

Not Just the “What” But Also the “How Much” You Eat Matters

Fred Hutch researchers explore the association between energy intake (through food and drink) and chronic disease risk, including cancer.

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In the age of intermittent fasting, plant-based diets and Whole30, fad diets boast about their long-term health benefits, while simultaneously overcomplicating what it means to have a healthy lifestyle. The reality is, it's hard to precisely measure the accuracy of these claims, let alone, keep even the most devout ketotarian from reaching for that pasta or chocolate cake long enough to be able to quantify long-term effects on chronic disease and lifespan. Fortunately, we likely don't need some restrictive diet to experience healthful benefits and many of these can be achieved through maintaining a simple energy balance, where energy in equals energy out. In other words, energy balance is achieved when energy consumed through foods and beverages (energy in) is equal to the energy burned through basal metabolic functions and physical activity (energy out).

Extensive literature has shown energy balance is important for overall health and disease prevention, however there is still a lot more to understand about this in relation to chronic disease risk factors. The Nutrition and Physical Activity Assessment (NPAAS) Group from the Public Health Sciences Division at Fred Hutch — which includes [Drs. Ross Prentice](#), [Johanna Lampe](#) and [Marian Neuhouwer](#) — is substantially interested in understanding energy intake through diet and its relationship to mortality and other clinical outcomes. In their recent study published in [The American Journal of Clinical Nutrition](#), Prentice et al. investigated the total energy expenditure (TEE) for a cohort of postmenopausal women and asked how it related to mortality risk over a 19-year period.

The NPAAS group explained that the motivation for this study was to “provide a fresh look at the association between energy intake in relation to chronic disease risk, including cancer. Energy intake is poorly measured by self-reported diet and accordingly has been substantially overlooked in nutritional epidemiology research.” In this recently published work, the researchers uncovered an interesting age-dependent association between TEE and all-cause mortality that may prompt revision to the saying “you are what you eat,” as this research shows that how much you eat, might be just as important.

To evaluate how a person's energy intake and expenditure might relate to mortality, the researchers measured total energy expenditure (TEE) as “the number of calories a person

expends (or uses). It is the energy used, in a resting state, to support basic metabolic processes, plus that used during physical activity,” the research team stated. For a person in ‘energy balance,’ the amount of energy they expend (TEE) will be equal to the amount of energy they take in through consuming food and beverages. As you might expect, “long term energy intake in excess of TEE can lead to overweight and obesity, which are linked to over 15 types of cancer,” the NPAAS team explained.

To precisely and accurately measure TEE, the researchers used a chemical tool called doubly labeled water (DLW). This water is like “normal everyday water labeled with two stable isotopes: deuterium and oxygen-18,” the researchers noted. The “heavy” oxygen-18 and hydrogen-mimic deuterium isotopes allowed the researchers to trace these molecules through urine samples, which take about two weeks to be completely excreted. “The excreted isotope concentrations in the urine are measured by mass spectrometry and the results give a reliable estimate of carbon dioxide production and water (H_2O or in this case D_2O^{18}) excretion over the prior two weeks. Since CO_2 and H_2O are the end products of metabolism, the results give a reliable, quantitative measure of the number of kcals used (e.g., energy expenditure) over the two-week period. In weight stable people, energy expenditure is approximately equivalent to energy intake. This is why we can use this doubly labeled water test to determine the number of kcals a person ingests over a short time frame,” explained the NPAAS group.

The research team used doubly labeled water to measure TEE in over a thousand postmenopausal women enrolled in the [Women’s Health Initiative](#), with a median follow up period of 10 years. To help understand how TEE might be a factor influencing mortality in this group of women, the participants included healthy women with stable weight during this period, which helped rule out women with large weight gain or loss that could be indicative of other disease factors. Performing various statistical tests, the NPAAS researchers asked if there were any significant associations between TEE and subsequent all-cause mortality, which could indicate whether altered caloric intake might influence mortality risk. While overall, TEE was unrelated to overall mortality, there was an elevated risk with higher TEE among participants who had been weight-stale over preceding years, and the researchers uncovered some interesting trends when they investigated this relationship by age group. The NPAAS team exclaimed that “it was impressive to see a 2-fold estimated increase in total mortality risk with a 20% increase in TEE for study participants at age 60. The magnitude of this increase was lower at about a 1.5 fold at age 70, and had a null value of 1.0 at age 80.”

Therefore, their findings showed that higher total energy expenditure was associated with a higher mortality rate in younger women (60-69 yrs.) and conversely a lower mortality rate in older women (70-80 yrs.). This work highlights that “not just what one eats, but how much one eats, may be a critical factor in determining mortality risk in older women,” the researchers noted. Furthermore, this work supports “that total energy expenditure is likely a very important aspect of a person’s lifestyle.”

A limitation of this study is that “a part, but by no means all of these total mortality elevations could be attributed to body fat accumulation (due to excess kcals intake) prior to DLW testing.” In

the future, continuing to focus on how energy intake (rather than energy expenditure) through diet influences mortality and other clinical outcomes is of interest. The NPAAS group is currently building upon the “the DLW assessment as well as any weight variation during the two-week test period to develop a novel biomarker for total energy intake, which we are currently studying in relation to chronic disease incidence (including cancer) and incidence.” Drs. Prentice, Lampe and Neuhausser conclude by acknowledging that this work was possible thanks to “a strong team of researchers across the country who contributed valuably to this research. Four people who stand out among our co-authors are JoAnn Manson of the Harvard Medical School who is an expert in body mass in relation to disease outcomes, Dale Schoeller of the University of Wisconsin who is an expert in the doubly labeled procedure and energy expenditure research, Lesley Tinker of Fred Hutch who was crucial in the study operations, and Aaron Aragaki here at the Hutch who expertly carried out statistical aspects of this presentation.”

Fred Hutch/UW/Seattle Children’s Cancer Consortium members Marian Neuhausser, Johanna Lampe and Ross Prentice contributed to this study.

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