Functional Biochemical and Nutrient Indices in Frail Elderly People Are Partly Affected by Dietary Supplements but Not by Exercise[1]

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ABSTRACT A decline in dietary intake due to inactivity and, consequently, development of a suboptimal nutritional status is a major problem in frail elderly people. However, benefits of micronutrient supplementation, all-round physical exercise or a combination of both on functional biochemical and hematologic indicators of nutritional and health status in frail elderly subjects have not been tested thoroughly. A 17-wk randomized controlled trial was performed in 145 free-living frail elderly people (43 men, 102 women, mean age, 78 ± 5.7 y). Based on a 2 × 2 factorial design, subjects were assigned to one of the following: *1*) nutrient-dense foods, *2*) exercise, *3*) both (*1*) and (*2*) or *4*) a control group. Foods were enriched with micronutrients, frequently characterized as deficient [25–100% of the recommended daily allowance (RDA)] in elderly people. Exercises focused on skill training, including strength, endurance, coordination and flexibility. Dietary intake, blood vitamin levels and nutritional and health indicators, including (pre)albumin, ferritin, transferrin, C-reactive protein, hemoglobin and lymphocytes were measured. At baseline, 28% of the total population had an energy intake below 6.3 MJ, up to a maximum of 93% having vitamin intakes below two thirds of the Dutch RDA. Individual deficiencies in blood at baseline ranged from 3% for erythrocyte glutathione reductase-α to 39% for 25-hydroxy vitamin D and 42% for vitamin B-12. These were corrected after 17 wk in the two groups receiving the nutrient-dense foods, whereas no significant changes were observed in the control or exercise group. Biochemical and hematologic indicators at baseline were within the reference ranges (mean albumin, 46 g/L; prealbumin, 0.25 g/L; hemoglobin, 8.6 mmol/L) and were not affected by any of the interventions. The long-term protective effects of nutrient supplementation and exercise, by maintaining optimal nutrient levels and thereby reducing the initial chance of developing critical biochemical values, require further investigation. Other indicative functional variables for suboptimal nutritional status, in addition to those currently selected, should also be explored. J. Nutr. 129: 2028–2036, 1999.

KEY WORDS: • *biochemical indicators* • *elderly humans* • *nutrient-dense foods* • *physical exercise* • *dietary intake*

Older adults are a heterogeneous group. Individuals differ with respect to the progress of aging due to several biological factors. During the aging process, physical frailty may develop. A more sedentary lifestyle, a reduction in metabolic cell mass and, consequently, lower energy expenditure and dietary intake are important contributors to the progression of frailty. A decline in intake is in turn associated with the risk of developing a suboptimal nutritional state or multiple micronutrient deficiencies. Although the small intestine, pancreas and liver are believed to undergo few clinically relevant changes with normal aging due to their large reserve capacity (Russell 1992, Saltzman and Russell 1998), alterations in absorption and metabolism of several nutrients (including dietary vitamin B-6, vitamin B-12, folate, calcium, iron and zinc) accompany the process of becoming frail. Various disease states such as atrophic gastritis and relatively high levels of medication also contribute to alterations in absorption and metabolism (Ahmed 1992, Saltzman and Russell 1998, Tucker 1995).

Blood concentrations of water-soluble vitamins often show the fastest decline in elderly people with inadequate dietary intake because body reserves are limited (Machlin 1984), but marginal deficiencies of vitamin D and minerals such as iron, magnesium and zinc are reported as well (Commissie Voeding van de Oudere Mens Voedingsraad 1995, Payette and Gray-Donald 1991, Schrijver et al. 1985, Tucker 1995, van-der Wielen et al. 1995).

To date, only a few studies have investigated the influence of nutrient supplementation and/or exercise on multiple indicators of nutritional status in elderly people classified as frail or "at risk" (Fiatarone et al. 1994, Gray-Donald et al. 1995, Lipschitz et al. 1985, Meredith et al. 1992). Physical exercise is reported to increase energy expenditure (Poehlman 1992, Titchenal 1988), resulting in a possible increment in total dietary intake (Mensink and Arab 1989). Additionally, a slowing down or reversal of the overall age-related decline in

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physiologic functioning may occur (Fielding 1995). This may be reflected in the enhancement of a multitude of bodily processes, including nutrient metabolism (Morris and Hardman 1997), organ system functioning (Young 1997), hormone secretion (Lee et al. 1998, Martin et al. 1997) and perhaps gastrointestinal nutrient absorption (Lovat 1996). Mann et al. (1987) showed that multivitamin supplementation increased blood levels of the water-soluble vitamins. This was not observed for fat-soluble vitamins, thereby confirming the theory that greater storage pools of the fat-soluble vitamins exist in the liver and fat tissue.

To date, well-controlled trials investigating possible benefits of all-round physical exercise and/or physiologically dosed micronutrient-dense foods on functional biochemical indicators of nutritional status in frail elderly people have not been published. Previous studies investigated the effects of nutritional supplements only, had small sample size or focused on other outcomes.

For this trial, we hypothesized that either supplementation with a physiologic dose of micronutrients (resulting in a beneficial increase in nutrient status) or a progressive all-round exercise program (which would increase daily energy expenditure and dietary intake) would affect selected biochemical and hematologic indicators of nutritional and health status in a group of community-dwelling frail elderly people. Because exercise might also lead to more efficient nutrient absorption and overall metabolism, a combination of both interventions may be even more beneficial. Nutrient intake, blood nutrient levels as indicators of available body pools (Garry and Koehler 1989) and functional biochemical indicators of overall nutritional and health status were addressed.

MATERIALS AND METHODS

Subjects. The study population consisted of 217 free-living frail elderly Dutch people. The following criteria were used: requirement of health care, such as home care or meals-on-wheels service; age ($\geq$ 70 y); no regular exercise; body mass index (BMI)[3] below average ($\leq$25 kg/m^2 on the basis of self-reported weight and height) or recent weight loss; no use of multivitamin supplements; and ability to understand the study procedures.

All subjects gave their written informed consent. The study protocol was approved by the Medical Ethical Committee of the Division of Human Nutrition and Epidemiology of the Wageningen Agricultural University. Pre- and postintervention measurement(s) were available for 165 subjects. Reasons for drop out (n = 52, 24%) were mainly health problems, including (terminal) disease, hospital admittance, a recent fall and/or fracture. Valid (pre- and postintervention) biochemical variables were available for 145 subjects. Four subjects were excluded because the time between pre- and postintevention measurement was <13 wk as a result of hospitalization; three subjects were not able to visit our research center after intervention because of illness and therefore ended the trial with incomplete blood samples. Venipuncture did not succeed in one subject and 12 subjects were excluded from analyses because of multivitamin use.

Design. Enrollment took place between January and June 1997. Subjects were randomly assigned to one of four intervention groups. The first group (nutrition) received nutrient-dense products and a social program; the second group (exercise) received regular products and an exercise program; the third group (combination) received nutrient-dense products with an exercise program; and the fourth group (control) received regular products and a social program. The intervention period was 17 wk, and data were collected at baseline (wk 0) and after 17 wk (in wk 18). Dietary intake data were collected at baseline and during the last week of intervention (wk 17).

[3] Abbreviations used: BMI, body mass index; CRP, C-reactive protein; EGR, erythrocyte glutathione reductase; ETK, erythrocyte transketolase; PASE, Physical Activity Scale for Elderly; RDA, recommended daily allowance; T4, thyroxine.

Nutrient-dense products. Subjects were asked to consume two products a day, one from a series of fruit products and one from a series of dairy products. Availability of a variety of products was intended to prevent monotony and to increase acceptability of the products. Fresh 100-g servings of fruit-based products (two types each of both fruit juice and compote) and 100-g servings of dairy products (vanilla custard, two types of fruit yogurt and 75 g of cheese curd with fruits) were provided weekly. Daily consumption of two enriched products delivered ~100% of the Dutch recommended daily allowance (RDA) (Commissie Voeding van de Oudere Mens Voedingsraad 1995, Commissie Voedingsnormen Voedingsraad 1989) of the following vitamins: D, E, thiamin, riboflavin, B-6, folic acid, B-12 and C and ~25–100% of the Dutch RDA of the following minerals: calcium (25%), magnesium (25%), zinc (50%), iron (50%) and iodine (100%). Subjects in the control and exercise group received the natural amount of the regular products (amount of vitamins and minerals in regular products at the highest 15% of the concentration in enriched products). Both the enriched and regular products had an energy content of ~0.48 MJ/product.

Exercise program. The main objective of the exercise program was to maintain and/or improve mobility and performance of daily activities essential for independent functioning by maintaining versatility in movement. Perhaps nutritional status could also be improved via more efficient nutrient absorption and metabolism (Lovat 1996, Martin et al. 1997, Morris and Hardman 1997, Young 1997). Emphasis was placed on skill training; muscle strength, coordination, flexibility, speed and endurance were improved by exercises such as walking, stooping and chair stands. Materials included balls, ropes, weights and elastic bands. The second objective was to improve nutritional status through increasing daily activity level, overall energy expenditure and, consequently, dietary intake.

Group sessions were organized twice a week for 45 min and were of moderate, gradually increasing intensity. Because participants were assumed to be fairly inactive at baseline, two sessions per week was considered the maximum number that would achieve adequate compliance. From earlier studies, we knew that with such a program, beneficial effects in functional capacity and muscle strength could be detected (Lord et al. 1996, McMurdo and Rennie 1993). Sessions were supervised by skilled teachers to improve safety and prevent incorrect or harmful movements. To guarantee uniformity, sessions were extensively rehearsed with all teachers together, and an instruction video and manual were prepared in advance. A social program served as a control (for attention) program for the exercise program. Sessions of 90 min were organized once every 2 wk by a skilled creative therapist. This program focused on creative activities, social activities and lectures on topics of interest to elderly people. Transport to and from all sessions was arranged.

Questionnaires. A general questionnaire asked for information on age, sex, marital status, education, living conditions, illness, medicine and supplement use, and smoking habits. Physical activity was assessed using the validated Physical Activity Scale for Elderly (PASE) (Schuit et al. 1997, Washburn et al. 1993).

Anthropometry. All anthropometric measurements were performed with subjects wearing underclothes. Body weight was measured to the nearest 0.01 kg using a digital scale (ED-6-T; Berkel, Rotterdam, The Netherlands) and height was measured to the nearest 0.001 m using a wall-mounted stadiometer. BMI was calculated as weight in kilograms divided by height in meters squared (Fidanza 1991).

Dietary intake. A 3-d (two weekdays and one weekend day; nonconsecutive) estimated dietary record was obtained by three trained dietitians at baseline (wk 0) and in the last week of intervention (wk 17). During a home visit before the intervention period, dietitians provided subjects with a clear explanation of the way to record and estimate portion sizes in household measures. During a second visit, they checked the diary and weighed the portion sizes of the most frequently consumed foods in household measures. Subjects who had problems with writing could use a voice tape recorder. In case of problems occurring during the 3 d of recording, subjects could telephone the dietitians during the daytime or evening. Food consumption data were coded (with frequent cross-checking by all three dietitians), and energy and nutrients were calculated with the com-

TABLE 1

Baseline characteristics of the study population

Variable	Control (n = 34)	Exercise (n = 35)	Combination (n = 39)	Nutrition (n = 37)
Women, %	68	71	72	70
Age,[1] *y*	78.7 ± 6.8	76.5 ± 4.5	78.8 ± 6.1	78.9 ± 4.8
Activity score[2,3]	59 (34–117)	59 (27–96)	62 (30–115)	59 (34–103)
Subjective health[1,4]	7.0 ± 1.5[5]	7.0 ± 1.2	7.1 ± 1.2	6.9 ± 1.7
Height,[1] *m*	1.64 ± 0.07	1.65 ± 0.10	1.65 ± 0.08	1.65 ± 0.10
Weight,[1] *kg*	65.9 ± 10.8	66.4 ± 12.1	67.7 ± 7.8	66.1 ± 8.7
Body mass index,[1] *kg/m²*	24.1 ± 3.2	24.3 ± 3.1	24.9 ± 2.5	24.3 ± 2.3
One or more diseases, %	85	91	95	86
Living alone, %	68	69	69	68
Falling experienced, %	41	51	46	51
Prescribed medicines,[3] *n*	2.5 (0–7)	2.0 (0–6)	2.0 (0–5)	3.0 (0–6)
Supplement usage,[6] %	24	29	38	22
Currently smoking, %	18	11	8	14
Outside daily during sunny periods, %	68	71	77	76
Avoidance of sunlight, %	32	23	36	27

[1] Mean ± SD.
[2] Range Physical Activity Scale for Elderly: 0–400.
[3] Median (P_{10}; P_{90}).
[4] Range: 1–10.
[5] n = 33.
[6] Subjects using multisupplements excluded from all analyses.

puterized Dutch Food Composition Table of 1997 and a supplement (1995) for folate and vitamin B-12 (Stichting Nederlands Voedingsstoffenbestand 1995 and 1997).

Biochemistry. Pre- and postintervention blood samples were collected from fasting subjects between 0700 and 0900 h for all indicators, except samples for complete blood count and vitamin C; for practical reasons, these samples were collected in our research center at 1200 h and immediately put on ice before further processing. Within 1 h of collecting samples for vitamin C analysis, 0.5 mL EDTA plasma was mixed with 2.0 mL metaphosphoric acid (50 g/L, J. T. Baker Bakergrade, Deventer, The Netherlands) to deproteinize the vitamin C sample (analyzed with HPLC-fluorimetry, the CV between runs was 5–10%) (Fidanza 1991, van den Berg et al. 1993). A fresh 3-mL EDTA sample was used for a complete blood count (Coulter Counter type T-860, Coulter, Miami, FL).

For fasting blood samples, 3 mL serum was used for analyses of the serum proteins, including albumin (bromocresol-green), prealbumin, C-reactive protein (CRP), transferrin, ferritin and thyroxine (T4) (immunoturbidimetric principle). A Hitachi-911 automatic analyzer (Hitachi Instrument Division, Japan) and a AIA-600 Enzyme Immunoassay Analyzer (Tosoh, Toyama, Japan) were used with a CV between runs of 1–8%. For thiamin and riboflavin, erythrocyte transketolase (ETK) activity and erythrocyte glutathione reductase (EGR) activity were determined, respectively (kinetic spectrophotometric enzyme determination), with between-run CV of 7–9% (Fidanza 1991, van den Berg et al. 1993). Samples (3 mL) were hemolyzed after slow centrifugation (2000 *g*, twice for 5 min and once for 10 min) and washed with an equal amount of 9 g/L NaCl. After three washing procedures, the erythrocytes were diluted with an equal volume of Nonidet P40 (Boom, Meppel, The Netherlands). For vitamin B-6, serum pyridoxal-5′-phosphate (1 mL) was measured by HPLC-fluorometry with a between-run CV of 5–10% (Fidanza 1991, van den Berg et al. 1993); for vitamin B-12, a 0.5-mL plasma sample was analyzed with the IMx automated immunoassay system (Kuemmerle et al. 1992), and 25-hydroxy vitamin D concentrations were analyzed in a 0.5-mL serum sample for vitamin D with a between-run CV of 5–10% (van den Berg et al. 1991).

All samples were stored at −80°C until analysis. Pre- and postintervention samples were analyzed in the same batch. Analyses were performed by the TNO Nutrition and Food Research Institute, Zeist, The Netherlands, the Department of Clinical Chemistry, University Hospital Nijmegen, The Netherlands (B-12), and the Division of Human Nutrition and Epidemiology, Wageningen Agricultural University, The Netherlands (Coulter counter).

Statistical analysis. Data were analyzed using SAS (version 6, SAS Institute, Cary, NC). Means ± SD, medians (10th–90th percentiles) or percentages of (baseline) values were calculated for all intervention groups. The prevalence of subjects deviating from the reference was calculated as a frequency. Absolute changes ± SD per intervention group were calculated and compared with changes in the control group using an unpaired *t* test. Because many subjects had a lower CRP level than the detection limit of 0.30 mg/L, we set those values at 0.15 mg/L in order to calculate changes on a continuous scale for the whole population. Multiple regression was used to determine the effect of both interventions and a possible interaction on the change in biochemical variables. Because no evidence of an interaction was observed between interventions, comparisons were made between the supplemented group and the nonsupplemented group, and the exercising group and the nonexercising group. For all changes in the variables studied, confounding by baseline age, supplement use and corresponding baseline biochemical value was checked (e.g., for change in albumin, the model was adjusted for baseline albumin and so forth). In the adjusted regression model, only the corresponding baseline biochemical value was added as a confounder because age and supplement use did not contribute significantly to the model. A P-value ≤ 0.05 was considered significant.

RESULTS

On average, 70% of the participants (mean age, 78 y) were women (**Table 1**). In general, none of the baseline variables differed among the four intervention groups except for age (exercise group slightly younger, $P = 0.20$) and the percentage of subjects using single-nutrient supplements (combination group slightly higher, $P = 0.36$). Most population characteristics did not change over the intervention, e.g., change in subjective health (range 1–10) varied between −0.2 and + 0.2 points among the four groups ($P = 0.37$). Only body weight showed a trend toward a decline in the control (−0.3 kg) and nutrition group (−0.1) and a small increase in both the exercise (0.1 kg) and combination (0.2 kg) groups ($P = 0.33$).

The baseline values of dietary intake for men and women

TABLE 2

Baseline daily dietary intake of the study population, percentages of subjects deviating from two thirds of the Dutch recommended dietary allowance (RDA) and dietary intake found in apparently healthy Dutch elderly[1,2]

Parameter	Men[3] (n = 43)	Women[3] (n = 102)	Percentage below two thirds of the Dutch RDA[1,4]		Dutch men of a healthy population[2,3]	Dutch women of a healthy population[2,3]
			% men	% women		
Energy intake, *MJ/d*	8.8 ± 2.0	6.9 ± 1.5	14	34	9.3 ± 2.0	7.7 ± 2.3
Carbohydrate, *g/d*	249 ± 71	196 ± 42	0	4	241 ± 37	204 ± 35
Protein, *g/d*	76 ± 22	62 ± 15	0	3	79 ± 15	71 ± 14
Fat, *g/d*	78 ± 23	65 ± 19			97 ± 15	80 ± 18
Thiamin, *mg/d*	1.37 ± 0.79	0.99 ± 0.55	5	16	1.19 ± 0.28	0.94 ± 0.27
Riboflavin, *mg/d*	1.44 ± 0.58	1.26 ± 0.40	26	16	1.65 ± 0.44	1.63 ± 0.56
Vitamin B-6, *mg/d*	1.52 ± 0.58	1.33 ± 1.18	5	3	1.59 ± 0.40	1.29 ± 0.34
Vitamin B-12, *μg/d*	4.1 ± 2.1	3.0 ± 1.2	5	11	5.8[5]	5.0[5]
Vitamin C, *mg/d*	113 ± 59	92 ± 37	14	12	120 ± 58	118 ± 56
Vitamin D, *μg/d*	3.6 ± 2.0	3.1 ± 1.7	79	93	6.4 ± 2.4	4.8 ± 1.8
Vitamin E,[6] *mg α-toc/d*	6.1 ± 3.0	4.8 ± 1.7	65	66	12.9[5]	10.5[5]
Vitamin A,[7] *mg ret eq/d*	0.99 ± 0.73	0.79 ± 0.52	44	32	1.02[5]	0.86[5]

[1] Dutch RDA, Commissie Voeding van de Oudere Mens Voedingsraad 1995, Commissie Voedingsnormen Voedingsraad 1989.
[2] Data based on various populations (Bergstein and Van Die 1988, Cruz et al. 1996, Commissie Voeding van de Oudere Mens Voedingsraad 1995, van Asselt et al. 1998, van-der Wielen et al. 1996).
[3] Mean ± SD.
[4] Energy: % below 6.3 MJ/d.
[5] Median values.
[6] α-Tocopherol.
[7] Retinol equivalents.

and percentage of subjects below two thirds of the Dutch RDA (Commissie Voeding van de Oudere Mens Voedingsraad 1995, Commissie Voedingsnormen Voedingsraad 1989) are presented in **Table 2**. Comparing the mean intake data of our population with that of healthy Dutch elderly people (Amorim Cruz et al. 1996, Bergstein and Van Die 1988, Commissie Voeding van de Oudere Mens Voedingsraad 1995, van-der Wielen et al. 1996, van Asselt et al. 1998), energy intake in our population was lower, as were protein and fat intakes. Vitamins intakes of riboflavin, B-12, C, D and E were especially below the intake of healthy Dutch elderly people. When two thirds of the Dutch RDA is taken as a cut-off value, macronutrient intake was adequate in our population, whereas vitamin D, E and A in particular were below this cut-off value. Fourteen percent of the men and 34% of the women had energy intakes below 6.3 MJ, the level at which several micronutrient deficiencies can be expected. Mean intake data of each of the three intervention groups (i.e., nutrition, exercise and combination group) were compared with the control group (**Table 3**). Both the exercise and the combination group had a slightly lower energy ($P = 0.051$) and carbohydrate intake ($P < 0.05$) than the control group at baseline. At the end of the intervention, the combination and nutrition group had significantly increased their intakes of those micronutrients, which had been added to the nutrient-dense foods. No significant increases were found in the exercise group compared with the control group.

Blood levels of several selected vitamins and their changes over 17 wk were evaluated; significant increases were detected in 25-hydroxyvitamin D, vitamin B-12, ascorbic acid and pyridoxal-5′-phosphate in both the nutrition and combination group compared with the control group (**Table 4**). ETK-α (as a measure for thiamin) and EGR-α (as a measure for riboflavin) both decreased. The change in ETK-α tended to be significant in the nutrition group ($P = 0.07$) and the change in EGR-α was significant ($P < 0.05$) in the combination group. Because values >1.25 are unfavorable (Schrijver et al. 1985), this is considered a beneficial decrease. The beneficial effects of supplementation are also reflected in the percentages of subjects with values outside the reference values pre- and postintervention (Table 4). Overall, very few subjects in the supplemented groups (between 0 and 15%) were classified as deficient after intervention. No significant differences in the changes were found between the exercise group and the control group. Because no evidence of interaction was found, we focused on the main effects (i.e., the supplemented group vs. the nonsupplemented group, and exercise vs. nonexercise). For all micronutrients under study, we adjusted the models for the corresponding baseline values. Significantly greater increases were found in micronutrient levels in the supplemented group compared with the nonsupplemented group (all $P < 0.003$), whereas no significant difference in changes occurred in the exercisers vs. nonexercisers (all $P > 0.15$, data not shown).

In general, all baseline values of the other selected biochemical and hematologic indicators fell within or above the range of the reference values, meaning that no clinical deficiencies of any indices were observed (**Table 5**). No significant differences in the increases in the intervention groups compared with the control group were found. Only in albumin, prealbumin and T4 was a slight improvement ($P \leq 0.05$) noted in the nutrition group compared with the control group. Hemoglobin, hematocrit and number of red blood cells tended ($P < 0.05$) to decline in all groups, whereas the mean number of white blood cells and lymphocytes increased slightly but not significantly ($0.14 < P < 0.97$) compared to baseline.

For CRP (an indicator for acute phase proteins), statistical analyses were conducted for the total group in which values below detection rate were set at a fixed level of 0.15 mg/L. In addition, analyses were done only for subjects who had measurable values ($n = 22$). The mean change in the group receiving nutrient-dense foods was −0.3 ± 1.2 mg/L ($n = 6$); in the exercise group, the mean change was −1.3 ± 1.2 mg/L ($n = 5$),

TABLE 3

Dietary intake, changes after 17 wk and percentage of subjects below two thirds of the Dutch RDA for the four intervention groups[1,2,3]

Variable	Control (n = 34)	Exercise (n = 34)	Combination (n = 38)	Nutrition (n = 37)
Energy intake, *MJ/d*				
Baseline	7.7 ± 2.2	7.2 ± 1.8[4]	7.1 ± 1.4[4]	7.8 ± 1.8
Change	−0.4 ± 2.1	0.2 ± 1.2	0.1 ± 1.3	−0.4 ± 1.4
Pre-/Postintervention < reference, %	21/38	32/21	34/34	22/30
Carbohydrate, *g/d*				
Baseline	223 ± 65	209 ± 60*	196 ± 43*	222 ± 59
Change	−7 ± 66	2 ± 34	9 ± 38	−16 ± 39
Pre-/Postintervention < reference, %	6/9	0/0	3/0	0/3
Protein, *g/d*				
Baseline	68 ± 22	65 ± 20	67 ± 16	66 ± 15
Change	0.8 ± 14	4 ± 17	−0.8 ± 14	−0.7 ± 15
Pre-/Postintervention < reference, %	3/6	0/0	3/0	0/0
Fat, *g/d*				
Baseline	69 ± 27	68 ± 18	67 ± 17	72 ± 22
Change	−3 ± 23	2 ± 18	0.9 ± 18	−2 ± 21
Pre-/Postintervention < reference, %	—	—	—	—
Thiamin, *mg/d*				
Baseline	1.16 ± 0.55	1.05 ± 0.55	1.15 ± 0.89	1.06 ± 0.55
Change	−0.11 ± 0.60	−0.05 ± 0.64	0.78 ± 0.51***	0.86 ± 0.67***
Pre-/Postintervention < reference, %	9/21	15/6	16/0	8/5
Riboflavin, *mg/d*				
Baseline	1.34 ± 0.52	1.19 ± 0.46	1.33 ± 0.47	1.38 ± 0.40
Change	0.16 ± 0.45	0.15 ± 0.33	1.25 ± 0.55***	1.34 ± 0.71***
Pre-/Postintervention < reference, %	21/18	26/6	13/0	11/0
Vitamin B-6, *mg/d*				
Baseline	1.35 ± 0.35	1.67 ± 2.02	1.23 ± 0.32	1.32 ± 0.43
Change	0.03 ± 0.36	−0.37 ± 2.06	1.22 ± 0.41***	1.27 ± 0.46***
Pre-/Postintervention < reference, %	3/3	6/3	0/0	3/0
Vitamin B-12, *μg/d*				
Baseline	3.47 ± 2.06[5]	3.12 ± 1.30	3.44 ± 1.38	3.45 ± 1.52
Change	0.72 ± 2.34	0.91 ± 3.13	2.13 ± 1.50**	3.42 ± 4.24**
Pre-/Postintervention < reference, %	12/6	9/3	8/0	8/3
Vitamin C, *mg/d*				
Baseline	91.2 ± 34.5	108.6 ± 42.9	88.7 ± 45.3	105.4 ± 54.4
Change	3.1 ± 42.1	−19.3 ± 50.4	70.0 ± 40.6***	69.2 ± 59.7***
Pre-/Postintervention < reference, %	12/15	3/9	16/0	16/3
Vitamin D, *μg/d*				
Baseline	3.5 ± 2.3	3.1 ± 2.1	3.3 ± 1.3	3.2 ± 1.5
Change	0.2 ± 1.6	−0.4 ± 2.4	10.6 ± 4.6***	11.6 ± 6.6***
Pre-/Postintervention < reference, %	85/79	94/100	92/3	84/8
Vitamin E, *mg α-tocopherol/d*				
Baseline	4.8 ± 1.8	5.0 ± 1.8	5.5 ± 2.4	5.4 ± 2.8
Change	0.2 ± 2.3	−0.3 ± 2.6	10.5 ± 4.4***	11.6 ± 6.4***
Pre-/Postintervention < reference, %	79/68	74/79	59/0	57/0
Vitamin A, *mg retinol equivalents/d*				
Baseline	0.83 ± 0.54	0.86 ± 0.53	0.80 ± 0.49	0.93 ± 0.79
Change	0.04 ± 0.76	0.02 ± 0.74	−0.04 ± 0.54	−0.03 ± 0.63
Pre-/Postintervention < reference, %	35/32	29/24	42/37	32/32

[1] Means ± SD.
[2] Recommended daily allowances (Commissie Voeding van de Oudere Mens Voedingsraad 1995, Commissie Voedingsnormen Voedingsraad 1989).
[3] Two subjects excluded because of an incomplete postintervention diary.
[4] $P = 0.05$ compared with control group.
[5] $n = 33$.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ compared with control group.

and in the combination group, it was −8.5 ± 17.0 mg/L ($n = 5$) vs. an increase in the control group of 7.3 ± 12.9 mg/L ($n = 6$).

In **Table 6**, adjusted (for baseline values) differences in change in selected biochemical and hematologic variables between the nutrient-dense and regular food groups and the exercise vs. nonexercise groups are shown. Only the levels of albumin and prealbumin were significantly improved after 17 wk of consuming nutrient-dense foods. No meaningful differences were found in the other variables between either consumers of nutrient-dense foods and regular foods, or between exercisers and nonexercisers.

DISCUSSION

Nutrient-dense foods containing a physiologic dose of those micronutrients, frequently characterized as deficient in frail

TABLE 4

Blood vitamin levels, changes after 17 wk of the study population, values of a Dutch healthy elderly population and reference values for deficiencies[1,2]

Variable[1]	Control (n = 34)	Exercise (n = 35)	Combination (n = 39)	Nutrition (n = 37)	Dutch healthy elderly[2] Men	Dutch healthy elderly[2] Women	Reference values for deficiencies[2]
25-Hydroxy vitamin D, *nmol/L*							
Baseline	36 ± 20	40 ± 20	39 ± 16	37 ± 20	42	42	<30
Change	5 ± 9	4 ± 12	31 ± 18***	35 ± 18***			
Pre-/Postintervention < reference, %	44/38	29/26	33/0	51/0			
ETK-α[3]							
Baseline	1.15 ± 0.13	1.13 ± 0.10	1.12 ± 0.13	1.11 ± 0.12	1.10	1.10	>1.25
Change	0.04 ± 0.17	0.01 ± 0.13	0.00 ± 0.14	−0.03 ± 0.14[4]			
Pre-/Postintervention < reference, %	24/18	11/11	15/15	8/3			
EGR-α[5]							
Baseline	1.08 ± 0.13	1.08 ± 0.08	1.06 ± 0.09	1.04 ± 0.06	1.13	1.13	>1.25
Change	−0.03 ± 0.08	−0.03 ± 0.05	−0.07 ± 0.08*	−0.05 ± 0.07			
Pre-/Postintervention < reference, %	6/3	3/0	3/0	3/0			
Pyridoxal-5-phosphate, *nmol/L*							
Baseline	33 ± 22	34 ± 21	36 ± 29	39 ± 25	49	51	<20
Change	−3 ± 16	−0 ± 27	19 ± 26***	32 ± 29***			
Pre-/Postintervention < reference, %	24/24	23/17	26/3	14/0			
Vitamin B-12, *pmol/L*							
Baseline	252 ± 136	236 ± 94	299 ± 139	280 ± 112	277	280	<221
Change	−8 ± 43	−5 ± 40	54 ± 75***	78 ± 66***			
Pre-/Postintervention < reference, %	47/44	54/51	28/15	41/11			
Ascorbic acid,[6] μ*mol/L*							
Baseline	53 ± 27	65 ± 19	60 ± 25	67 ± 21	90	61	<23
Change	−1 ± 20	−2 ± 20	18 ± 31**	12 ± 15**			
Pre-/Postintervention < reference, %	19/19	0/3	13/0	3/0			

[1] Mean ± SD.
[2] Haller et al. (1996), Lowik et al. (1990), Lowik et al. (1992), Ooms (1994), Schrijver et al. (1985), van Asselt et al. (1998), van-der Wielen et al. (1995).
[3] Erythrocyte transketolase-α.
[4] $P = 0.07$.
[5] Erythrocyte glutathione-α.
[6] Control, n = 31; exercise, n = 34; combination, n = 38, nutrition, n = 34.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ with respect to control group.

elderly people, significantly improved blood vitamin levels and corrected individual deficiencies. However, despite these individual vitamin deficiencies at baseline, mean values of selected biochemical and hematologic indicators, were not below reference values. Therefore, in these frail elderly people, none of the selected indicators seemed to be considerably affected by either nutritional supplementation or the specifically designed all-round exercise program.

In affluent societies, nutritional deficiencies are not common in healthy elderly people (Lowik et al. 1990), but low dietary intakes and clinically relevant deficiencies are evident in institutionalized elderly people. This latter group is physically inactive, may have reduced energy needs and is deteriorating in health (Rosenberg 1994). Our population of community-dwelling frail elderly people can be (to a lesser extent) regarded as such a group. From several selected indicators, it appeared that we studied an elderly group whose health profile was indeed worse than that of apparently healthy Dutch elderly people. Their mean BMI was lower than that of the Dutch elderly in the European Seneca study (24 kg/m^2 vs. 26 kg/m^2 in men and 28 kg/m^2 in women) (de Groot et al. 1996); self-rated health was lower (7.0 vs. 7.7) as was their activity level (PASE score 64 vs. 85) (Schuit 1997, Schuit et al. 1997). Mean scores on physical fitness tests were below average as well (Chin A Paw et al., unpublished data). In addition, 34% of our female subjects had a low energy intake (<6.3 MJ) and relatively low intakes of several vitamins. Blood vitamin deficiency rates of the total group varied from 42% for vitamin B-12 and 39% for serum 25-hydroxy vitamin D to 3% for EGR-α (a functional measure of riboflavin). For most vitamins, blood concentrations in our study population were lower than values in healthy Dutch elderly people (Haller et al. 1996, Lowik et al. 1990, 1992 and 1993, Ooms 1994, Schrijver et al. 1985, van-der Wielen et al. 1995, van Asselt et al. 1998).

On the group level, however, no clinically relevant deficiencies of functional variables were noted. Indicators of poor protein status or of chronic or acute illness such as low albumin, prealbumin and transferrin levels, low lymphocyte count or high CRP levels were not notably prevalent in our frail population. This may provide an explanation for the fact that despite the observed significant improvement in blood vitamin levels in the supplemented groups (confirming that our nutrient-dense foods had indeed been consumed and that the vitamins provided were indeed circulating in blood), we did

TABLE 5

Biochemical and hematologic indicators, changes after 17 wk of the study population and references values for clinical deficiencies[1]

Variable[1]	Control (n = 34)	Exercise (n = 35)	Combination (n = 39)	Nutrition (n = 37)	Reference values for clinical deficiencies[2]
Albumin, *g/L*					
Baseline	45 ± 3	46 ± 2	46 ± 3	46 ± 3	<35
Change	−1 ± 2	−0 ± 2	−0 ± 2	0 ± 2[3]	
Prealbumin, *g/L*					
Baseline	0.24 ± 0.04	0.25 ± 0.04	0.24 ± 0.05	0.25 ± 0.06	<0.10
Change	−0.01 ± 0.03	−0.00 ± 0.02	−0.00 ± 0.02	0.01 ± 0.02**	
C-reactive protein, *mg/L*					
Baseline	1.3 ± 2.5	1.1 ± 2.5	3.2 ± 9.8	1.3 ± 2.5	>10
Change	0.9 ± 6.2	−0.1 ± 1.9	−0.2 ± 13.4	−0.1 ± 1.7	
Ferritin, *μg/L*					
Baseline	124 ± 86	135 ± 96	153 ± 121	99 ± 68	<20 (men); <10.0 (women)
Change	3 ± 52	−14 ± 28	−1 ± 35	4 ± 24	
Transferrin, *g/L*					
Baseline	2.99 ± 0.57	2.96 ± 0.52	2.89 ± 0.42	3.16 ± 0.59	<2.30
Change	−0.00 ± 0.23	0.09 ± 0.35	−0.01 ± 0.21	−0.02 ± 0.18	
Thyroxine, 10^{-5} *g/L*					
Baseline	7.5 ± 1.6	7.6 ± 1.5	7.4 ± 1.4	7.4 ± 1.2	<4.0
Change	−0.1 ± 0.7	−0.2 ± 0.6	−0.2 ± 1.3	0.4 ± 0.8*	
Hemoglobin, *mmol/L*					
Baseline	8.4 ± 0.7	8.6 ± 0.7	8.8 ± 0.7	8.6 ± 0.7	<8.7 (men); <7.5 (women)
Change	−0.2 ± 0.4	−0.3 ± 0.3	−0.3 ± 0.3	−0.2 ± 0.3	
Hematocrit					
Baseline	0.41 ± 0.03	0.42 ± 0.03	0.43 ± 0.03	0.42 ± 0.03	<0.43 (men);<0.36 (women)
Change	−0.01 ± 0.02	−0.00 ± 0.01	−0.01 ± 0.01	−0.01 ± 0.02	
Red blood cells, $\times 10^{12}$*/L*					
Baseline	4.49 ± 0.43	4.57 ± 0.37	4.69 ± 0.37	4.53 ± 0.38	<4.22 × 10^{12} (men); <3.77 × 10^{12} (women)
Change	−0.09 ± 0.20	−0.06 ± 0.16	−0.19 ± 0.13*	−0.09 ± 0.17	
White blood cells, $\times 10^{9}$*/L*					
Baseline	8.10 ± 1.98	7.35 ± 1.66	8.11 ± 2.56	7.18 ± 1.52	<4.0 or >12.0 × 10^{9}
Change	0.04 ± 1.55	0.20 ± 1.35	0.01 ± 1.49	0.29 ± 1.14	
Lymphocytes, %					
Baseline	27.3 ± 7.4	27.8 ± 6.9	29.5 ± 7.2	29.8 ± 5.6	<20 or >50
Change	0.3 ± 5.8	0.9 ± 5.4	1.3 ± 5.7	0.2 ± 4.5	

[1] Mean ± SD.
[2] Reference values based on laboratory stated lower limits and studies from van-der Wielen (1995).
[3] $P = 0.05$; *$P < 0.05$; **$P < 0.01$ with respect to control group.

not detect many clinically relevant beneficial changes in the selected indicators. Only albumin and prealbumin improved significantly after the 17-wk nutritional intervention, although levels were regarded as adequate at baseline. However, the relevance of these increases is equivocal, i.e., the change in (pre)albumin may be attributed only to chance. In a subgroup with measurable values of CRP, supplementation and exercise seemed to be beneficial, but due to a small sample size, this finding should also be interpreted with caution.

Mann et al. (1987) observed that 4 mo of daily multivitamin supplementation with tablets improved blood levels of the water-soluble vitamins in elderly people. For the fat-soluble vitamins, this was not shown. In our supplemented groups, the water-soluble vitamins increased significantly. Because we measured only vitamin D, a fat-soluble vitamin that frequently is low in elderly people, we cannot comment on improvement of fat-soluble vitamins in general.

Until now, the clinical importance of improved vitamin levels as such has not been evaluated in well-controlled intervention trials. Very few studies have focused on the effects of both exercise and nutrition on several nutritional and health indicators in frail elderly people (Fiatarone et al. 1994), and only very limited information is available about improvements in functional (biochemical and hematologic) indicators by either type of intervention (Lipschitz et al. 1985, Meredith et al. 1992). Also, as far as we know, studies with an all-round progressive exercise program combined with provision of a physiologic dose of micronutrients have not been performed in community-dwelling frail elderly people. It was hypothesized that the physical exercise program would improve activity level, energy expenditure and hence dietary intake. In addition, other beneficial effects on a multitude of bodily processes may be attributed to exercise as well. Gastrointestinal dysmotility, for example, may be caused by hypothyroidism and may be enhanced by physical exercise (Lovat 1996). Others have postulated that not only thyroid hormone levels (Lee et al. 1998, Zerath et al. 1997) but also growth hormone (Martin et al. 1997), insulin and glucose dynamics and lipoprotein metabolism (Morris and Hardman 1997) can be affected by certain types of programmed exercise. Serum albumin has been positively associated with skeletal muscle mass (Baumgartner et al. 1996) and may therefore be influenced by physical activity. Perhaps several other (still unknown) beneficial effects on metabolism and organ function in aging persons may be induced by regular exercise. Our program may unintentionally have been of too low an intensity or of too short duration to induce any change in energy expenditure and dietary intake, or gastrointestinal absorption and metabolism. Hence, individual deficient nutrient blood levels were not corrected in the exercising group during the intervention period. Yet, the

TABLE 6

Adjusted (for the baseline value) differences in the change (95% confidence intervals) of biochemical variables, according to type of intervention (n = 145)

	Nutrient-dense vs. regular foods Difference (95% CI)	Exercise vs. no exercise Difference (95% CI)
Albumin, *g/L*	0.6 (0.0;1.2)	0.2 (−0.4;0.9)
Prealbumin, *g/L*	0.01 (0.00;0.02)	−0.00 (−0.01;0.01)
C-reactive protein,[1] *mg/L*	0.4 (−1.5;2.3)	0.3 (−1.5;2.2)
Ferritin, *μg/L*	7 (−4;18)	−7 (−18;5)
Transferrin, *g/L*	−0.06 (−0.14;0.02)	0.04 (−0.04;0.13)
Thyroxine, 10^{-5} *g/L*	0.2 (−0.1;0.5)	−0.3 (−0.6;−0.0)
Hemoglobin, *mmol/L*	0.0 (−0.1;0.1)	−0.1 (−0.2;0.0)
Hematocrit	−0.00 (−0.01;0.00)	−0.00 (−0.01;0.00)
Red blood cell, $n \times 10^{12}$/*L*	−0.06 (−0.11;−0.00)	−0.03 (−0.08;0.03)
White blood cell, $n \times 10^{9}$/*L*	0.01 (−0.43;0.46)	−0.06 (−0.50;0.39)
Lymphocytes, %	0.5 (−1.2;2.2)	1.0 (−0.6;2.7)

[1] Difference in C-reactive protein calculated only for subjects with measurable values: nutrient-dense vs. regular (n = 11): −3.2 (−9.4;3.0); exercise vs. no exercise (n = 11): −4.1 (−10.3;2.1).

expected beneficial effects of exercise might be expressed in the long term as maintenance of bodily tissues, organ systems and biochemical variables. Additionally, it is possible that favorable effects on biochemical indicators could have been found in a frailer, bedridden, elderly population.

Our findings are in agreement with observations of Lipschitz et al. (1985) who studied supplementation in a "meals-on-wheels elderly population." They observed no change in serum ferritin levels, hemoglobin levels (not even in persons with anemia) or lymphocyte count but found a modest rise in serum albumin and in several selected nutrient concentrations. Additionally, Meredith et al. (1992) found normal nutritional biochemical values at baseline and no change in these variables after a refeeding program during physical rehabilitation in elderly men.

It has been suggested that the failure of most functional indicators to improve with nutritional support implies that abnormalities are age or disease related rather than nutrition related (Lipschitz et al. 1985). Other explanations also exist. Slight alterations in (micro)nutrient metabolism due to organ dysfunction may prevent the corrected blood nutrient levels from being of benefit. Another possibility is the occurrence of normal blood plasma or red cell concentrations as a result of resorption from other tissues in chronically deficient people. For the activity coefficients of ETK and EGR, long-term deficiency may be masked by decreased synthesis or kinetic functions of the apoenzyme involved, thereby establishing a new balance (Buttery et al. 1982, Cooperman 1984, Glatzle et al. 1970, Warnock 1970). Perhaps the reference values for clinically relevant deficiencies require some reevaluation against recently postulated "optimal nutrient levels." The relatively short intervention period of this study should also be noted. Long-term protective effects of nutrient supplementation on biochemical and hematologic variables may occur because of maintenance of the optimal nutrient levels. However, benefits from this maintenance may be measurable only after many years.

Alternatively, because no multiple clinically relevant deficiencies at baseline were found, no relevant improvements might be expected after 17 wk of intervention. The fact that our variables did not change after intervention is consistent with earlier studies (Lipschitz et al. 1985, Meredith et al. 1992). It suggests that improving these currently selected biochemical and hematologic indicators in these specific community-dwelling frail elderly populations may not necessarily be the first aim. On the other hand, the risk of developing a "delayed" suboptimal nutritional state in the long term as a result of exhausted body reserves may be present in these frail groups. This may not be detected immediately because a renewed but unfavorable balance through tissue resorption may be initiated in the first place. Long-term effects of supplementation and also exercise should therefore be investigated; the mechanisms at work within subjects that are deficient must be understood. In addition, the relationships between and effects on other functional indicators such as incidence of (infectious) diseases, osteoporosis and physical fitness and functioning should be the topic of further research in this frail elderly community-dwelling population.

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LITERATURE CITED

Ahmed, F. E. (1992) Effect of nutrition on the health of the elderly. J. Am. Diet. Assoc. 92: 1102–1108.

Amorim Cruz, J., Moreiras, O. & Brzozowska, A. (1996) Longitudinal changes in the intake of vitamins and minerals of elderly Europeans. SENECA Investigators. Eur. J. Clin. Nutr. 50 (suppl. 2): S77–S85.

Baumgartner, R. N., Koehler, K. M., Romero, L. & Garry, P. J. (1996) Serum albumin is associated with skeletal muscle in elderly men and women. Am. J. Clin. Nutr. 64: 552–558.

Bergstein, I. & Van Die, I. (1988) Vitamine D en de voeding van ouderen. Ned. Tijdschr. Diët. 43: 169–172.

Buttery, J. E., Milner, C. R. & Chamberlain, B. R. (1982) The NADH-dependent transketolase assay: a note of caution. Clin. Chem. 28: 2184–2185.

Commissie Voeding van de Oudere Mens Voedingsraad (1995) Voeding van de Oudere Mens, 1st ed., pp. 1–85. Voedingsraad, The Hague, The Netherlands.

Commissie Voedingsnormen Voedingsraad. (1989) Nederlandse Voedingsnormen, 2nd ed., pp. 1–293. Voedingsraad, The Hague, The Netherlands.

Cooperman, J. M. (1984) Riboflavin. In: Handbook of Vitamins. Nutritional, Biochemical and Clinical Aspects (Machlin, J. L., ed.), pp. 299–327. Marcel Dekker, New York, NY.

de Groot, C.P.G.M., Perdigao, A. L. & Deurenberg, P. (1996) Longitudinal changes in anthropometric characteristics of elderly Europeans. SENECA Investigators. Eur. J. Clin. Nutr. 50 (suppl. 2): S9–S15.

Fiatarone, M. A., O'Neill, E. F., Ryan, N. D., Clements, K. M., Solares, G. R., Nelson, M. E., Roberts, S. B., Kehayias, J. J., Lipsitz, L. A. & Evans, W. J. (1994) Exercise training and nutritional supplementation for physical frailty in very elderly people. N. Engl. J. Med. 330: 1769–1775.

Fidanza, F. (1991) Nutritional Status Assessment: A Manual for Population Studies, pp. 1–486. Chapman and Hall, New York, NY.

Fielding, R. A. (1995) Effects of exercise training in the elderly: impact of progressive-resistance training on skeletal muscle and whole-body protein metabolism. Proc. Nutr. Soc. 54: 665–675.

Garry, P. J. & Koehler, K. M. (1989) Problems in Interpretation of Dietary and Biochemical Data from Population Studies. In: Present Knowledge in Nutrition. pp. 407–414.

Glatzle, D., Korner, W. F., Christeller, S. & Wiss, O. (1970) Method for the detection of a biochemical riboflavin deficiency. Stimulation of NADPH2-dependent glutathione reductase from human erythrocytes by FAD in vitro. Investigations on the vitamin B2 status in healthly people and geriatric patients. Int. Z. Vitaminforsch. 40: 166–183.

Gray-Donald, K., Payette, H. & Boutier, V. (1995) Randomized clinical trial of

nutritional supplementation shows little effect on functional status among free-living frail elderly. J. Nutr. 125: 2965–2971.
Haller, J., Weggemans, R. M., Lammi, K. C. & Ferry, M. (1996) Changes in the vitamin status of elderly Europeans: plasma vitamins A, E, B-6, B-12, folic acid and carotenoids. SENECA Investigators. Eur. J. Clin. Nutr. 50 (suppl. 2): S32–S46.
Kuemmerle, S. C., Boltinghouse, G. L., Delby, S. M., Lane, T. L. & Simondsen, R. P. (1992) Automated assay of vitamin B-12 by the Abbott IMx analyzer. Clin. Chem. 38: 2073–2077.
Lee, M. S., Kang, C. W., Shin, Y. S., Huh, H. J., Ryu, H., Park, J. H. & Chung, H. T. (1998) Acute effects of chundosunbup qi-training on blood concentrations of TSH, calcitonin, PTH and thyroid hormones in elderly subjects. Am. J. Chin. Med. 26: 275–281.
Lipschitz, D. A., Mitchell, C. O., Steele, R. W. & Milton, K. Y. (1985) Nutritional evaluation and supplementation of elderly subjects participating in a "meals on wheels" program. J. Parent. Enteral Nutr. 9: 343–347.
Lord, S. R., Lloyd, D. G., Nirui, M., Raymond, J., Williams, P. & Stewart, R. A. (1996) The effect of exercise on gait patterns in older women: a randomized controlled trial. J. Gerontol. A Biol. Sci. Med. Sci. 51: M64–M70.
Lovat, L.B. (1996) Age related changes in gut physiology and nutritional status. Gut 38: 306–309.
Lowik, M.R.H., Hulshof, K. F., Schneijder, P., Schrijver, J., Colen, A. A. & van Houten, P. (1993) Vitamin C status in elderly women: a comparison between women living in a nursing home and women living independently. J. Am. Diet. Assoc. 93: 167–172.
Lowik, M.R.H., Schrijver, J., Odink, J., van den Berg, H., Wedel, M. & Hermus, R. J. (1990) Nutrition and aging: nutritional status of "apparently healthy" elderly (Dutch Nutrition Surveillance System). J. Am. Coll. Nutr. 9: 18–27.
Lowik, M.R.H., van den Berg, H., Schrijver, J., Odink, J., Wedel, M. & van Houten, P. (1992) Marginal nutritional status among institutionalized elderly women as compared to those living more independently (Dutch Nutrition Surveillance System). J. Am. Coll. Nutr. 11: 673–681.
Machlin, L. J. (1984) Handbook of Vitamins—Nutritional, Biochemical and Clinical Aspects. Marcel Dekker, New York, NY.
Mann, B. A., Garry, P. J., Hunt, W. C., Owen, G. M. & Goodwin, J. S. (1987) Daily multivitamin supplementation and vitamin blood levels in the elderly: a randomized, double-blind, placebo-controlled trial. J. Am. Geriatr. Soc. 35: 302–306.
Martin, F. C., Yeo, A. L. & Sonksen, P. H. (1997) Growth hormone secretion in the elderly: ageing and the somatopause. Bailliere's Clin. Endocrinol. Metab. 11: 223–250.
McMurdo, M. E. & Rennie, L. (1993) A controlled trial of exercise by residents of old people's homes. Age Ageing 22: 11–15.
Mensink, G. B. & Arab, L. (1989) Relationships between nutrient intake, nutritional status and activity levels in an elderly and in a younger population; a comparison of physically more active and more inactive people. Z. Gerontol. 22: 16–25.
Meredith, C. N., Frontera, W. R., O'Reilly, K. P. & Evans, W. J. (1992) Body composition in elderly men: effect of dietary modification during strength training. J. Am. Geriatr. Soc. 40: 155–162.
Morris, J. N. & Hardman, A. E. (1997) Walking to health. Sports Med. 23: 306–332.
Ooms, M. E. (1994) Vitamin D status and sex hormone binding globulin: determinants of bone turnover and bone mineral density in elderly women. In: Osteoporosis in Elderly Women. Vitamin D Deficiency and Other Risk Factors, pp. 69–83. Urije Universiteit, Amsterdam, The Netherlands.
Payette, H. & Gray-Donald, K. (1991) Dietary intake and biochemical indices of nutritional status in an elderly population, with estimates of the precision of the 7-d food record. Am. J. Clin. Nutr. 54: 478–488.
Poehlman, E. T. (1992) Energy expenditure and requirements in aging humans. J. Nutr. 122: 2057–2065.
Rosenberg, I. H. (1994) Nutrition and aging. In: Principles of Geriatric Medicine and Gerontology (Hazzard, W. R., Bierman, E. L., Blass, J. P., Ettinger, W. H., Halter, J. B. & Andres, R., eds.), pp. 49–59. McGraw-Hill, New York, NY.
Russell, R. M. (1992) Changes in gastrointestinal function attributed to aging. Am. J. Clin. Nutr. 55: 1203S–1207S.
Saltzman, J. R. & Russell, R. M. (1998) The aging gut. Nutritional issues. Gastroenterol. Clin. N. Am. 27: 309–324.
Schrijver, J., van Veelen, B.W.C. & Schreurs, W.H.P. (1985) Biochemical evaluation of the vitamin and iron status of an apparently healthy Dutch free-living elderly population. Comparison with younger adults. Int. J. Vitam. Nutr Res. 55: 337–349.
Schuit, A. J. (1997) Regular Physical Activity in Old Age, Effect on Coronary Heart Disease Risk Factors and Well-Being, pp. 1–163. Wageningen Agricultural University, Wageningen, The Netherlands.
Schuit, A. J., Schouten, E. G., Westerterp, K. R. & Saris, W. H. (1997) Validity of the Physical Activity Scale for the Elderly (PASE): according to energy expenditure assessed by the doubly labeled water method. J. Clin. Epidemiol. 50: 541–546.
Stichting Nederlands Voedingsstoffenbestand (1995) Dutch Nutrient Data Base/Nederlandse Voedingsmiddelentabel. Voorlichtingsbureau voor de Voeding, The Hague, The Netherlands.
Stichting Nederlands Voedingsstoffenbestand (1997) Dutch Nutrient Data Base/Nederlandse Voedingsmiddelentabel. Voorlichtingsbureau voor de Voeding, The Hague, The Netherlands.
Titchenal, C. A. (1988) Exercise and food intake. What is the relationship? Sports Med 6: 135–145.
Tucker, K. (1995) Micronutrient status and aging. Nutr. Rev. 53: S9–S15.
van Asselt, D.Z.B., de Groot, L.C.P.G.M., Van Staveren, W. A., Blom, H. J., Wevers, R. A., Biemond, I. & Hoefnagels, W. H. (1998) Role of cobalamin intake and atrophic gastritis in mild cobalamin deficiency in older Dutch subjects. Am. J. Clin. Nutr. 68: 328–334.
van den Berg, H., Heseker, H., Lamand, M., Sandström, B. & Thurnham, D. (1993) Flair Concerted Action No. 10 Status Papers. Int. J. Vitam. Nutr. Res. 63: 247–316.
van den Berg, H., Schrijver, J. & Boshuis, P. G. (1991) Vitamin D (25-OHD) in serum by competitive protein-binding assay. In: Nutritional Status Assessment. A Manual for Population Studies (Fidanza, F., ed.), pp. 203–209. Chapman and Hall, London, UK.
van-der Wielen, R.P.J. (1995) Vitamin intake and status in elderly Europeans, pp. 1–167. Department of Human Nutrition, Wageningen Agricultural University, Wageningen, The Netherlands.
van-der Wielen, R.P.J., de Wild, G. M., de Groot, L.C.P.G.M., Hoefnagels, W. H. & Van Staveren, W. A. (1996) Dietary intakes of energy and water-soluble vitamins in different categories of aging. J. Gerontol. A Biol. Sci. Med. Sci. 51: B100–B107.
van-der Wielen, R.P.J., Lowik, M. R., van den Berg, H., de Groot, L.C.P.G.M., Haller, J., Moreiras, O. & Van Staveren, W. A. (1995) Serum vitamin D concentrations among elderly people in Europe. Lancet 346: 207–210.
Warnock, L. G. (1970) A new approach to erythrocyte transketolase measurement. J. Nutr. 100: 1957–1962.
Washburn, R. A., Smith, K. W., Jette, A. M. & Janney, C. A. (1993) The Physical Activity Scale for the Elderly (PASE): development and evaluation. J. Clin. Epidemiol. 46: 153–162.
Young, A. (1997) Ageing and physiological functions. Philos. Trans. R. Soc. Lond. B Biol. Sci. 352: 1837–1843.
Zerath, E., Holy, X., Douce, P., Guezennec, C. Y. & Chatard, J. C. (1997) Effect of endurance training on postexercise parathyroid hormone levels in elderly men. Med. Sci. Sports Exerc. 29: 1139–1145.