and
4. no limitations in basic and moderate activities of daily living as well as no more than moderate limitations on more demanding physical performance measures based on the PROMIS-Haq questionnaire [23].

Frailty Status

Based on the Fried frailty phenotype [4], "at least pre-frail" participants were those presenting at least one of the following symptoms:

1. significant unintentional weight loss (self-reported, ROME-III questionnaire [24]),
2. fatigue (SHARE study original questionnaire [25]),

Table 1. Baseline characteristics by ageing state at time 1

Baseline	*N*	Overall	Health states at time 1[1]				*p* value
			HA (*n* = 470)	Healthy pre-frail[2] (*n* = 106)	PA (*n* = 784)	AA (*n* = 544)	
Age, mean (SD), years	1,904	74.8 (4.3)	73.8 (3.7)	73.6 (3.6)	74.7 (4.2)	75.9 (4.7)	<0.0001
Women, *N* (%)	1,904	1,163 (61.1)	283 (60.2)	72 (67.9)	436 (55.6)	372 (68.4)	<0.0001
BMI, mean (SD)	1,903	26.3 (4.2)	25.0 (3.7)	24.9 (3.5)	26.7 (4.0)	27.3 (4.6)	<0.0001
Physical activity, *N* (%)							
Low	1,903	319 (16.8)	43 (9.2)	14 (13.2)	112 (14.3)	150 (27.6)	
Moderate		576 (30.3)	132 (28.1)	30 (28.3)	260 (33.2)	154 (28.3)	<0.0001
High		1,008 (53.0)	295 (62.8)	62 (58.5)	411 (52.5)	240 (44.1)	
Education, mean (SD), years	1,902	12.8 (4.3)	13.6 (3.7)	14.0 (3.1)	12.9 (4.1)	11.6 (5.0)	<0.0001
MoCA score, mean (SD)	1,904	25.8 (3.3)	27.6 (1.6)	27.3 (1.6)	25.3 (3.1)	24.5 (3.9)	<0.0001
Grip strength, mean (SD), kPa	1,901	60.6 (18.3)	65.8 (17.3)	53.3 (16.1)	65.6 (17.1)	50.3 (16.4)	<0.0001
Gait speed, mean (SD), m/s	1,900	1.1 (0.2)	1.2 (0.2)	1.2 (0.2)	1.2 (0.2)	1.0 (0.2)	<0.0001
GDS score, median (IQR)	1,904	1.0 (0.0–2.0)	0.0 (0.0–1.0)	1.0 (0.0–2.0)	1.0 (0.0–2.0)	2.0 (1.0–5.0)	<0.0001

Baseline characteristics presented as means and standard deviations or frequencies and percentages; analysed for the overall population as well as health states (HA, healthy pre-frail, PA, AA) and compared using ANOVA and χ^2 tests. MoCA, Montreal Cognitive Assessment; GDS, Geriatric Depression Scale. [1] Time 1 calculated as the aggregation of the baseline and year 1 visits. [2] Healthy pre-frail ager: participants fulfilling criteria of healthy ageing, at the same time also pre-frail or frail. This group was excluded from subsequent analyses.

3. slowness (gait speed <0.67 and 0.7 m/s, according to sex and height),
4. low activity (SHARE study original questionnaire [25]), and
5. weakness (hand-grip strength measured with the Martin vigorimeter, lowest 20% of the cohort based on age groups, sex, and country of origin).

Health States and Ageing Trajectories

Combining the healthy ageing definition and pre-frail/frail definitions in two consecutive years to increase reliability and avoid regression to the mean, we defined 3 health states:

- healthy agers (HA): participants fulfilling criteria of healthy ageing and who were not pre-frail or frail
- premature agers (PA): participants who did not meet the healthy ageing definition and at the same time were not pre-frail or frail
- accelerated agers (AA): participants who did not match the definition for HA and were at the same time either pre-frail or frail

Thus, healthy ageing and frailty status were determined for each of the 4 assessments (baseline, year 1, year 2, and year 3). We calculated the health states of all participants at 2 time points: aggregated baseline + year 1 assessments (time 1) and aggregated year 2 + year 3 assessments (time 2). We excluded all participants (n = 268) who fulfilled both the NHS criteria as HA and the Fried criteria of at least pre-frail (pre-frail or frail) at the same time because we aimed to assess the transition between these two health states. Once the health states for each time point were estimated (HA, PA, AA), there were 9 trajectories between time 1 and time 2, of which 3 were stable (i.e., remaining in the same health state: HA to HA, PA to PA, and AA to AA), 3 were deteriorating (i.e., change to a less advantageous category: HA to PA, HA to AA, and PA to AA), and 3 were improving trajectories (i.e., change to a more advantageous trajectory: AA to PA, AA to HA, and PA to HA).

Statistical Analysis

Baseline characteristics by health state are presented as means and standard deviations or frequencies and percentages and compared using ANOVA and χ^2 tests. Based on the pre-established definitions of the three health states, we calculated the total prevalence per category at the baseline, time 1, and time 2. We stratified prevalence by the age group (70–74 years old and 75 years or older) and sex. Data are given as percentages. In addition, we used a multinomial regression to calculate the odds of being in an improving or declining trajectory versus staying in the same category based on age and sex as independent variables and additionally adjusting for centre. Multiple imputation was used to estimate missing components of healthy ageing (baseline: 1.6%, year 1: 10.6%, year 2: 14.7%, year 3: 16.2%) and frailty status (baseline: 2.6%, year 1: 11.2%, year 2: 15.6%, year 3: 17.8%). Five imputed datasets were created. The imputation model assumed that data were missing at random and included age, sex, and BMI variables. We conducted multinomial logistic regression to evaluate the association of age (as a continuous variable) and sex (dichotomous) with the three trajectories (stable, improving, and deteriorating trajectory). Results from the multinomial logistic regression of ageing trajectories on the five imputed datasets were combined using MIANALYZE to generate the final inferences of ageing trajectories and estimated odds ratios and 95% confidence intervals using the stable trajectory as a reference. All statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA). Figures were prepared using R version 3.5.2 (R Core team, 2018) and RStudio version 1.1.463 (RStudio team, 2018), with the package networkD3 [26].

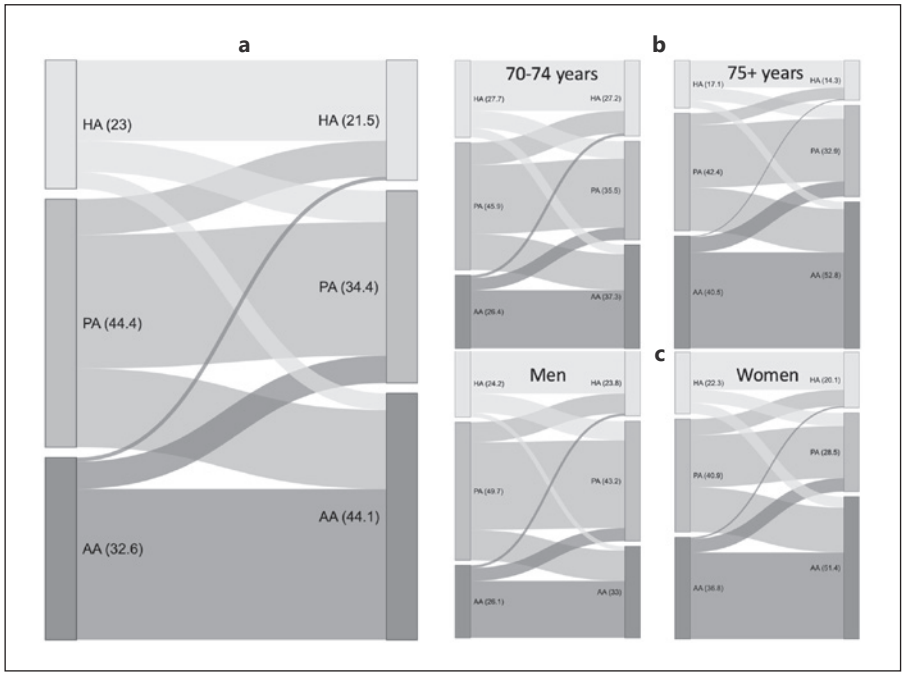

Fig. 1. Sankey diagram of ageing trajectories in DO-HEALTH participants: overall (**a**), by age (70–74, 75+) (**b**), and by gender (women, men) (**c**). Percentages of the total population are shown in parentheses.

Results

From the total population of DO-HEALTH, 11.7% of participants (n = 253) were missing at least one component of healthy ageing or frailty status at the baseline or year 1 visit. Baseline characteristics of all participants in the non-imputed data (n = 1,904) are presented in Table 1. Overall, the mean age of the population was 74.8 years, there were 61% of women, and 53% of participants reported high physical activity (≥3 times a week). Individuals satisfying the NHS's criteria of healthy ageing were significantly younger, had lower BMI, reported higher physical activity hours per day, more years of education, better cognitive function, and less depressive symptoms ($p < 0.0001$).

Ageing Trajectories in DO-HEALTH

After the imputation of missing components of healthy ageing and frailty status for the analysis of the trajectories, 268 participants fulfilled the criteria for both healthy ageing and pre-frail; thus, we excluded them from the main analysis. Therefore, the main analysis included 1,889 participants (87.6%) of the 2,157 original DO-HEALTH participants. A flow chart of the inclusion process is presented as online supplementary data (online suppl. Fig. 1; see www.karger.com/doi/10.1159/000523923 for all online suppl. material).

At time 1, 23.1% of the participants were HA, 44.4% PA (not HA but not pre-frail), and 32.6% were AA (not HA and at least pre-frail). At time 2, 21.5% were HA, 34.3% were PA, and 44.1% were AA. Between the two time points, 65.3% of participants remained in the same health state, 12.0% improved to a healthier state, and 22.8% progressed to a less advantageous state (Fig. 1a). Comparing the changes within each time point, most people remained in their assigned category. For example, among those classified as HA in year 1, 74% were HA at time 1 (baseline and year 1), while 26% would have been classified as PA (online suppl. Table 1).

Ageing Trajectories by Age Groups

We sub-analysed the trajectories for participants of 70–74 years of age and those 75 years old or older (Fig. 1b). In the younger group, 27.8% were HA, whereas only 17.1% in the older group were HA ($p < 0.0001$). In contrast, only 26.3% of people in the younger group were AA versus 40.5% in the older group ($p < 0.0001$).

During follow-up, there were no significant differences by age groups for those following a stable trajectory or a deteriorating trajectory (p = 0.20 and p = 0.74, respectively). More people in the younger group improved to a healthier state compared to those 75 years and older, but the results were only marginally significant (13.4% vs. 10.2%, p = 0.05). The odds of being in an improving tra-

Table 2. Association of age and sex with trajectories of ageing in DO-HEALTH

Characteristic	Odds ratio (95% CI) of ageing trajectories		
	recovering trajectory	stable	deteriorating trajectory
Age, years	0.94 (0.90, 0.98)	Ref	0.99 (0.96, 1.02)
Women versus men	0.94 (0.69, 1.28)	Ref	1.35 (1.07, 1.72)

Results from age and gender are reported from a multinomial logistic regression model with stable trajectories as reference, including age, gender, centre, treatment group, and BMI as explanatory variables.

jectory were 6% lower (OR = 0.94, 95% CI = 0.90–0.98) for every additional year of age, after adjusting for sex, study centre, and BMI. There was no significant difference for deteriorating trajectories by age groups in the adjusted models (Table 2).

Ageing Trajectories by Sex

We sub-analysed the trajectories for women and men (Fig. 1c). At time 1, significantly more women (36.8%) than men (26.1%) were AA ($p < 0.0001$), while there was no difference by sex among HA (women 22.4%, men 24.2%; $p = 0.36$). During follow-up, there were no significant differences by sex for those following a stable trajectory or an improving trajectory ($p = 0.07$ and $p = 0.37$, respectively). More women followed a deteriorating trajectory (24.9% vs. 19.4%, $p = 0.01$). After adjustment for age, study centre, treatment group, and BMI, the odds of following a deteriorating trajectory was 35% higher for women. There was no significant difference by sex for following a good trajectory in the adjusted models (Table 2).

Sensitivity Analysis

To consider the category of people who were excluded due to being "HA" but at least pre-frail (HF), we conducted a sensitivity analysis including 4 categories per time (HA, PA, AA, and HF) and 16 trajectories. We observed that the majority of people in this HF category (81/181) followed a deteriorating trajectory to either PA or AA, and only 16/181 remained in the same category (online suppl. Fig. 2). In the logistic regression models, our results remain virtually the same, where greater age is associated with lower odds of improving trajectories (multivariate adjusted OR: 0.94, 95% CI: 0.91–0.97) and being a women to be associated with higher odds of deteriorating trajectories (multivariate adjusted OR: 1.30, 95% CI: 1.06–1.57).

Discussion

Among the DO-HEALTH participants of age 70 years and older and followed for 3 years, we observed dynamic trajectories of ageing in a third of all participants, with 12.0% improving to a better and 22.8% declining to a lower healthy ageing state. Notably, however, in the multivariate adjusted analyses, the odds of improvement to a healthier state declined by 6% for each additional year of age, while the odds of deteriorating were 35% higher for women.

Biological Mechanisms

Little is known about the biological alterations that occur during healthy ageing and promote cumulative decline and depletion of the homoeostatic reserve, but lifestyle stress, alterations of the immune system, and epigenetic modifications are proposed as important mechanisms [27]. Biological age is known to undergo a strong inter-individual variability [28], and so far, no single indicator has been identified to reliably estimate the physiological ageing process.

Prevention of deteriorating trajectories is feasible even at an older age. Previous studies have shown that interventions such as muscle strength training and protein intake can improve frailty status and frailty components in a short time frame (3 months up to 12 months) [29].

Previous systematic reviews have shown that physical activity and exercise can prevent frailty and improve physical function [30, 31]. For example, a recent publication looking at physical activity trajectories in the Toledo Study of Healthy Aging found that sustaining high physical activity during ageing might lead to lower risk of disability and thus healthy ageing [32].

Results in Relation to Other Studies

This is the first prospective European-wide study assessing ageing trajectories using generally accepted frailty and healthy ageing definitions. A recent review [33] on the relationship of successful ageing and frailty showed that only four cross-sectional studies so far applied both definitions [34–37], and none of them assessed trajectories of ageing. All applied the same definition of frailty [4] used in this study, but they employed different approaches to describe "successful ageing," rendering a comparison with our study difficult.

Rather than statistically modelling trajectories of ageing and disability post hoc as previous studies did [8–15], we defined a priori three ageing health states targeting nine possible trajectories over 2 years. Therefore, our re-

sults are not directly comparable to studies showing data-driven trajectories. Despite this, our study shows that improving trajectories to a healthier state is possible, supporting what three previous studies had suggested [13–15]. In a study by Han et al. [15], only 30.5% of participants remained in the same trajectory, and the other 69.5% switched class at least once, with the majority (68.9%) having switched to a more disabled and only a minority improving to a less disabled state (2.9%). In contrast, in our study, we had a shorter follow-up and the majority of our participants had stable trajectories (65.3%). Other data-driven studies of trajectories of ageing in people older than 65 years did not identify improving trajectories [8–12]. Our study further extends previous studies conducted in people older than 65 years [13–15] by finding a comparatively large amount of improving trajectories (12.0%), thus suggesting that older adults keep their ability to improve up to a high age.

Sex and Age Differences

In our study, we found that women were more likely to follow a deteriorating trajectory than men. This is in line with other studies [10, 12] which showed that women were more likely to be in a less advantageous trajectory; for instance, in a study conducted among participants older than 50 years from the English Longitudinal Ageing study [12], using the biomarker-driven "healthy ageing phenotype," women started at higher levels but declined more steeply. Within participants of the Yale Precipitating Event study aged 70 or older, women declined faster in self-reported function but preserved their physical capacity better than men [10]. In a recent cohort study, women had higher cognitive baseline performances but faster later-life cognitive declines than men [38]. Our findings are in line with prior studies which found younger persons to be more likely to follow an improvement trajectory [13, 14], which may indicate that resilience decreases with age.

Strengths and Limitations

The strength of this study is the prospective design and the comprehensive assessment of overall health in DO-HEALTH. We were able to collect all necessary data for both definitions used in our analysis from validated questionnaires and standardized physical examinations carried out by trained study nurses and medical doctors. With one clinical visit and three phone calls per year, we minimized the risk of missing important changes during the follow-up.

Our study has also some limitations. Our data arise from a trial conducted among relatively healthy older adults without major comorbidities and most of them reported engaging in high or moderate physical activity; the results are thus not directly generalizable to the overall population. This being a secondary analysis of the DO-HEALTH study represents a limitation itself as the primary study was not originally designed to assess trajectories of healthy ageing. While frailty is a widely used concept in clinical geriatric medicine, no clear consensus has been reached on a common definition for healthy ageing. Also, the characteristics of HA and pre-frail older adults were not mutually exclusive, and we had to exclude approximately 12% of participants because the overlapping of healthy ageing and frailty did not fit our a priori health states (HA, PA, and AA). The overlap found within our population highlights the weakness of these definitions, and assessing this should be a focus of further studies. When we included the subgroup of "HA but pre-frail" in a sensitivity analysis, the subgroup appeared the most unstable, with only 8% remaining in the same category over time, but the associations with age and gender remained virtually the same. Finally, the follow-up time of 3 years in DO-HEALTH is relatively short. However, the four clinical visits allowed increasing reliability and avoiding regression to the mean, by averaging the first 2 years and comparing them to the average of the last 2 years.

Implications/Clinical Context

This study provides new insights into ageing trajectories and emphasizes the importance of considering improvement in older adults who possibly only temporarily find themselves in a less advantageous health state. In fact, transitions in between different health states could be based on very small changes within the overall functional level. This is of relevance for the treating physicians. Future studies assessing trajectories of ageing should consider possible associations with mortality, hospitalization, quality of life, and medication intake, as well as investigating the role of nutritional factors and physical activity.

Conclusions

Among relatively healthy adults of age 70 years and older without major comorbidities, trajectories of ageing were dynamic even within a follow-up of 3 years. This shows that improvement to a more advantageous health state is possible even for older adults. Our observation

that women have a 35% lower change to improve to a healthier state needs consideration in future efforts to support healthy ageing in the older adult population.

Acknowledgment

The authors explicitly express their gratitude to all participants and teams of the 7 recruitment sites for their dedication in collecting all DO-HEALTH data.

Statement of Ethics

All participants of DO-HEALTH had given their written informed consent and the study. The study was approved by the ethical and regulatory agencies of all 5 countries. This study protocol was approved by the University of Zurich Ethical Committee (BASEC: 2018-01767).

Conflict of Interest Statement

As part of the DO-HEALTH independent and investigator-initiated clinical trial, Prof. Bischoff-Ferrari reports as the PI of the DO-HEALTH trial, with grants from the European Commission, from the University of Zurich, from NESTEC, from Pfizer Consumer Healthcare, and from Streuli Pharma plus nonfinancial support from DSM Nutritional Products and nonfinancial support from Roche Diagnostics. Further, Prof. Bischoff-Ferrari reports speaker fees from Wild, Pfizer, Vifor, Mylan, Roche Diagnostics, and independent and investigator-initiated grants from Pfizer and from Vifor, outside the submitted work. Prof. Orav consults for the University of Zurich for the studies related to DO-HEALTH as well as for the Baim Research Institute, Boston, MA, USA (Member of DSMBs). Dr. Krützfeldt received support from the Swiss National Foundation and the Uniscientia, Philhuman, and Heuberg Foundations. Dr. Abderhalden is currently an employee of MSD, Switzerland. The other authors have no competing interests to declare.

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Author Contributions

Virginia Ghisla, Patricia O. Chocano-Bedoya, and Heike A. Bischoff-Ferrari drafted the manuscript with input of all co-authors. Statistical analysis was conducted by Patricia O. Chocano-Bedoya and Lauren A. Abderhalden with input by Endel John Orav, Heike A. Bischoff-Ferrari, and John A. Kanis. Data collection according to GCP was conducted by Andreas Egli and Heike A. Bischoff-Ferrari. Heike A. Bischoff-Ferrari is the principal investigator of the DO-HEALTH and together with Jan Krutzfeldt obtained funding for this study. Virginia Ghisla and Patricia O. Chocano-Bedoya contributed equally to this work and share first authorship.

Data Availability Statement

In a first step, no data will be made available to researchers external to DO-HEALTH research group to allow primary researchers to fully exploit the dataset. The data will be shared in a second step according to a controlled access system.

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