

A study of relationships between bone-related vitamins and minerals, related risk markers, and subsequent mortality in older British people: the National Diet and Nutrition Survey of People Aged 65 Years and Over

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Abstract

Summary Follow-up of a British national survey of older people found that in men, all-cause mortality was predicted by baseline plasma concentrations of phosphorus, albumin, creatinine and α_1 -antichymotrypsin, and food energy intake and in women by plasma alkaline phosphatase, creatinine, α_1 -antichymotrypsin, 25-hydroxy-vitamin D (marginally), and phosphorus intake.

Introduction Predictive power, for all-cause mortality, of bone-related vitamin and mineral indices and intakes, measured at baseline (primary objective), was studied in the British National Diet and Nutrition Survey (community-living subset) of People Aged 65 Years and Over. A secondary objective was to identify cross-sectional relationships between indices at baseline to help explain mortality predictions.

Methods Mortality status was recorded for 1,054 (mean age 76.6 ± 7.4 years, 49.0% female) participants from baseline survey in 1994/1995 until September 2008. Seventy-four per cent of male and 62% of female participants died. Cox proportional hazards models were used to relate baseline nutrient and risk marker estimates to subsequent survival. Results below 1.0 signified lower risk at greater nutrient (status or intake) values and vice versa.

Results In both sexes, all-cause mortality was significantly predicted by body weight and mid-upper arm circumference. In men, it was predicted by baseline plasma concentrations (per SD) of: phosphorus (hazard ratio 1.18, 95% confidence

interval (CI)=1.06–1.30), albumin (hazard ratio 0.84, 95% CI =0.74–0.94), creatinine (hazard ratio 1.20, 95% CI=1.08–1.33) and α_1 -antichymotrypsin (hazard ratio 1.21, 95% CI=1.11–1.33). In women, it was predicted by plasma albumin (hazard ratio 0.83, 95% CI=0.72–0.96), alkaline phosphatase (hazard ratio 1.08, 95% CI=1.01–1.16), creatinine (hazard ratio 1.37, 95% CI=1.13–1.66), α_1 -antichymotrypsin (hazard ratio 1.27, 95% CI=1.11–1.45) and marginally by 25-hydroxy-vitamin D (hazard ratio 0.87, 95% CI=0.75–1.00). In men, it was predicted by dietary intake (per SD) of food energy; in women, by intake of phosphorus. Adjustment for plasma α_1 -antichymotrypsin or plasma creatinine reduced the significance of plasma phosphorus in men.

Conclusion Mortality prediction by higher plasma phosphorus in older British men may imply impaired renal function and/or acute phase status. Further studies are needed on which associations are causal and modifiable.

Keywords British National Survey of Older Adults · Mortality prediction · Plasma indices and intakes of bone-related nutrients

Introduction

Relationships between biochemical status indices and risk of premature mortality can help predict causal relationships and, thereby, clarify physiological and pathological mechanisms that may be related to disease and mortality risk factors in ageing humans. In a series of studies [1–4], we have recently focussed on the mortality outcomes of the subset of community-living participants from the country-wide British National Diet and Nutrition Survey (NDNS) of People Aged 65 Years and Over, for which the fieldwork was performed in 1994–1995 [5]. The primary objective of the present paper has been to explore the predictive

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significance of a selection of biochemical indices for nutrient and status indices that are bone-related, plus related lifestyle and risk indices, nearly all of which were measured as part of the original (baseline) population surveillance protocol (a secondary objective was to identify potentially relevant cross-sectional relationships between indices at baseline, which might help explain some of the observed nutrient–mortality relationships).

Certain nutrient status indices are known to be modified by, and hence to reflect, acute phase status and/or renal status, hence, potentially, to reflect mortality risk (since chronic inflammatory states or impaired kidney function frequently underlie disease processes that lead ultimately to death) [6]. For instance, several recent studies [7–9] have reported an association between raised serum calcium and/or phosphorus concentrations and an increased risk of mortality, and have attributed this association to impaired kidney function or inflammation as being potentially the cause of both the abnormal serum mineral levels and the increased risk. For this reason, we included a biochemical index of acute phase status (α_1 -antichymotrypsin) in the study. Since, in a previous study of mortality predictors in this survey sample, self-reported physical activity, measured hand grip strength and smoking habit at baseline were all shown to be significant predictors of all-cause mortality [3], these three potential risk modulator indices were also studied, as possible effect modulators, in the present study. The well-established links between bone health status and muscular strength and/or physical activity provided a further justification for the inclusion of self-reported physical activity and measured grip strength in the present study.

A key question, which is pertinent in all of these mortality risk studies, is whether the observed links between baseline nutrient status and future mortality are likely to be driven by (potentially correctable) nutritional imbalances or by the more intractable and unalterable processes of ageing and chronic disease.

Subjects and methods

Subjects

The NDNS 65+ years survey procedures have been described in detail elsewhere [5]; therefore, only a brief summary is given here. At baseline, in 1994–1995, two separate population samples were randomly selected: one from community-living people aged 65 years and over and the other from long-stay institutions. Only the community-living sample has been included. Participants were drawn from 80 randomly selected postcode sectors in mainland Britain, allocated to four sequential 3-month fieldwork “waves” corresponding to the four seasons, beginning in October 1994.

Survey measurements

Demographic, socioeconomic and other information, including a four-category self-assessment of usual physical activity plus a three-category self-assessment of current smoking habit (none, 1–20 cigarettes/day, >20/day) [5], were obtained by a trained interviewer in the participant’s home. A 4-day weighed dietary record was also obtained by the interviewer. Participants were requested to keep a 4-day weighed record of all food and drink consumed, which was found to produce acceptable levels of compliance and completion [5]. They were issued with a Soehnle Quanta digital food scale to weigh all food consumed at home, and details of any food and drink consumed outside were recorded in a separate diary so that interviewers could purchase duplicate items.

Anthropometric indices were measured by a trained nurse. Hand grip strength was measured by a hand dynamometer, designed by the Department of Medical Physics, Queen’s Medical Centre, Nottingham, UK, using the mean of four measurements, two on each hand [5]. Physical activity was derived from a lifestyle (including activity and disability) questionnaire, subsequently summarised in a four-category index, from ‘very active’ to ‘very inactive’ [5]. After separate consent, a fasting early morning venous blood sample was taken by a trained nurse. The blood sample was subdivided and used for a wide range of analyses [5]. Of these, the assays that are relevant to the present study were: (a) plasma 25-hydroxy vitamin D (25(OH)D) by a commercial kit assay (Incstar, Minnesota, USA) based on competitive protein binding to an antibody to an analogue of 25(OH)D raised in rabbits [5, 10]; (b) plasma α_1 -antichymotrypsin and plasma albumin by antibody-based nephelometric assays (Dako A/S, adapted for a Roche Cobas Bio autoanalyzer) [5]; (c) plasma calcium, phosphorus, creatinine and total plasma alkaline phosphatase by colourimetric assays (Roche clinical assay kits, for a Roche Cobas autoanalyzer) [5]; the enzyme rate assay for alkaline phosphatase being based on the hydrolysis of *p*-nitrophenyl phosphate (Roche do.) [5]; and (d) plasma intact parathyroid hormone (PTH), measured for an adjunct study by a commercial immunoassay (Nichols-Allegro, Nichols Diagnostics, San Juan Capistrano, CA, USA) [11] (plasma calcium, phosphorus, alkaline phosphatase, 25(OH)D and parathyroid hormone are all bone-related indices). Plasma α_1 -antichymotrypsin was selected as a medium-duration plasma acute phase indicator, which tends to remain raised during chronic inflammatory states. In-house quality assessments and inter-laboratory exchanges were undertaken in order to monitor the accuracy and stability of the assays. Between-run quality control sample coefficients of variation (%) for the principal plasma index assays were: plasma phosphorus, 2.3;

calcium, 2.7; alkaline phosphatase, 2.6; creatinine, 6.0; albumin, 7.8; antichymotrypsin, 8.0; parathyroid hormone, 8.3; and 25(OH)D, 15.0.

Ethics and approvals

The study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Local Research Ethics Committees representing each of the 80 postcode sectors used. The protocol was also approved by the Ethical Committee of the MRC Dunn Nutrition Unit (of which the Micronutrient Status Laboratory is now part of MRC Human Nutrition Research) in Cambridge. Written informed consent was obtained from all subjects.

Follow-up mortality study

The present study included 1,054 participants comprising 538 men and 516 women with partial or complete data available for the analyses of interest here, all of whom agreed to be flagged on the National Register of Births and Deaths and whose status (i.e. as still alive or registered as having died) was known unequivocally in September 2008. No exclusions, other than those resulting from willingness to participate or the availability of blood samples, were imposed, and there was no evidence of sampling bias. Because of missing values (principally due to incomplete consent availability for the blood sampling), the analyses of the blood biomarker variables are typically based on a subset of 800–900 participants and of 555 for the parathyroid hormone dataset. Mortality outcomes were obtained from the National Health and Service (NHS) register of deaths, up to September 2008.

Statistical analyses

Cox proportional hazards models were used, with years of survival as the time scale, to estimate the risk of all-cause mortality. The data were censored to September 2008 in participants who survived. The proportional hazards assumption was examined by comparing the cumulative hazard plots, grouped as exposure; no appreciable violations were observed. Standardised values (*z*-scores) were used for each of the explanatory variables, thus expressing the hazard ratios per standard deviation rather than per measurement unit, achieving an enhanced conformity between indices. Adjustment was made for potential confounders, including age and sex, in all models. Multivariable Cox regression model was used to test the independent effect of nutrient status indices or nutrient intake estimates after adjustments for acute phase indicators, functional and anthropometric measures. Since rela-

tionships between indices, rather than estimates of prevalence were of interest, the weighting factors used in the Survey Report [5] were not used here. All tests of statistical significance were based on two-sided probability; $P < 0.05$ was deemed significant.

Results: survey follow-up

Of the community-living survey participants who gave consent for follow-up flagging of the NHS Register of deaths and who had provided at least one index value reported in this follow-up study, 94.5% could be accounted for by known deaths and known survivors. As noted previously in “Subjects and methods”, the blood biomarker analyses are confined to that subset of the participants who provided a blood sample, generally comprising 800–900 participants.

Baseline characteristics

Table 1 provides mean and median baseline values, subdivided by sex, for the indices explored in this report. The Survey Report [5] provided baseline index values for all of the original survey participants, together with further details about the selection procedures and the methodologies used.

Correlations between plasma status indices, and functional and lifestyle measures

Table 2 shows associations of the plasma status indices with baseline markers of physical function (hand grip strength and physical activity) and with current smoking habit. For men, five of the seven plasma indices were significantly associated with hand grip strength, but for women, none of the seven were associated with this index of physical function. For men, the pattern of associations with a physical activity score was similar to that for grip strength, and for women, four of the plasma indices were associated with the physical activity score. For men, three of the plasma indices were associated with smoking habit, but for women, only one (plasma phosphorus) was associated with this lifestyle index. Plasma PTH was not significantly correlated with any of the function and lifestyle indices (not shown).

Hazard ratios for all-cause mortality

Table 3 lists the age- and sex-adjusted hazard ratios for all-cause mortality for both sexes combined and subdivided by sex. For the combined sexes, significant predictors of mortality included plasma 25(OH)D (‘protective’), plasma

Table 1 Summary of selected status indices and nutrient intakes in the survey respondents who are included in the present study ($n=1,054$)

	Men				Women			
	n^a	Mean (SD)	Median	Range	n^a	Mean (SD)	Median	Range
Age (years)	538	75.8 (6.9)	75.0	65–96	516	77.3 (7.9)	76.0	65–99
Body weight (kg)	532	75.2 (12.2)	74.6	38.7–121	509	64.0 (12.7)	63.3	32.5–112.9
Height (m)	528	1.69 (0.07)	1.69	1.49–1.98	503	1.55 (0.07)	1.55	1.20–1.75
Body mass index (BMI, kg/m ²)	527	26.3 (3.7)	26.1	16.3–43.2	502	26.6 (4.8)	26.2	14.4–44.6
Waist circumference (cm)	531	97.8 (10.9)	98.0	48–129	511	87.7 (11.7)	86.2	27–131
Mid-upper arm circumference (mm)	537	300 (33)	300	189–409	515	293 (40)	291	176–431
Grip strength (kg)	526	30.0 (11.0)	292	0–98.2	489	17.0 (7.7)	16.2	0–55.6
Biochemical indices								
Plasma calcium (mmol/l)	377	2.33 (0.15)	2.32	1.83–2.82	365	2.35 (0.17)	2.33	1.92–2.86
Plasma phosphorus (mmol/l)	376	0.99 (0.17)	0.98	0.56–2.45	365	1.10 (0.17)	1.10	0.61–2.16
Plasma 25-hydroxy-vitamin D (nmol/l)	446	58.4 (27.7)	53.2	5–207	417	49.6 (23.7)	46.3	7–138
Plasma parathyroid hormone (ng/l)	265	31.1 (16.1)	27.0	6–117	290	36.9 (22.8)	31	9–173
Plasma alkaline phosphatase (IU/l)	433	87.9 (35.6)	81.1	34–433	398	98.4 (95.6)	88.1	42–1369
Plasma creatinine (μ mol/l)	433	94.5 (41.5)	94.0	0–611	399	82.7 (24.4)	80.5	0–192
Plasma albumin (g/l)	430	42.9 (6.0)	42.8	22.1–63.7	407	42.7 (5.6)	42.5	26.1–66.0
Plasma α_1 -antichymotrypsin (g/l)	430	0.38 (0.094)	0.365	0.16–1.14	408	0.39 (0.089)	0.385	0.22–1.01
Estimated average daily dietary intakes								
Energy (MJ)	538	7.95 (1.94)	7.95	3.44–17.3	516	5.95 (1.42)	5.88	1.91–9.77
Calcium (mg)	538	832 (289)	817	237–2,398	516	697 (255)	659	189–2,081
Phosphorus (mg)	538	1,224 (340)	1,195	325–2,695	516	973 (271)	964	262–2,075
Vitamin D (μ g)	538	4.46 (3.57)	3.46	0.1–29.8	516	3.41 (2.79)	2.52	0.1–21.1

^a The values for n in this table and the maximum values for n in the following tables are limited to the numbers definitely known to have died or to have been still alive at the time of the follow-up analysis, i.e. they excluded those (approx. 5% of the original participants) who were lost to follow-up. Where individual index values of n are lower than the maximum in each table, it was because of missing values since not all of the respondents provided blood (or sufficient blood) for every one of the assays [1]

phosphorus ('deleterious', i.e. higher levels = greater risk) and dietary energy ('protective'). Dietary calcium was also 'protective', but it lost its significance when adjusted for dietary energy; dietary phosphorus was 'protective', but again lost much of its significance when adjusted for dietary energy. The following 'risk indices' were significantly 'deleterious': plasma creatinine (kidney function), plasma alkaline phosphatase (marginally significant: bone health), plasma α_1 -antichymotrypsin (acute phase status). Plasma albumin was significantly 'protective', and of the functional and anthropometric indices shown, grip strength, body weight and mid-upper arm circumference were 'protective', body mass index being only modestly protective. Notably, plasma calcium was not a significant predictor, and it remained so after adjustment for plasma albumin [12] (not shown).

Mortality prediction by 25(OH)D was more significant during the winter months (October to March) than the summer months (April to September). During the six winter months, the hazard ratio (95% CI) for both sexes combined was 0.85 (0.74–0.98, $P=0.02$), whereas

during the six summer months, it was 0.92 (0.82–1.03, $P=0.14$). Mortality prediction by 25(OH)D was attenuated (to $P=0.042$, 0.045, respectively), but was not completely abolished by adjustment for either grip strength or for a physical activity score (on a scale of 1–4: very active to very inactive, by questionnaire; Table 2). Mortality prediction by plasma phosphorus was attenuated (to a $P=0.033$, 0.041, respectively) by adjustment for either plasma creatinine or for plasma α_1 -antichymotrypsin (Table 3).

For men (Table 3), significant biochemical and dietary predictors of all-cause mortality were: plasma phosphorus, plasma creatinine and plasma α_1 -antichymotrypsin (all 'deleterious'), and plasma albumin and dietary intake of energy (both 'protective'). For women (Table 3), the significant predictors were plasma alkaline phosphatase, creatinine and α_1 -antichymotrypsin (all 'deleterious'), 25(OH)D (marginally 'protective'), and plasma albumin and phosphorus intake ('protective'). If food energy was included in the model for women, then phosphorus intake still retained its prediction significance ($P=0.01$).

Table 2 Linear regression of plasma bone-related indices versus selected functional and lifestyle indices

	Versus hand grip strength ^{a,b}		Versus physical activity score ^{a,c}		Versus smoking habit ^{a,d}	
	<i>t</i> value	<i>P</i>	<i>t</i> value	<i>P</i>	<i>t</i> value	<i>P</i>
Plasma indices: men						
P-calcium	−0.4	0.7	+1.2	0.2	−1.1	0.3
P-phosphorus	−2.2	0.03	+2.4	0.015	−0.2	0.9
P-25(OH)D	+3.5	0.0005	−3.3	0.001	−2.4	0.02
P-alkaline phosphatase	−2.1	0.04	+1.4	0.15	+3.7	0.0003
P-albumin	+2.7	0.007	−1.9	0.05	−1.1	0.3
P-creatinine	−0.7	0.5	+2.0	0.04	+0.3	0.7
P- α_1 -antichymotrypsin	−2.8	0.005	+3.0	0.003	+4.4	<0.0001
Plasma indices: women						
P-calcium	−0.8	0.5	−0.8	0.4	+0.5	0.6
P-phosphorus	−0.9	0.4	−0.8	0.4	+2.5	0.01
P-25(OH)D	+1.6	0.12	−4.1	<0.0001	−1.8	0.08
P-alkaline phosphatase	−0.4	0.7	+2.3	0.02	+1.3	0.2
P-albumin	+0.2	0.8	−4.2	<0.0001	+0.9	0.4
P-creatinine	−0.5	0.6	−0.3	0.7	+0.1	0.9
P- α_1 -antichymotrypsin	−1.5	0.12	+2.3	0.02	+1.6	0.1

^a Regressions adjusted for age and confined to those subjects for whom mortality data were available. Alkaline phosphatase, creatinine and α_1 -antichymotrypsin were log-transformed before the analyses. *df*=378–435. *P* plasma

^b Continuous variable: mean estimate for both hands. Higher values denote greater hand grip strength [5]

^c Four discrete categories: from 1=very active to 4=very inactive [5]

^d Three discrete categories: 0 = non-smoker; 1 = <20 cigarettes/day; 3 = >20 cigarettes/day [5]

Other potentially influential factors

About 19% of the study respondents were regularly taking over-the-counter dietary supplements which contained vitamin and/or mineral components, at baseline, and of these, three quarters (i.e. 14% overall) were taking vitamin D supplements, but only 5% (i.e. 0.5% overall) were taking over-the-counter supplements that contained calcium and/or phosphorus. The mortality prediction patterns were similar in the (86%) non-vitamin D supplement users, as in the entire cohort, with the exception of plasma 25(OH)D and of dietary phosphorus adjusted for dietary energy in women, both of which lost significance ($P>0.05$) when the vitamin D-containing supplement users were excluded (not shown).

Exclusion of those respondents (approx. 14%) who died <2 years after the baseline fieldwork made little difference to any of the index predictions of mortality, again with the exception of plasma 25(OH)D and of dietary phosphorus adjusted for dietary energy in women, both of which lost significance ($P>0.05$, not shown).

Only approximately 3% of the participants were taking any drugs for the treatment of musculoskeletal disorders at

baseline, and exclusion of these made essentially no difference to the mortality prediction patterns or significances (not shown).

Primary vascular disease mortality

When the dataset was reanalysed, with primary vascular disease mortality as the outcome (i.e. International Classification of Diseases version 9: 390-359 or version 10: I01-I99), then only the following three indices were significant predictors of mortality at $P<0.01$: grip strength, plasma creatinine and antichymotrypsin. Plasma albumin, diet energy and diet phosphorus were marginally significant, with *P* values between 0.03 and 0.06.

Multivariable models

In the multivariable Cox regression models, for combined sexes, mid-upper arm circumference, grip strength, plasma creatinine, albumin and α_1 -antichymotrypsin were all significantly ($P<0.05$) associated with all-cause mortality (results not shown). For men, the significant predictors were grip strength, plasma creatinine and α_1 -antichymotrypsin, and for women, they were mid-upper

Table 3 Age-adjusted hazard ratios for the anthropometric, biochemical and nutritional indices for all-cause mortality, showing both sexes combined, and each sex separately

	Age-adjusted all-cause mortality: hazard ratios (95% CI) [<i>P</i>]		
	Both sexes combined Died (<i>n</i> = 717), alive (<i>n</i> = 337)	Men Died (<i>n</i> = 399), alive (<i>n</i> = 139) ^a	Women Died (<i>n</i> = 318), alive (<i>n</i> = 198) ^a
Indices (per SD)			
Body weight	0.84 (0.77–0.93) [<0.001]	0.84 (0.74–0.95) [0.005]	0.85 (0.74–0.97) [0.02]
Body mass index (BMI)	0.90 (0.83–0.98) [0.02]	0.90 (0.79–1.03) [0.1]	0.90 (0.81–1.01) [0.07]
Waist circumference	0.99 (0.99–1.08) [0.9]	0.95 (0.85–1.07) [0.4]	1.04 (0.92–1.17) [0.6]
Mid-upper arm circumference	0.85 (0.77–0.93) [<0.001]	0.86 (0.76–0.99) [0.03]	0.83(0.74–0.95) [0.005]
Grip strength	0.79 (0.71–0.88) [<0.001]	0.72 (0.64–0.82) [<0.001]	0.97 (0.80–1.17) [0.8]
Plasma calcium (mmol/l)	0.96 (0.88–1.05) [0.3]	0.99 (0.88–1.12) [0.9]	0.92 (0.81–1.05) [0.2]
Plasma phosphorus (P) (mmol/l)	1.13 (1.04–1.23) [0.004]	1.18 (1.06–1.30) [<0.001]	1.04 (0.91–1.20) [0.5]
Plasma P adj. plasma creatinine	1.10 (1.01–1.20) [0.03]	1.17 (1.05–1.30) [0.004]	–
Plasma P adj. for plasma α_1 -antichymotrypsin	1.09 (1.00–1.18) [0.04]	1.10 (1.00–1.21) [0.05]	–
Plasma 25OHD (nmol/l)	0.89 (0.82–0.98) [0.01]	0.91 (0.82–1.02) [0.1]	0.87 (0.75–1.00) [0.06]
Plasma parathyroid hormone (ng/l)	1.03 (0.93–1.15) [0.5]	1.03 (0.88–1.21) [0.7]	1.05 (0.91–1.21) [0.5]
Plasma alkaline phosphatase(U/l)	1.08 (1.01–1.15) [0.02]	1.06 (0.89–1.26) [0.5]	1.08 (1.01–1.16) [0.03]
Plasma creatinine (μ mol/l)	1.24 (1.13–1.35) [<0.001]	1.20 (1.08–1.33) [<0.001]	1.37 (1.13–1.66) [<0.001]
Plasma albumin (g/l)	0.83 (0.76–0.91) [<0.001]	0.84 (0.74–0.94) [0.004]	0.83 (0.72–0.96) [0.01]
Plasma α_1 -antichymotrypsin (g/l)	1.22 (1.14–1.32) [<0.001]	1.21 (1.11–1.33) [<0.001]	1.27 (1.11–1.45) [<0.001]
Daily dietary intakes (per SD)			
Energy	0.86 (0.79–0.94) [0.001]	0.85 (0.76–0.95) [0.003]	0.90 (0.77–1.05) [0.2]
Calcium	0.88 (0.81–0.95) [0.002]	0.88 (0.79–0.98) [0.02]	0.89 (0.78–1.01) [0.07]
Calcium adjusted for diet energy	0.93 (0.84–1.03) [0.2]	0.96 (0.84–1.10) [0.6]	
Phosphorus	0.85 (0.78–0.92) [<0.001]	0.87 (0.78–0.96) [0.005]	0.82 (0.72–0.95) [0.007]
Phosphorus adjusted for diet energy	0.88 (0.78–0.98) [0.02]	0.93 (0.81–1.07) [0.3]	0.79 (0.86–0.95) [0.01]
Vitamin D	0.94 (0.88–1.01) [0.1]	0.90 (0.82–0.99) [0.03]	1.03 (0.91–1.16) [0.6]

^a As explained in the legend of Table 1, these were the study maximum values for *n*; the actual values for each index were the same as in Table 1

arm circumference, plasma creatinine, albumin and α_1 -antichymotrypsin. None of the nutrient status indices or nutrient intake estimates survived into the final multivariable models.

Discussion

Background

Because the predictive value of conventional risk factors for disease and mortality appears to diminish with advancing age [13], recent attention has focused on the discriminative ability of novel risk markers in elderly cohorts [14]. The primary purpose of the present paper was to explore the predictive significance of a subset of the biochemical status indices and nutrient intakes that were measured at baseline as part of the original population surveillance protocol of the NDNS of People Aged 65 Years and Over, with a

specific focus on bone-related nutrients and related risk indices, including hand grip strength (proxy for physical, i.e. muscular, robustness versus frailty) and physical activity score (proxy for muscular activity, together with probable sunlight exposure).

Calcium and phosphorus are major components of bone mineral whose blood concentrations reflect (inter alia) the adequacy of supply, and of metabolic control, of these nutrients in relation to bone health. Plasma 25(OH)D is the preferred index of vitamin D status, which in turn reflects the adequacy of vitamin D supply and, hence, the supply adequacy of its derived hormone, calcitriol, which controls calcium absorption, distribution and delivery. Its adequacy is further reflected by plasma PTH levels since this hormone also reacts to, and controls, bone mineral status and delivery. Plasma alkaline phosphatase activity is another indicator of bone mineral status (in the NDNS survey [5], only total alkaline phosphatase activity was measured, whose activity includes a bone-specific alkaline

phosphatase which is considered to be a more specific bone mineral status indicator). Plasma creatinine levels reflect kidney function, plasma α_1 -antichymotrypsin is a medium-term acute phase indicator (of inflammatory processes), and plasma albumin is an indicator of general and hepatic health, especially in older adults. Of the functional and anthropometric indices reported here, grip strength obviously reflects functional muscular strength; arm circumference is also a proxy for muscle status and muscle wasting. The other anthropometric indices reported (body weight, BMI, waist circumference) reflect body fatness and thus tend to be reduced in frail older people, especially in the event of chronic illness. Of the nutrient intakes that were estimated (from weighed food intake records) during the survey at baseline [5], only the major bone-related nutrient intakes (calcium, phosphorus and vitamin D) are reported here. Whereas calcium and phosphorus are derived from the diet alone, a major source of vitamin D is, of course, the action of sunlight on vitamin D precursors in the skin. About 5% of the survey participants were recorded as taking regular over-the-counter dietary supplements that contained one or more of these three nutrients.

In a previous recent study [1], we showed that plasma zinc (amongst other redox-active nutrient status indices) robustly predicted subsequent all-cause mortality in this survey cohort. We note here that a considerable proportion of the body's zinc content is found in the bone, with possible implications for bone health and metabolic activity.

Several recent studies have reported significant prediction of (better) survival by higher blood vitamin D status indices or vitamin D supplementation [15–26] and/or by lower serum or plasma PTH levels [15, 26–28]. Three recent studies [7–9] have reported poorer survival at higher levels of serum calcium and/or phosphorus, usually attributed to impaired kidney function and/or inflammatory processes, and one of these [8] has also reported an association between mortality and raised serum alkaline phosphatase.

Strengths and limitations of study

Important strengths of the present study were that, as far as possible, the population sample was chosen as being statistically representative of the community-living people of mainland Britain in 1994–1995. A wide range of nutrition-related factors were measured at baseline, including questionnaire-derived socio-demographic information, a 4-day weighed diet estimate, anthropometric measurements, haematology, blood and urine biochemistry (including a large number of nutritional indices), dental assessment [29], etc.; the follow-up period for mortality outcomes was substantial, i.e. 13–14 years.

On the other hand, the survey was originally designed primarily to characterise food choices and nutritional status rather than having specific focus on bone health or subsequent mortality outcomes. Another inevitable weakness, associated inevitably with any cross-sectional national survey, is the fact that the baseline measures were sampled at a single time point only. It is thus, in principle, unable to address issues of long-term causal pathways or of intervening events occurring after the baseline measures. Also, cost considerations and the primary purposes of the original survey limited some of the measurements; thus, for instance, plasma PTH concentrations were measured on a subset only and other potentially relevant indices, such as bone-specific alkaline phosphatase, other bone turnover markers, bone density, etc. were not measured. Although some information was available to us about cause(s) of death, there were too few subjects for whom the primary cause of death was attributed to a musculoskeletal category, in the International Classification of Diseases attributions, to permit a meaningful investigation of mortality by cause of death; therefore, we have focussed primarily on predictors of all-cause mortality.

It is well known that variable misreporting of dietary intakes is a major unresolved problem for the interpretation of all surveys that include the estimation of nutrient intakes. Our survey sought to minimise this problem by the use of robust 4-day diet estimates based on weighed food intakes; however, it is clear from data in the published report [5] (Section 5.2.2 and Table 5.6 (a)) that 41% of the surveyed men and 59% of the women had estimated energy intakes below their calculated basal metabolic rates, suggesting frequent underreporting and/or misreporting of usual intakes. Nevertheless, any measurement error that is attributable to such misreporting would clearly result in the attenuation of the observed relationships rather than the strengthening of relationships. We nevertheless acknowledge that some uncertainty remains in this respect.

Discussion and interpretation of mortality and inter-index observations

Biochemical indices

The observation that plasma albumin concentration was a robust predictor of all-cause mortality in both sexes, higher concentrations being associated with lower risk (qv Table 3), concurs with the traditional viewpoint that plasma albumin has a positive surrogacy for relatively good (physiological) health status in older people. Table 2 shows that plasma albumin was also significantly associated with hand grip strength in men and with physical activity score in women.

Plasma calcium concentrations failed to predict all-cause mortality in this study even after adjustment for plasma albumin concentrations [12]. Likewise, plasma calcium was not significantly associated with hand grip strength, physical activity score or smoking habit in either sex at baseline (Table 2).

25(OH)D was significantly related to hand grip strength in men, to physical activity score in both sexes and to smoking habit in men (Table 2). However, it was only a modest predictor of mortality, higher levels being ‘protective’ as previously reported [15–25], and its significance was readily lost when health- and lifestyle-related adjusters (sunlight exposure, hand grip strength and physical activity) were introduced; it thus appeared to be relatively weak as a mortality predictor in this population where, for instance, plasma 25(OH)D concentrations tend to be generally lower than those observed in the USA. Nevertheless, it is likely that good bone health promotes better physical function and independent living in the elderly; thus, we would have expected the introduction of variables such as physical activity and hand grip strength into the model to attenuate the associations. As expected, the power of its prediction was somewhat greater when the measurement was made in the winter season than when it was made during the summer months, suggesting that the winter nadir [5] may be a more relevant predictive index than the summer maximum. Plasma PTH exhibited no significant predictive power in the present study, possibly because relatively few measurements were available for this index.

Plasma phosphorus was significantly correlated with hand grip strength and with physical activity score in men, but only with smoking habit in women. In men, it was also a robust predictor of mortality, being ‘deleterious’, i.e. higher levels predicting greater risk. As noted above, an association between relatively high serum phosphorus levels and increased morbidity or mortality has been reported previously in other populations [7–9] and is frequently attributed to an association between raised serum phosphorus and either impaired kidney function (due, for instance, to vascular calcification) or chronic inflammatory processes in older people. Adjustment for either plasma creatinine (kidney function index) or for plasma α_1 -antichymotrypsin (inflammation index) did indeed reduce the significance of the plasma phosphorus prediction. It is intriguing, but difficult to explain, that in the present study, the predictive power of plasma phosphorus was confined to the men, being essentially absent from the women (Tables 2 and 4).

Another intriguing, but unexplained, sex difference was that mortality prediction from grip strength was essentially confined to the male subjects (Table 3) and, moreover, that hand grip strength was correlated with several of the plasma status indices in the men, but not in the women (Table 2).

Possibly, men who retain robust grip strength into old age are generally healthier than those who do not, whereas grip strength may be less predictive of good health in older women. Although previous studies on this are not conclusive [30], there appears to be some evidence for stronger mortality prediction by grip strength in older men than older women [31, 32].

Dietary and supplemental intakes

As noted previously [2–4], dietary energy intake (especially when converted to a z-score) was a significant predictor of mortality in men, higher intakes being associated with lower mortality risk. This might be explained by lower mortality risk in those with relatively better appetites and higher energy expenditures (see above). Dietary calcium intakes added little or nothing to the mortality prediction by energy intakes; however, dietary phosphorus intakes were predictive in women only and were not greatly attenuated by the addition of dietary energy to the model. The higher observed food energy and nutrient intakes in men than women here may be attributable primarily to sex differences in lean body mass and also, perhaps, to some differences in energy expenditure.

Vitamin D intake was not a significant predictor in either sex. Intakes of this vitamin are considerably below the reference or recommended intakes for the majority of this age group, 10 $\mu\text{g}/\text{day}$ being the recommendation for people aged 65 years and over in the UK [33–35] and 15 $\mu\text{g}/\text{day}$ for people aged 70 years and over in the USA [36, 37]; yet, <5% of these British community-living survey participants had (estimated) vitamin D intakes of 10 $\mu\text{g}/\text{day}$ or above [5].

Use of over-the-counter dietary supplements appeared not to be a major driver of the association between the nutrients studied (by status or intake) and mortality prediction, except possibly in the case of 25(OH)D. One possible reason why the observed ranges of intakes and status indices were very wide may be that only a subset of the survey respondents was regularly using dietary (nutrient) supplements [5]. A wide range of parathyroid hormone concentrations may imply the existence of secondary hyperparathyroidism in some of the subjects [11].

There was some evidence that the (modest) predictive power of 25(OH)D could be attenuated by deletion of those subjects who died within 2 years of the baseline survey, suggesting that it may be disproportionately driven by subjects with a preexisting morbidity. There were too few respondents who were taking prescribed drugs for treatment of musculoskeletal conditions at baseline, and too little information available about chronic medical conditions at baseline, for it to be

possible to include these potential factors meaningfully in the prediction models used in the present study.

Anthropometry

With regard to the anthropometric indices that were included in the present study, it is noteworthy that in both sexes, both body weight and mid-upper arm circumference were robust predictors of mortality, higher values of both predicting lower risk. Body weight was the stronger predictor in men, whereas arm circumference was a stronger predictor in women. Body mass index, in both sexes, provided little prediction and waist circumference (as an index of fatness) offered essentially none. However, reduced body weight did predict shorter survival in both sexes rather than the opposite prediction, as is generally observed in younger adults. The fact that none of the selected nutrient status indices or nutrient intake estimates survived into multivariable models seems consistent with the view that these nutrient predictors of mortality may reflect physiological or pathological processes, such as renal function or acute phase status.

Conclusion

A number of baseline (survey) indices having known associations with bone health significantly predicted subsequent all-cause mortality (i.e. survival duration) in older British adults. Some of the status indices (especially plasma phosphorus in men) may reflect acute phase status or impaired kidney function; others (including dietary intakes of certain nutrients) may reflect the robustness of appetites and of dentition [29] and the ‘healthiness’ of lifestyles [1–4]. Future studies should attempt to determine, firstly, which indices are the most frequent and robust predictors of all-cause and specific-cause mortality in different populations and, secondly, whether these predictions can imply causal relationships such that dietary or other interventions might promote disease-free longevity.

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Conflicts of interest None.

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