Calorie Restriction, Longevity and Muscle Function: Emerging Research and Clinical Considerations

Webinar Questions Answered by Jacob Mey, PhD, RD

- Individuals with slowed metabolism such as those with hypothyroidism, who remain physically fit, would you hypothesize that they would have a longer lifespan due to the slower metabolism?
    - Not my area, but it appears to be a sound theory, supported by at least some literature: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2653451

- Any insight on how murine models for obesity and/or diabetes respond to CR from a lifespan/health-span perspective?
    - Generally speaking, when you are dealing with overt disease like obesity or diabetes, the CR benefit primarily impacts the secondary aging factors, leading to improved longevity comparatively to other diseased mice, but not moreso than healthy mice undergoing CR.

- Could you speak to biomarkers of aging in humans that can serve as a proxy for longevity?
    - I don't think we have great biomarkers of longevity defined, other than measures we can use that are a part of primary aging. See https://pubmed.ncbi.nlm.nih.gov/32559388/

- Valter Longo has a FMD program. Is this different than these 3 studies?
    - The FMD induced a calorie deficit, but it is not consistent, likely targeted at the 5-days of FMD per month. Whether that has the same impact as sustained CR is unknown.

- What are average calories for those on the mainland in the one blue zone study?
    - Beyond the ~11% calorie reduction, additional information on the comparison of Okinawa and mainland can be found here: https://pubmed.ncbi.nlm.nih.gov/17986602/

- BIOSPHERE II - appears to have had access to sunlight from earth. How and what type of soil was used for food production?
    - I am not sure.

- Is caloric restriction best done before reaching geriatric age? Or is it ok to continue as an individual ages?
    - Based upon the animal models, as soon as calorie restriction is initiated, those individuals begin to mimic life-time calorie restriction models. However, certainly, the less amount of life left, the less benefit can be gained.

- How did the control group in the CALORIE study also have a reduction in DNA damage?
    - Sometimes, being part of a study leads people to live healthier lifestyles, knowing they are being measured over time – part of the placebo effect.

- What is the recommended /suggested calorie restriction for longevity? And what would happen if you started to refeed with their "normal" diet. Also, what was and is the macro nutrient composition of the calorie restriction? What is the Tipping Point, where long term calorie restriction promotes longevity and prevents malnutrition? is it 11% or 25% reduction from baseline?
    - Great question, largely unknown to all the questions. You can find additional information about the CALERIE trials starting here: https://calerie.duke.edu/

- What was the MACRO distribution in the Calorie II study?
    - https://calerie.duke.edu/

- In the CAL ll how much weight loss was due to lean muscle mass?
    - 2 kg

- If your resting metabolic rate decreases, doesn't this reduce muscle mass and increase the risk of falls as we age?
    - Metabolic rate does not impact muscle mass or falls in isolation to my knowledge.

- I hope Dr Mey addresses that Blue Zone longevity is only partially due to the resident's diet. There is a significant social/community aspect to those areas, plus the residents are usually far more physically active throughout their lives and strive to live a purposeful life. Thoughts?
    - Agree

- Why is lower body core temperature indicative of faster paced aging?
    - It is not, it is related to the aging process and decreases with age.

- Did participants lose lean mass to the point of protein-malnutrition?
    - No

- How were participants monitored during and after the study for disordered eating characteristics or developing disordered eating habits or diagnosis?
    - Validated questionnaires. See https://pubmed.ncbi.nlm.nih.gov/18248104/ and https://pubmed.ncbi.nlm.nih.gov/32940695/

- I don't see a reference on the BMI-mortality graph. Please provide.
    - I am not sure which graph you are referring to. Its either https://www.bmj.com/content/353/bmj.i2156 or https://pubmed.ncbi.nlm.nih.gov/24452240/

- For these Calorie trials, how did participants specifically change aspects of their diets in order to achieve a calorie deficit?
    - Standard nutrition recommendations – see more here: https://calerie.duke.edu/

- We have the study showing 30 grams of protein at each meal with exercise in mature people improves muscle mass so should we do a study with lower calories and the higher protein to show that it may preserve muscle and bone strength?
    - I think we have a lot to learn still about what optimal protein and calorie intake is at various life situations. I recommend keeping an eye out for precision nutrition studies in older adults.
    - I am not sure how it would improve bone strength, but in younger individuals protein intake up to ~2.2g/kg/bw is protective to lean body mass during intensive weight loss/calorie deficits.

- What effect does exercise, weightlifting or creatine supplement have?
    - Unsure what this is related to, but all are well-evidenced to support muscle mass and strength.

- Why would decrease grip strength be a positive?
    - A decrease in grip strength is not positive.

- I may have missed this, but what was the age range of the participants in the 2nd clinical trial?
    - Recruitment was 21-50 years, participants were 37.9 years on average

- Isn't fasting (various types) also an evidence-based approach to reduce aging?
    - Independent of calorie restriction, no, it is not.

- Have you seen any research or have any thoughts regarding mild caloric restriction and encouragements to resistance training (for bone density and retaining muscle mass) and adequate or even higher protein needs?
    - I have not, but it sure sounds like an interesting approach.

- Do you know of any of the current ongoing research studies regarding longevity and calorie restriction? And/or how to learn more about the ongoing research?
    - I do not, but you can:

        - 1) attend relevant scientific conferences
        - 2) follow aging organizations (hadpg.org, afar.org, nia.nih.gov, etc)
        - 3) go here: https://grantome.com/ and search aging – you will see actively funded projects on the topic area.

- We know that exercise is critical to lower morbidity (and perhaps mortality). However, calorie restriction may be more challenging for those with active lifestyles. Is there any data on the physical activity levels in the CALERIE studies?
    - Yes, this information is available in the CALERIE publications.

- How does calorie restriction compare to fasting regarding increased longevity?
    - It has not been compared.

- Do the benefits come from the calorie restriction or the weight loss? Do we know at this point?
    - Weight loss has one set of benefits, especially with excess adiposity/obesity. The CALERIE trials uniquely showed independent effects of calorie restriction in healthy-weight individuals. The animal data is very clear that calorie restriction has unique benefits in pre-clinical models.

- What would be optional protein intake be 0.08 grams or 1.2 g/kg?
    - Depends on the individual, but there is mounting evidence to support an increase in the 0.8 gPro/kg/d RDA for healthy aging.

- Did those in calorie restriction group with adequate nutrient intake report appetite and hunger changes?
- So, would Intermittent Fasting be a long-term practice to achieve similar benefits?
    - Unknown.

- Some patients have come to the clinic trying to lose weight and following extremely low-calorie diets (50% calorie needs). They seem to be unable to continue losing weight. How can we fix their metabolism? Should they continue following a restrictive diet?
    - It is not a metabolism issue. Metabolic adaptation to weight loss maxes out around ~20%. An inability to lose weight can come from eating more than one thinks, moving less than one thinks,

- Fasting seems to be the latest trends. Did the calorie restriction in the study include fasting or was it just a reduction in calories?
    - No structured fasting regimen.

- Where does physical activity fit?
    - Unclear question.

- Any research on how calorie restriction can affect athletic performance?
    - It will reduce it compared to an adequately fed athlete.

- Have you thought about studying bariatric pts that have a large decrease in caloric intake?
    - It is definitely a major area of research. At Pennington Biomedical, we recently opened a Bariatric and Metabolic Institute or (BMI) – where we have a clinical that focuses on Obesity management, including one of the top Bariatric surgeons in the world, Dr. Phil Schauer. See his publication in the New England Journal of Medicine, which includes prestigious co-authors, like Pennington Biomedical's Executive Director, Dr. John Kirwan: https://www.nejm.org/doi/full/10.1056/nejmoa1600869

- How does one prevent continued weight loss with calorie restriction, or not continually needing to decrease calories due to lower BMR?

    - The body self-regulates with metabolic adaptation, so weight loss stops despite persistent calorie restriction from baseline. You do need to maintain that lower kcal intake, or you will gain weight on less calories than you would have previously.

- Would it be more ideal to use whatever calories achieve a BMI 23-25 as a useful way to know how many calories are recommended?
    - See above, this amount will adjust depending on your baseline.

- Do the studies discuss the make-up of the diet relative to calorie restriction? One must wonder if it was just caloric restriction vs. the diet make-up itself, which may be a factor.
    - Certainly, overall dietary pattern plays a role in health, but we do not have evidence that it impacts aging, unless you move into nutrition geometry – e.g., murine model studies using very low protein diets, or manipulating macronutrient ratios dramatically.

- How were optimal calories calculated? estimates or metabolic carts?
    - Metabolic carts. At Pennington we also have full metabolic chambers – a single-room living quarters where it's essentially a 24/7 metabolic cart – everything in and out (including gasses) is measured. You can eat, exercise, etc all in the chamber.

- How did the researchers ensure adequate nutrients with calorie restricted humans?
    - We have a metabolic kitchen with expert dietetic staff.

- How does one apply this info to the general public health to persons over 65 yrs? Micronutrient needs?
    - Unknown.
    - Unchanged.

- Is there any research on calorie restriction on currently obese adults in terms of longevity?
    - Yes, the initial CALERIE trial was in overweight/obesity; CALERIE-II was in normal weight.

- Were these human subjects given MVI/minerals supplements to enable them to meet micronutrient needs?
    - With such a slight calorie reduction (e.g. 11-25%) micronutrient needs are less a concern than for example, post-bariatric surgery weight loss where calorie reduction is upwards of 75% and digestive processes are altered.

- Has this been compared to a similar diet with no calorie restriction? As the American diet typically does not maximize health, has this ever been compared to a healthful diet WITHOUT the calorie restriction?
    - Yes, this was the control group.

- Were daily calories for participants in the CR groups typically updated as they lost weight over the course of the trials?
    - No, that is the function of CR – a change from baseline.

- Did any studies control for calorie restriction maintainability? What are your thoughts on purposeful calorie restriction vs. methods such as intuitive eating?
    - The data on the actual intake (~11-12% restriction) is the effective data on maintainability. This persisted up through 2 years.
    - Intuitive eating is a 3rd party narrative (e.g., whole30, goop, noom, etc) moreso than a research validated method. Mindfulness strategies are research-verified approaches, which would be an interesting comparison. However, unless the mindfulness approach resulted in calorie restriction, I doubt it could rival the benefits of calorie restriction per se.

- I'm still a little gray on what the bottom limit would be for calorie restriction then (when it becomes harmful vs lengthening life span). Or is it that we should be lowering the standards for recommended daily energy intake (e.g., 25-30 kcal/kg)?

        - It is likely the body will adjust (metabolic adaptation + hunger/satiety changes) to a level that is sustainable. It appears to be about 11-12% less than baseline based on the cohort studies and CALERIE data. This is not evidenced to the point of recommending changes to established kcal guidelines, rather a research venture into longevity.

- Are there implications in any of these studies for individuals that have neuromuscular diseases - on older adults vs. younger adults; or on those that are obese vs. healthy weight?
    - It's a great questions, but I am not familiar with that literature.

- Did the studies measure the types of calories consumed, for example calories from food vs calories from liquids (juice, pop, alcohol) and the benefits of less calorie intake for older adults?
    - Diet records were obtained; the CALERIE studies were not conducted in older adults.