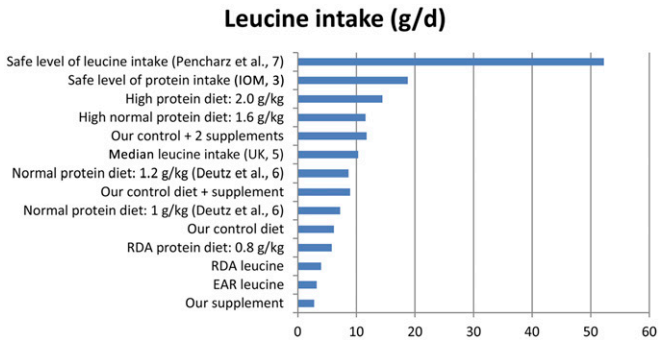

FIGURE 1 Leucine intake in grams per day for different amounts of protein and supplement intake compared with international standards for protein and leucine intakes. Leucine intake per day was calculated on the basis of a 95-kg subject. The supplement, control diet, control diet plus 1 supplement, and control diet plus 2 supplements (training day) are shown in the context of the EAR and RDA for leucine, the median leucine intake in the United Kingdom (5), and the safe level of leucine intake (7) as well as different levels of protein intake considered to be safe (3, 6). EAR, Estimated Average Requirement; RDA, Recommended Dietary Allowance.

intake would be 8.9 g leucine (6.1 + 2.8 g from supplement) and 11.7 g leucine on a training day (6.1 + 2 supplements) (Figure 1). This would correspond to leucine intakes in a protein diet containing 1.2 g or 1.6 g protein/kg body weight per day, respectively (Figure 1). To compare, the calculated leucine intake in the intervention group was below the median daily leucine intake of 10.3 g leucine/d (in a 95-kg subject) as reported in the United Kingdom (5), and for older adults the current recommended level of protein intake is 1.0–1.2 g/kg per day, or 1.2–1.5 g/kg per day when combined with a chronic condition (6). Together, this substantiates that the additional leucine intake due to the supplement is not supraphysiologic but within the range of reported intakes in dietary surveys and the current international recommendations.

Acute studies have been conducted to define a maximum tolerable level of leucine consumption per day. In a recent study, Pencharz et al. (7) based their advice on the upper level of leucine intake on the maximum amount of leucine that could still be oxidized. They estimated on the basis of these acute studies that a dose <550 mg leucine/kg body weight per day would pose no risk to health. This corresponds to a daily consumption of 52.3 g leucine when calculating with a 95-kg subject, which is much higher than the estimated leucine consumption over the day in our intervention study. A supplementation study during 6 mo with 3 times 2.5 g leucine/d in addition to the normal diet (~0.95 g protein/kg body weight per day) was conducted in older patients with type 2 diabetes (8). Leucine supplementation resulted in a modest increase of ~10% in fasted plasma leucine concentrations after 2–4 wk without a progressive increase at later time points. In this controlled study, no adverse effects of leucine were reported. Intakes of protein and leucine in our study were within the normal range (Figure 1); consequently, we did not anticipate elevated concentrations of insulin-like growth factor I (IGF-I) and mammalian target of rapamycin (mTOR) activation beyond normal physiologic levels. We agree, however, with Bernstein et al. that longer-term studies on relevant clinical outcome variables related to the risk of chronic disease should be considered as further proof of safety.

High-protein diets (25% of energy intake) support weight maintenance (9). In the present study, we show that the specialized supplement provides the benefit of preserving muscle mass during weight loss in older obese individuals. Whether consuming the supplement would also support weight maintenance was not studied, but muscle preservation may also have long-lasting benefits during weight maintenance.

In summary, the amount of protein and particularly leucine in the present study can be considered at the high end of the normal distribution of intake. The safest way to proceed is to grow older without becoming obese.

AMV reported no conflicts of interest related to this study. JdV-vdB and SV are employed by Nutricia Research. Nutricia Research was not involved in onsite data collection, except for audits at the research center. PJMW received research grants from Nutricia Research, Utrecht, The Netherlands, and Baxter Healthcare USA.

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Regular physical activity: a little is good, but is it good enough?

Dear Editor:

Ekelund et al. (1) nicely showed that physical inactivity causes an approximate twofold increase in the numbers of deaths compared

with those attributable to obesity [BMI (in kg/m^2) >30] in a European cohort (n = 334,161) that was followed up to 12.4 y on average. Physical activity (PA) levels were estimated by using a standardized questionnaire or in-person interviews and were found to be inversely associated with all-cause mortality at all levels of BMI and waist circumference. Another important finding from their study is that substantial survival benefits may be achieved by fairly small amounts of moderate-intensity PA: that is, ~20 min/d of brisk walking, which is below the current PA recommendations of ≥30 min/d on most, if not all, days of the week (or ≥150 min/wk). These important findings in Caucasians are in line with those recently reported in an Asiatic cohort, in whom 15 min/d or 90 min/wk of moderate-intensity PA was associated with lower all-cause mortality, even for persons at risk of cardiovascular disease (2).

The medical relevance of the study by Ekelund et al. (1) should be acknowledged. It was certainly well powered to show the mortality benefits of small PA doses and thus to provide further epidemiologic support for PA promotion worldwide. And yet we are concerned about the possibility that the finding that even small PA amounts are clinically relevant might be misinterpreted by the general public as well as by some health professionals. Indeed, recognizing the benefits of small PA doses is important but at the same time might somehow dilute what we think is also a main message arising from the bulk of research in the field: that is, that the main epidemiologic benefits of exercise can be even stronger at high PA doses, with recent research also showing greater gains in life expectancy (+4.5 y; 95% CI: 4.3, 4.7 y) with PA levels equivalent to ≥450 min/wk of brisk walking (3).

On the other hand, there is growing evidence that the largest epidemiologic benefits of PA against a major cause of death worldwide, cancer, are dose-related, at least for some main cancer types, particularly colon cancer. In fact, the last World Cancer Research Fund report on PA and cancer prevention establishes the evidence of a dose-response effect for colorectal cancer, and especially for colon cancer (4). Engaging in ≥150 min/wk of recreational PA (e.g., walking) is associated with lower all-cause mortality after colorectal cancer diagnosis (5). Yet, ≥7 h/wk (≥60 min/d) of moderate-to-vigorous PA has been reported to be associated with lower risk of total cancer mortality (HR: 0.89; 95% CI: 0.84, 0.94; $P < 0.001$), with the link being especially strong for colon (HR: 0.70; 95% CI: 0.57, 0.85; $P < 0.001$), liver (HR: 0.71; 95% CI: 0.52, 0.98; $P = 0.012$), and lung (HR: 0.84; 95% CI: 0.77, 0.92; $P < 0.001$) cancers (6). Furthermore, a recent meta-analysis from our group showed a considerably lower cancer-related mortality in those humans engaging in the highest PA levels—that are, elite athletes of various sport disciplines (n = 12,119, mostly men), including Tour de France finishers—than in the general population (standard mortality ratio: 0.60; 95% CI: 0.38, 0.94; $P = 0.03$) (7).

Another concern is ensuring that the PA levels of cancer survivors are high enough, because current PA recommendations of ≥150 min/wk of moderate PA might actually be insufficient for this population, as we recently reviewed (8). In the cohorts of US cancer survivors in whom PA was measured objectively by using accelerometry, average levels of moderate PA (brisk walking) were even below 20 min/d (see reference 7 for a review). In contrast, we recently reported, also with the use of accelerometry, that the vast majority of a cohort of Spanish middle-aged cancer survivors of both genders performed, on average, 356 min/wk (~50 min/d) of moderate-to-vigorous PA (9). Despite such apparently good news, these high PA levels were not accompanied by a "healthy" cardiometabolic profile. Notably, 33% of the subjects were obese and the mean levels of cardiorespiratory fitness (CRF; determined as peak oxygen uptake) of this cohort was 7.7 metabolic equivalents (METs), with ~50% of subjects not reaching a CRF of 8 METs. Any CRF value <8 METs is indicative of an increased risk of mortality and cardiovascular events in middle-aged men and women aged 40–60 y, on average (10), and cardiovascular disease is the leading cause of morbidity and mortality among long-term cancer survivors. In fact, men with a CRF <8 METs have a more than threefold higher risk of dying of digestive disease (bowel, colorectal, liver cancer) than do those with a CRF ≥11 METs (11).

In summary, although ~20 min/d of PA is certainly much better than inactivity, as elegantly shown by Ekelund et al. (1), we question whether this fairly small dose might be enough to bring a substantial clinical benefit in certain cases, especially for cancer prevention and among cancer survivors. Further epidemiologic research is also needed using objective and reliable assessment of PA, ideally with accelerometry, to determine the optimal PA dose associated with the highest epidemiologic benefits in different population groups.

None of the authors declared a conflict of interest.

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Reply to H Pareja-Galeano et al.

Dear Editor:

We appreciate the interest from Pareja-Galeano et al. in our study and acknowledge that they considered our study well powered and clinically relevant. Similar to others (1), our results suggested that the greatest reduction in the hazard of mortality was found between the "inactive" and the "moderately inactive" group. This reduction was observed across general and abdominal obesity groups, suggesting health benefits from increasing physical activity (PA) regardless of adiposity. On the basis of our validation study (2), we estimated that the difference between the "inactive" and "moderately inactive" group was equivalent to ~20 min of brisk walking each day. This equates to 140 min/wk, which is almost in line with current PA recommendations for public health (3–5).

We do not dispute the health benefits associated with higher levels of PA, which Pareja-Galeano et al. have highlighted, but the key message from our study was that there would be substantial public health benefits from people in the inactive group engaging in even a small amount of PA each day.

None of the authors had a conflict of interest to declare.

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Biomarkers of dairy fat

Dear Editor:

There were 2 interesting articles in a recent issue of the Journal in which odd-chain fatty acids (15:0 and 17:0) were used as circulating biomarkers of dairy fat (1, 2). In one of the studies (1), serum pentadecanoic acid (15:0) was shown to be inversely associated with incident type 2 diabetes, and in the other study (2) the association of pentadecanoic acid and heptadecanoic acid (17:0) with the risk of incident stroke was studied and no significant association was found. These odd-chain fatty acids are considered to be validated biomarkers for dairy fat and they correlated with dairy consumption in many studies (1–4). However, the association between the intake of dairy fat and the relative serum content of heptadecanoic acid has not been clear in all studies (5, 6). In a large cohort study [EPIC (European Prospective Investigation into Cancer and Nutrition)], there was a strong positive ecologic correlation ($r = 0.8$, $P \leq 0.01$) between the total intake of fish and plasma concentration of heptadecanoic acid, whereas there was no correlation between heptadecanoic acid or pentadecanoic acid and dairy products (6). Accordingly, we have seen in our studies (MA Lankinen et al., 2015) a positive correlation between pentadecanoic and heptadecanoinc acids with DHA in plasma phospholipids. The fatty acid heptadecanoic acid is present in the fat of fish (0.31–2.0% depending on fish species) (7, 8). Salmon contains ~40 mg heptadecanoic acid and 20 mg pentadecanoic acid per 100 g (9). Therefore, we are a bit concerned if these odd-chain fatty acids are considered to be a valid biomarker for dairy fat intake in populations who consume considerable amounts of fish. In populations with a high consumption of dairy fat and a low consumption of fish, odd-chain fatty acids are probably valid biomarkers for dairy fat intake. In populations who consume fish, the presence of odd-chain fatty acids in fish should be taken into account to avoid misleading conclusions.

Neither of the authors had a conflict of interest.

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Note: Yakoob et al. chose not to submit a reply.

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