Dietary intervention trials – study design & novel technologies

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Course Description

Aim of the course: Developing knowledge and skills for designing, analyzing, and interpreting dietary intervention trials.

Dietary intervention trials have played a key role in establishing the causality between diet or nutrient intake and health outcomes and in the determination of dietary requirements and levels of supplementations to achieve specific outcomes. In this course, we will discuss the concepts and elements of nutritional RCTs, how to design, conduct, analyze, and interpret nutritional RCTs through case studies, and will address novel challenges/opportunities in nutritional RCTs. New technologies such as nutritional omics and the concept of personal or precision nutrition will be discussed. Students will need to read the relevant scientific literature prior to the lectures. Attendance and participation in lectures are required. Upon successful completion of the course, students will have a better understanding on how to plan and design a nutritional RCT and will be familiar with different types of outcome measurements and different analytical approaches.

Learning Objectives

Upon successful completion of this course, you should be able to:
- Describe the challenges and history of nutritional intervention trials.
- Apply nutritional epidemiological principles to plan and design nutritional trial.
- Determine compliance to specific dietary regimen.
- Develop a clinical trial protocol, including all key elements (eligibility criteria, hypothesis, defining appropriate aims, calculating sample size, etc.).
- Discuss novel technologies in your planned RCT.
- Explain novel analytic approaches of nutritional genomics, genetics, and metabolomics.

Recommended textbooks:

1. Nutrition research methodologies. Edited on behalf of The Nutrition Society. Editor-in-Chief: Professor Susan A Lanham-New © 2015 by John Wiley & Sons, Ltd

Lecture 1

<u>Required:</u>
1. Shai, Iris, et al. "Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet." *New England Journal of Medicine* 359.3 (2008): 229-241.
2. Estruch, Ramón, et al. "Primary prevention of cardiovascular disease with a Mediterranean diet." *New England Journal of Medicine* 368.14 (2013): 1279-1290.

<u>Optional:</u>
1. Satija, Ambika, et al. "Perspective: are large, simple trials the solution for nutrition research?." *Advances in Nutrition* 9.4 (2018): 378-387.

Lecture 2

<u>Required</u>
1. Howard, Barbara V., et al. "Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial." *Jama* 295.6 (2006): 655-666.
2. Martínez-González, Miguel A., et al. "Cohort Profile: Design and methods of the PREDIMED-Plus randomized trial." *International journal of epidemiology* 48.2 (2019): 387-388o.

<u>Optional:</u>
1. Harrington D, Designs for clinical trials, Springer 2012

Lecture 5

<u>Required:</u>
1. Shai, Iris, et al. "Dietary evaluation and attenuation of relative risk: multiple comparisons between blood and urinary biomarkers, food frequency, and 24-hour recall questionnaires: the DEARR study." *The Journal of nutrition* 135.3 (2005): 573-579.
2. Gepner, Yftach, et al. "Differential effect of initiating moderate red wine consumption on 24-h blood pressure by alcohol dehydrogenase genotypes: randomized trial in type 2 diabetes." *American journal of hypertension* 29.4 (2016): 476-483.

<u>Optional:</u>
1. Golan, Rachel, et al. "Halo effect of a weight-loss trial on spouses: the DIRECT-Spouse study." *Public health nutrition* 13.4 (2010): 544-549.

Lecture 6

<u>Required:</u>
1. Shai, Iris, et al. Dietary intervention to reverse carotid atherosclerosis. *Circulation.* 2010;121(10):1200-8
2. Gepner, Yftach, et al. "Effect of distinct lifestyle interventions on mobilization of fat storage pools: The CENTRAL MRI randomized controlled trial." *Circulation* 137 (2018): 1143-1157.
3. Rinott, Ehud, et al. "Effects of diet-modulated autologous fecal microbiota transplantation on weight regain." *Gastroenterology* (2020).

<u>Optional:</u>

1. Gepner, Yftach, et al. "Effects of initiating moderate alcohol intake on cardiometabolic risk in adults with type 2 diabetes: a 2-year randomized, controlled trial." *Annals of internal medicine* 163.8 (2015): 569-579.
2. Golan R et al. Effects of initiating moderate wine intake on abdominal adipose tissue in adults with type 2 diabetes: a 2-year randomized controlled trial. Public Health Nutrition 2017 Feb;20(3):549-555
3. Gepner, Yftach, et al. "The beneficial effects of Mediterranean diet over low-fat diet may be mediated by decreasing hepatic fat content." *Journal of hepatology* 71.2 (2019): 379-388.

Course Structure

Attendance and participation in lectures are mandatory. Students are expected compete pre-class readings ahead of time, attend all classes, and participate actively in classroom discussions.

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Course Schedule & Assessment of Student Learning

Session topics	Objectives	Readings	Activities/ Assignments
Session 1: Nutritional Research: spectrum, challenges and evolution ***Iris Shai*** 1. Significance and evolution 2. Challenges in dietary RCTs 3. Cohorts vs. dietary RCTs 4. Types of dietary RCTs 5. Evidence based nutrition	**Upon Successful completion of this session, you should be able to:** 1. Describe the challenges, history and significance of dietary RCTs. 2. Identify key dietary RCTs conducted in the past years 3. Describe different types of clinical trials	**Required:** 1. Shai I et al. Weight Loss with a Low-Carbohydrate, Mediterranean, or Low-Fat Diet. *New England Journal of Medicine*. 2008;359(3):229-41. 2. Estruch R et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *New England Journal of Medicine*. 2018 Jun 21;378(25):e34. **Optional:** 1. Satija A et al. Perspective: are large, simple trials the solution for nutrition research? *Advances in Nutrition*. 2018 Jul 1;9(4):378-87.	**Homework:** *NA*
Session 2: Dietary RCTs protocol components I ***Iris Shai*** 1. Clinicaltrials.gov 2. Protocol structure • Gap of knowledge • Hypothesis • Aims • Study structure/duration • Study population	**Upon Successful completion of this session, you should be able to:** 1. Develop first parts of your dietary RCT protocol 2. Apply basic protocol elements in clinical trials design of dietary RCTs	**Required:** 1. Howard, Barbara V., et al. "Low-fat dietary pattern and risk of cardiovascular disease: The Women's Health Initiative Randomized Controlled Dietary Modification Trial." *JAMA* 295.6 (2006): 655-666. 2. Martínez-González MA, et al. Cohort Profile: Design and methods of the PREDIMED-Plus randomized trial. *International journal of epidemiology*. 2019 Apr 1;48(2):387-80. **Optional:** 1. Harrington D, Designs for clinical trials, Springer 2011	**Homework:** NA

• Blinding • Randomization • Intervention groups • Run-in period			
Session 3: Dietary RCT protocol components II ***Iris Shai*** 1. Endpoints 2. Sample size and power calculations 3. Ethical & regulatory considerations 4. Budgetary plan	**Upon Successful completion of this session, you should be able to:** 1. Define the appropriate endpoints for you RCT. 2. Calculate sample size for your future trial 3. Discuss ethical and regulatory framework (history and current) 4. Present financial plan for your trial	**Optional:** 1. Harrington D, Designs for clinical trials, Springer 2011 2. Self – study ethical and regulatory framework – see further slides.	**Homework:** NA
Session 4: Dietary RCTs Protocol components III Data Analysis ***Iris Shai*** 1. Outcome variables 2. Missing data 3. Multiple testing 4. Outliers 5. Advanced analysis 6. Limitations 7. Motivating strategies	**Upon Successful completion of this session, you should be able to:** 1. Define outcome variables according to your aim 2. Describe potential methods for handling missing data and approaches to handle multiple comparison issues. 3. Describe advanced analysis techniques 4. Use your toolbox for planning up your protocol	NA	**Homework:** NA

Session 5: **Measurements for monitoring dietary compliance** *Iris Shai* 1. Adherence/compliance 2. Subjective measurements 3. Objective measurements	**Upon Successful completion of this session, you should be able to:** 1. Choose suitable measure of compliance/adherence to specific dietary regimen 2. Evaluate concerns regarding subjective and objective measurements of adherence 3. Describe how to build an assessment tool 4. Develop strategies for improving dietary compliance.	**Required:** 1. Shai I, et al. Dietary evaluation and attenuation of relative risk: multiple comparisons between blood and urinary biomarkers, food frequency, and 24-hour recall questionnaires: the DEARR study. *The Journal of nutrition* 135.3 (2005): 573-579. 2. Yftach Gepner, et al. Differential effect of initiating moderate red wine consumption on 24-h blood pressure by alcohol dehydrogenase genotypes: randomized trial in type 2 diabetes. *American journal of hypertension.* 2016 Apr;29(4):476-83 **Optional:** 1. Golan R, et al. Halo effect of a weight-loss trial on spouses: the DIRECT-Spouse study. *Public health nutrition. 2010 Apr;13(4):544-9.*	**Homework:** NA
Session 6: Endpoints and Novel Technologies in Nutritional RCTs *Iris Shai* 1. Endpoints in key nutritional RCTs 2. Novel technologies in nutritional RCTs	**Upon Successful completion of this session, you should be able to:** 1. Explain how to measure endpoints in RCTs. 2. Give original example of new methods and technologies used in RCTs	**Required:** 1. Shai I, et al. Dietary intervention to reverse carotid atherosclerosis. *Circulation.* 2010;121(10):1200-8 2. Yftach Gepner, et al. Effect of distinct lifestyle interventions on mobilization of fat storage pools: The CENTRAL MRI randomized controlled trial. *Circulation.* 2018 Mar 13;137(11):1143-1157. 3. Rinott Ehud, et al. Effects of Diet-Modulated Autologous Fecal Microbiota Transplantation on Weight Regain. *Gastroenterology.* 2021 Jan;160(1):158-173.e10. **Optional:** 1. Yftach Gepner, et al. Effects of initiating moderate alcohol intake on cardiometabolic risk in adults with type 2 diabetes: a 2-year randomized, controlled trial. *Annals of internal medicine.* 2015 Oct 20;163(8):569-79.	**Homework:** NA

		2. Golan, Rachel, et al. Effects of initiating moderate wine intake on abdominal adipose tissue in adults with type 2 diabetes: a 2-year randomized controlled trial. *Public Health Nutrition.* 2017 Feb;20(3):549-555. 3. Gepner, Yftach, et al. The beneficial effects of Mediterranean diet over low-fat diet may be mediated by decreasing hepatic fat content. *Journal of hepatology. 2019 Aug;71(2):379-388.*	

Please note, *session topics and activities may be subject to change during the course.*