Prospective association of vitamin D with frailty status and all-cause mortality in older adults: Results from the KORA-Age Study

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Abstract

Objective. To assess the prospective association of serum 25-hydroxyvitamin D [25(OH)D] levels with frailty status and all-cause mortality in a cohort of community-dwelling participants of the population-based KORA [Cooperative Health Research in the Region of Augsburg]-Age Study.

Methods. 727 non-frail participants, aged ≥65 years, with 25(OH)D measurement at baseline in 2009, were followed for 2.9 ± 0.1 years. Participants were classified as pre-frail or frail if they met 1–2 or ≥3, respectively, of the following five criteria: weight loss, exhaustion, physical inactivity, low walking speed, weakness. The association between 25(OH)D and frailty was assessed in 954 participants. Multivariable adjusted logistic regression models were calculated for each outcome.

Results. The incidence of pre-frailty and frailty was 21.2% and 3.9% respectively. After multivariable adjustment, participants with very low 25(OH)D levels (<15 ng/ml vs. ≥30 ng/ml) had a significantly higher odds for pre-frailty (OR = 2.43 [95% CI: 1.17–5.03]) and pre-frailty/frailty combined (OR = 2.53 [95% CI: 1.23–5.22]), but not for frailty alone (OR = 2.63 [95% CI: 0.39–17.67]). The association between 25(OH)D and mortality (OR = 3.39 [95% CI: 1.08–10.65]) was partly mediated by frailty status.

Conclusion. Very low 25(OH)D levels were independently associated with incident pre-frailty, pre-frailty/frailty combined and all-cause mortality.

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Introduction

Frailty denotes a multidimensional syndrome characterized by decreased physiological reserves and increased vulnerability (Fried et al., 2004). The prevalence of frailty is associated with incident falls, worsening disability, hospitalization and mortality (Fried et al., 2001). Frailty is common in older adults; in a recent meta-analysis, the prevalence of frailty in community-dwelling adults aged ≥65 years was found to be 10.7% (Collard et al., 2012). A widely used definition of frailty is the frailty phenotype developed by Fried et al. (2001), defined by the presence of three or more of the following criteria: weakness (as measured by grip strength), unintentional weight loss (>10 lb in the previous year), low walking speed, exhaustion and low physical activity (by self-report). The presence of one or two of these criteria denotes pre-frailty.

A potential modifiable risk factor for frailty is serum 25-hydroxyvitamin D [25(OH)D] deficiency, which is widespread among older adults (Holick, 2007). Low 25(OH)D levels are associated with low grip strength and poor lower extremity performance (Houston et al., 2007). Moreover, frailty is a potential intermediate in the relatively consistent inverse association between 25(OH)D levels and mortality (Schöttker et al., 2013).

There is evidence from several cross-sectional studies for a U-shaped or inverse association between 25(OH)D levels and frailty (Puts et al., 2005; Shardell et al., 2009; Ensrud et al., 2010; Wilhelm-Leen et al., 2010; Ensrud et al., 2011; Smit et al., 2012; Hirani et al., 2013; Tajar et al., 2013; Schöttker et al., 2014). However, results from longitudinal studies on the association between 25(OH)D levels and incident frailty are limited and partly inconsistent. Although low 25(OH)D levels were associated with incident frailty in some studies (Puts et al., 2005; Wong et al., 2013), no significant relationship was found in others (Ensrud et al., 2011; Shardell et al., 2012; Schöttker et al., 2014).
Moreover, a comparison of the results among the longitudinal studies is complicated by differing definitions of frailty as well as inconsistent outcomes. Further, few of the studies included older adults potentially unable to attend a study center, although these people are likely to be at high risk of frailty. Studies that did include this group used frailty definitions predominantly based on self-report (Puts et al., 2005; Schöttker et al., 2014). In this study, we sought to further assess the prospective association of 25(OH)D levels with frailty status and all-cause mortality in community-dwelling older adults. By analysing pre-frailty, frailty, single frailty criteria and mortality separately, we aimed to add a comprehensive approach to the discussion on the relationship between 25(OH)D, frailty and mortality. We hypothesized that, by offering home examinations to participants unable to attend the study center, we would be able to include more people at high risk of (pre-)frailty.

Methods

Study population

The Cooperative Health Research in the Region of Augsburg (KORA)-Age Study is a follow-up study of the four cross-sectional, population-based Multinational Monitoring of Trends and Determinants in Cardiovascular disease [MONICA]/KORA surveys (S1–S4), carried out between 1984 and 2001 in the region of Augsburg, Southern Germany (Holle et al., 2005). Study design, sampling method and data collection are described elsewhere in more detail (Peters et al., 2011). Briefly, an age- and sex-stratified sample of all S1–S4 participants born before 1944 (aged ≥65 years) were invited to participate in a personal interview and physical examination. Participants who were unable to attend the study center were examined at home, resulting in a total of 1,079 participants who took part in the baseline examination in 2009. Of these, 822 participants were re-examined in the follow-up examination in 2012. Written informed consent was obtained from all participants. The KORA studies have been approved by the ethics committee of the Bavarian Medical Association.

25(OH)D measurement

Non-fasting blood samples were collected at baseline and stored at −80 °C until analysis. A detailed description of the blood sample processing is provided in the Supplementary Material. 25(OH)D and parathyroid hormone [PTH] levels were assessed using an enhanced chemiluminescence immunoassay (ECLIA system; Cobas e 411, Roche, Mannheim, Germany). The intra- and inter-assay coefficients of variation were <5% and <10% respectively.

Frailty assessment

Frailty status was determined using an adapted version of the frailty phenotype proposed by Fried et al. (2001):

1. Weight loss: Criterion was met for participants who reported having lost >5 kg in the past 6 months.
2. Exhaustion: Criterion was met for participants who answered ‘never’ to the statement: ‘I felt energetic and active in the last two weeks’.
3. Physical inactivity: Criterion was met for participants who reported neither walking >30 minutes on working days nor performing any sports during summer and winter.
4. Low walking speed: Measured using the time needed to perform the ‘Timed up and go test’ [TUG], instructing the participants to stand up from a chair, walk three metres, turn around and sit down again. The criterion was met for participants in the highest quintile, stratified by sex and height (mean value).
5. Weakness: Measured with the mean value of three grip strength measurements using the JAMAR handheld dynamometer (Saehan Corp., Masan, Korea). The criterion was met for participants in the lowest quintile, stratified by sex and body mass index [BMI] quartiles.

Participants were classified as ‘non-frail’ if they met none of these criteria, as ‘pre-frail’ if they met 1–2 and as ‘frail’ if they met ≥3 criteria. This definition of frailty has been used in this study population before (Johar et al., 2014; Pabst et al., in press).

Assessment of covariates

The following covariates, all assessed at baseline, were included in the analyses: sex, age (in years), education years (<10, 10–12, >12), BMI, smoking status (non-smoker, ex-smoker, smoker), alcohol consumption (no [0 g/d], moderate [women: 0–< 20 g/d; men: 0–< 40 g/d] and high [women: ≥20 g/d; men: ≥40 g/d]), multimorbidity, cardiovascular diseases (heart disease/stroke) [CVD], diabetes and season of blood collection (Feb–Apr, May–Jul, Aug–Nov). More details on the covariable assessment are provided in the Supplementary Material. All covariables, except season, were previously found to be significantly associated with the presence of (pre-)frailty as well as low 25(OH)D levels (<20 ng/ml) after adjustment for sex and age at p ≤ 0.10 in this study population (Pabst et al., in press).

Home visits

Participants who were unable to attend the study center, e.g. because of physical constraints, were examined at home (N = 93 at baseline, N = 111 at follow-up). Owing to standardization problems, the TUG could not be applied at home visits. At follow-up, the ‘Chair rise test’ [CR], instructing the participants to stand up from a chair and sit down again five times, was applied, and missing TUG values were imputed from CR values. The imputation was based on 174 participants examined at the study center who had CR measurements as well as TUG measurements. The imputed values were calculated using a linear model adjusted for age, sex, BMI and disability (assessed with the health assessment questionnaire disability index (Fries et al., 1982)). The Pearson correlation coefficient of the measured and the imputed TUG values in the 174 participants was 0.68.

All-cause mortality and withdrawal over the follow-up period

A total of 98 participants died during the follow-up period. Mortality was ascertained by checking the vital status of all participants through the population registries inside and outside the study area. Death certificates were obtained from local health authorities. We used all-cause mortality (International Classification of Diseases-9 codes 001–999) as an outcome.

Some 159 participants withdrew from the study during follow-up. Of these, 84 filled in a non-responder questionnaire which provided the reason for withdrawal and enabled us to perform a crude estimation of the frailty status based on a set of questions (see Supplementary Material for more details).

Statistical analysis

Serum 25(OH)D levels were categorized into four groups, based on cut-points used by the US Institute of Medicine (IOM [Institute of Medicine], 2011) and the US Endocrine Society (Holick et al., 2011): <15, 15–< 20, 20–< 30 and ≥30 ng/ml. These categories have been used in previous studies on vitamin D and frailty, in both our (Pabst et al., in press) and other study populations (Ensrud et al., 2010). As 25(OH)D categories vary between studies, we performed a sensitivity analysis using a second categorization (<20/≥20 ng/ml) to allow comparisons.

Differences in characteristics according to 25(OH)D category were compared using χ² tests for categorical and ANOVA for continuous variables (logarithmic transformations were applied for skewed variables).

The prospective association between 25(OH)D levels at baseline and frailty status at follow-up was examined using binary logistic regression models (frail vs. non-frail; pre-frail vs. non-frail). As only 27 participants were frail at follow-up, we also examined the combined outcome (pre-frail/frail vs. non-frail). To assess the impact of home examinations, we excluded home-examined participants in a sensitivity analysis. Moreover, we examined whether 25(OH)D levels at baseline were associated with withdrawal from study or all-cause mortality during follow-up. Three models were calculated for each outcome: model 1, adjusted for sex, age, BMI, season of blood collection and baseline frailty status for the outcome frail vs. non-frail; model 2, additionally adjusted for education years, smoking status, alcohol intake, CVD, diabetes and multimorbidity; model 3, additionally adjusted for PTH level, to assess whether the association between 25(OH)D and the respective outcome was mediated by PTH. For withdrawal and all-cause mortality, baseline frailty status was not directly included in model 1, but added in an additional model 1b in order to assess whether the association of 25(OH)D with withdrawal or all-cause mortality was mediated by frailty. Complete case analysis was used and additionally, certain subgroups had to be excluded for specific analyses (e.g. participants pre-frail at follow-up...
Results

The characteristics of the complete study population (N = 954) are summarized in Table 1. A table presenting the characteristics of the reduced study population for the frailty analyses (N = 727, with participants being frail at baseline or with missing frailty status at baseline or follow-up excluded) can be found in the Supplementary Material (Supplementary Table S1). The incidence of pre-frailty and frailty after a follow-up period of 2.9 ± 0.1 years was 21.2% and 3.9% respectively. 31.1% of the participants had very low 25(OH)D levels (<15 ng/ml).

In total, the data of 80 home-examined participants (N = 5 at baseline, N = 75 at follow-up) were included in the analyses. Comparisons of the baseline characteristics and the follow-up status of participants according to examination place are shown in the Supplementary Tables S2 and S3 respectively. Home-examined participants were older, more likely to be pre-frail at baseline, less active and had lower 25(OH)D levels.

The associations between baseline 25(OH)D levels and frailty status at follow-up are shown in Table 2. Compared with participants with high 25(OH)D levels (≥30 ng/ml), participants with very low 25(OH)D levels had a 2.4-fold higher odds of becoming pre-frail [95% CI: 1.17–5.03] and a 2.5-fold higher odds of becoming pre-frail or frail [95% CI: 1.23–5.22] during follow-up (in multivariable adjusted models). Further adjustment for PTH only slightly attenuated the associations in magnitude. Using two 25(OH)D categories (as shown in the Supplementary Table S4) resulted in attenuated odds ratios [OR], but the associations remained statistically significant after multivariable adjustment. Exclusion of home-examined participants also attenuated the ORs (data not shown).

The associations between baseline 25(OH)D levels and single frailty criteria at follow-up are shown in Table 3. Participants with very low 25(OH)D levels had a 3.8-fold higher odds for low walking speed [95% CI: 1.53–9.25] and a 5.1-fold higher odds for physical inactivity [95% CI: 1.63–16.17] compared with those with high 25(OH)D levels. The associations of 25(OH)D with weight loss, exhaustion and weakness were weaker and not significant.

Very low 25(OH)D levels were significantly associated with all-cause mortality (OR = 4.93 [95% CI: 1.63–14.90] data shown in Table 4) in models adjusted for age, sex, BMI and season of blood collection. Additional adjustment for baseline frailty status attenuated the OR, but the association remained significant (OR = 3.40 [95% CI: 1.10–10.48]).

25(OH)D levels between 15 and 20 ng/ml but not very low levels (<15 ng/ml) were associated with a higher odds of withdrawing from the study during follow-up (data shown in Supplementary Table S5). Additional adjustment for baseline frailty status hardly changed the ORs. The main reason for withdrawal was poor health status (46.4%). Based on the crude frailty estimation, the incidence of pre-frailty and frailty among the non-responders was 58.3% and 17.9% respectively. Participants who withdrew had lower 25(OH)D levels, although the difference was not significant after adjustment for age and sex.

Fig. 1. Flow chart of the study population.
In this cohort of community-dwelling older adults, very low 25(OH)D levels (<15 ng/ml) at baseline were significantly associated with incident pre-frailty as well as pre-frailty and frailty combined over a follow-up period of about 2.9 years. We also found a strong association with frailty alone, which was not, however, statistically significant. Very low 25(OH)D levels at baseline were associated with a 5-fold higher odds of all-cause mortality. This association was attenuated by additional adjustment for baseline frailty status, suggesting a mediating role of frailty.

Our findings are generally consistent with those of previous prospective studies on vitamin D and frailty using a frailty definition based on Fried et al. (Fried et al., 2001). In a US study in 4,551 women aged ≥69 years, moderate (but not low) 25(OH)D levels (16.0–21.9 ng/ml; reference: 22.0–28.9 ng/ml) were associated with a...
Table 2
Prospective association between baseline serum 25(OH)D level and frailty status at follow-up.

<table>
<thead>
<tr>
<th>25(OH)D level in ng/ml</th>
<th>&lt;15</th>
<th>15–20</th>
<th>20–30</th>
<th>≥30 (Ref.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR</td>
</tr>
<tr>
<td>Frail vs. non-frail*</td>
<td>475</td>
<td>3.33 (0.64–17.35)</td>
<td>0.86 (0.09–9.79)</td>
<td>1.42 (0.19–10.86)</td>
</tr>
<tr>
<td>Pre-frail/Frail vs. non-frail</td>
<td>474</td>
<td>2.22 (1.11–4.43)</td>
<td>1.26 (0.62–2.54)</td>
<td>1.12 (0.57–2.19)</td>
</tr>
<tr>
<td>Pre-frail vs. non-frail</td>
<td>471</td>
<td>2.11 (1.05–4.22)</td>
<td>1.26 (0.62–2.54)</td>
<td>1.08 (0.55–2.12)</td>
</tr>
</tbody>
</table>

Model 1: Adjusted for age, sex, BMI, season of blood collection, *additionaly adjusted for baseline frailty status.
Model 2: Additionally adjusted for education, smoking status, alcohol consumption, CVD, diabetes mellitus, multimorbidity.
Model 3: Additionally adjusted for PTH.
Significant results (p < 0.05) are printed in bold.

OR: odds ratio; CI: confidence interval; 25(OH)D: 25-hydroxyvitamin D; BMI: body mass index; PTH: parathyroid hormone.

1.4-fold higher odds of incident frailty or mortality after the 4.5 years of follow-up (Ensrud et al., 2010). In another US study in 1,267 men aged ≥65 years, low 25(OH)D levels (≥20 vs. ≥30 ng/ml) was not associated with incident frailty (assessed with a self-created frailty index during follow-up. In another US study in 1,267 men aged 50–70 years, each 5 ng/ml decrement of 25(OH)D was associated with a 1.5-fold higher odds of dying, but not with incident frailty (Shardell et al., 2012). In a recent German study, vitamin D deficiency (<12 vs. ≥20 ng/ml) was not associated with incident frailty (suggested by a self-created frailty index using cut-off points based on Fried et al., 2001) in 9579 participants aged 50–74 years. For mortality, however, an association was found that was attenuated but still significant after adjustment for frailty (Schöttker et al., 2014). An additive joint effect of serum 25(OH)D (lowest vs. highest quartile) and frailty on all-cause mortality (HR = 2.98 [95% CI: 2.01–4.42]) was found in 4731 US adults aged ≥60 years in the third NHANES survey (Smit et al., 2012).

In contrast, studies that used different frailty definitions, which included dimensions such as illness, depression or cognitive function, found different results. In a Dutch study in 1,271 participants aged ≥65 years, 25(OH)D levels of <10 ng/ml (reference: ≥20 ng/ml) were associated with incident frailty (Putts et al., 2005). An Australian study in 4203 men aged 70–88 years, being in the lowest vitamin D quartile was associated with incident frailty. Moreover, adjustment for frailty largely influenced the association of low vitamin D levels and mortality (Wong et al., 2013). This suggests that the association between 25(OH)D and frailty largely depends on the definition of frailty. Examining the association between 25(OH) and the incident single frailty criteria might help to explore the underlying cause of the 25(OH)-frailty-relationship, but respective analyses are only provided by some studies (Ensrud et al., 2010; Shardell et al., 2012; Wong et al., 2013).

In our study, the association of low 25(OH)D levels with pre-frailty and pre-frailty/frailty was mainly based on the single frailty criteria physical inactivity and low walking speed. As a low 25(OH)D level at baseline can be the result of an inactive lifestyle, which was maintained during the follow-up period, we cannot rule out reverse causation.

Table 3
Prospective association between baseline serum 25(OH)D level and single frailty criteria at follow-up.

<table>
<thead>
<tr>
<th>25(OH)D level in ng/ml</th>
<th>&lt;15</th>
<th>15–20</th>
<th>20–30</th>
<th>≥30 (Ref.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss (N = 761)</td>
<td></td>
<td></td>
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<tr>
<td>Model 1</td>
<td>1.08 (0.30–3.87)</td>
<td>2.13 (0.61–7.35)</td>
<td>1.77 (0.52–5.99)</td>
<td>1.00</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.08 (0.30–3.93)</td>
<td>2.25 (0.62–8.07)</td>
<td>1.72 (0.50–5.90)</td>
<td>1.00</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.09 (0.29–4.11)</td>
<td>2.25 (0.62–8.14)</td>
<td>1.72 (0.50–5.92)</td>
<td>1.00</td>
</tr>
<tr>
<td>Exhaustion (N = 712)</td>
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<td></td>
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<tr>
<td>Model 1</td>
<td>1.26 (0.51–3.10)</td>
<td>0.78 (0.31–2.44)</td>
<td>0.77 (0.29–2.01)</td>
<td>1.00</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.14 (0.45–2.84)</td>
<td>0.78 (0.27–2.26)</td>
<td>0.74 (0.28–1.95)</td>
<td>1.00</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.04 (0.63–4.29)</td>
<td>0.90 (0.31–2.63)</td>
<td>0.79 (0.30–2.10)</td>
<td>1.00</td>
</tr>
<tr>
<td>Physical inactivity (N = 703)</td>
<td></td>
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</tr>
<tr>
<td>Model 1</td>
<td>4.72 (1.52–14.65)</td>
<td>0.55 (0.10–3.16)</td>
<td>2.43 (0.74–7.98)</td>
<td>1.00</td>
</tr>
<tr>
<td>Model 2</td>
<td>5.14 (1.63–16.17)</td>
<td>0.56 (0.09–3.34)</td>
<td>2.20 (0.65–7.38)</td>
<td>1.00</td>
</tr>
<tr>
<td>Model 3</td>
<td>4.49 (1.37–14.74)</td>
<td>0.52 (0.09–3.15)</td>
<td>2.14 (0.64–7.19)</td>
<td>1.00</td>
</tr>
<tr>
<td>Low walking speed (N = 611)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Model 1</td>
<td>3.52 (1.48–8.39)</td>
<td>1.45 (0.53–3.98)</td>
<td>2.34 (0.96–5.70)</td>
<td>1.00</td>
</tr>
<tr>
<td>Model 2</td>
<td>3.76 (1.53–9.25)</td>
<td>1.47 (0.52–4.19)</td>
<td>2.28 (0.92–5.69)</td>
<td>1.00</td>
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<tr>
<td>Model 3</td>
<td>3.10 (1.23–7.82)</td>
<td>1.34 (0.47–3.85)</td>
<td>2.18 (0.88–5.44)</td>
<td>1.00</td>
</tr>
<tr>
<td>Weakness (N = 657)</td>
<td></td>
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</tr>
<tr>
<td>Model 1</td>
<td>1.24 (0.59–2.63)</td>
<td>0.82 (0.34–1.96)</td>
<td>1.05 (0.49–2.25)</td>
<td>1.00</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.22 (0.56–2.68)</td>
<td>0.87 (0.35–2.19)</td>
<td>0.98 (0.45–2.16)</td>
<td>1.00</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.03 (0.45–2.34)</td>
<td>0.82 (0.32–2.07)</td>
<td>0.94 (0.43–2.07)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Logistic regression models: Occurrence of the respective criterion yes vs. no; participants were excluded if the criterion was already met at baseline or if the criterion was missing.
Model 1: Adjusted for age, sex, BMI and season of blood collection.
Model 2: Additionally adjusted for education, smoking status, alcohol consumption, CVD, diabetes mellitus, multimorbidity.
Model 3: Additionally adjusted for PTH.
Significant results (p < 0.05) are printed in bold.

OR: odds ratio; CI: confidence interval; 25(OH)D: 25-hydroxyvitamin D; BMI: body mass index; PTH: parathyroid hormone.
However, previous studies found a significant association between low 25(OH)D levels and additional frailty criteria (weight loss (Ensrud et al., 2010); exhaustion and lower extremity problems (Wong et al., 2013); weakness (Shardell et al., 2012)). Moreover, the association between vitamin D deficiency and physical frailty (as defined by Fried et al., 2001) is biologically plausible. One of the main functions of vitamin D in the human organism is maintaining calcium homeostasis and bone density (Mosekilde, 2005; Holick, 2007). 1,25-dihydroxyvitamin D [1,25-(OH)2D], the active form of vitamin D, directly mediates gene transcription in skeletal muscle cells and enhances muscle cell calcium uptake, phosphate transport and the differentiation into mature muscle fibers (Lips, 2006). 25(OH)D deficiency leads to low 1,25-(OH)2D levels and, as a consequence, to a rise in PTH levels, resulting in increased risk of bone turnover, osteoporosis and hip fractures (Lips, 2006; Holick, 2007). Furthermore, the production of inflammatory cytokines is induced. Both directly and indirectly through PTH regulation and inflammation, vitamin D seems to affect muscle strength and function (Janssen et al., 2002; Visser et al., 2003; De Martinis et al., 2006; Schap et al., 2006). There is evidence from meta-analyses confirming that vitamin D supplementation has a beneficial effect on global muscle strength and bone mineral density and is preventive of overall mortality (Zheng et al., 2013; Beaudart et al., 2014; Reid et al., 2014), but the effect on other health outcomes is still controversially discussed (Mao et al., 2013; Mao and Huang, 2013; Zhao et al., 2013; Autier et al., 2014).

Our study adds to the discussion on the relationship between 25(OH)D, frailty and mortality by providing separate analyses for pre-frailty, frailty, pre-frailty and frailty combined, single frailty criteria and mortality, which might help to untangle these concepts. However, our study had several limitations. We had a relatively small sample size and a small number of cases, so we may have overestimated the effects (Nemes et al., 2009). Incident frailty was particularly low in our study population, which may be the reason for the non-significant association between 25(OH)D and incident frailty alone. Despite the offer of being examined at home, about 15% of the participants withdrew from the study during follow-up. The withdrawn participants had lower 25(OH)D levels and, based on our non-responder questionnaire, we assume that a great proportion were pre-frail or frail. Thus, we may have underestimated the true association between 25(OH)D and frailty. 25(OH)D levels were only measured once; thus, variations over time could not be considered. Serum 25(OH)D levels are, however, relatively persistent, and a single baseline measurement was found to be a valid indicator of long-term exposure (Jorde et al., 2010). Considering the frailty definition, three of the five frailty components were self-reported, so recall bias and misreporting cannot be excluded. As in other studies (Shardell et al., 2009; Ensrud et al., 2010; Wilhelm-Leen et al., 2010; Ensrud et al., 2011; Shardell et al., 2012; Smit et al., 2012; Hirani et al., 2013), our frailty criteria differed slightly from the definition originally suggested by Fried et al. (2001), which complicates comparisons. Moreover, imputed TUG values based on CR values were used in home-examined participants. However, given that home-examined participants were more likely to be frail and had lower 25(OH)D levels, including these participants, who were probably underrepresented in other studies, in summary improved the accuracy of our estimation.

**Conflict of interest**

The authors declare that there are no conflicts of interest.

**Acknowledgments**

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ypmed.2015.01.010.

**References**


