ARIC Manuscript Proposal #2305

PC Reviewed: 2/11/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1a. Full Title: Genetic predictors of Metabolic Responses to Dairy Foods

b. Abbreviated Title: Genetic predictors of Metabolic Responses to Dairy Foods

2. Writing Group:

Mariaelisa Graff, Anne Justice, Kristin Young, Kari E. North, other Authors for the CHARGE consortium
Other investigators welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal.

MG

First author: Mariaelisa Graff

Address: Department of Epidemiology
University of North Carolina at Chapel Hill
137 E. Franklin St, Suite 306
CB #8050
Chapel Hill, NC 27514
Phone: 919-966-8491 Fax: 919-966-9800
E-mail: migraff@unc.edu

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author): Kari North

Address: Department of Epidemiology
University of North Carolina at Chapel Hill
137 E. Franklin St, Suite 306
CB #8050
Chapel Hill, NC 27514
Phone: 919-966-2148 Fax: 919-966-9800
E-mail: kari_north@unc.edu

3. Timeline (The following are estimates. Please see project phases and timeline below for more details):

Individual cohort statistical analyses: July 2014

Consortium meta-analyses: October 2014

Manuscript preparation: December 2014

Manuscript submission: March 2015

4. Rationale:

Obesity affects over a third of US adults and more than 400 million people worldwide, and its contribution to chronic diseases such as diabetes is a growing global concern. Environmental (eg, dietary) factors play an undeniable role in the rise in obesity and its complications, but a sizable minority of individuals seem resistant to weight gain despite exposure to a similar obesogenic environment. Some genetic associations with obesity risk have been well-replicated, but protection against adiposity and its complications have also been attributed to consumption of certain foods. Notably, dairy foods have been variably linked to adiposity, showing protective, detrimental or no differences in body weight in a range of observational and intervention studies that continue to accumulate (*Bowen, 2005; Berkey, 2005; Gunther, 2005; Thompson, 2005; Rajpathak, 2006; Zemel, 2005; Beydoun, 2008; Dove, 2009; Astrup, 2010; Faghih, 2011; Chen, 2012; Gilbert, 2011; Gilbert, 2011; Josse, 2011; Weaver, 2011; van Meijl, 2011; Abargouei, 2012; Lamri, 2013; Kratz, 2013*). Associations between dairy intake and glycemic traits are more consistently but not completely favorable, and appear, in some cases, to be independent of body weight (*Choi, 2005; Hoyt, 2005; Lawlor, 2005; Liu, 2006; Liu, 2009; Drouillet, 2007; Louie, 2011; Arnberg, 2012; Sluijs, 2012; Grantham, 2013; Kratz, 2013; Mozaffarian, 2013*). For both body weight and glycemic traits, exploration of genetic variability in conjunction with dairy food intake may explain a portion of the variability in responses to these foods.
The rationale for investigating the impact of genotype on responses to dairy foods is especially compelling in light of the evolutionary history of dairy intake. Most people (and non-human mammals) are unable to digest lactose post-weaning, but mutations near the lactase locus conferred sustained lactose tolerance in some groups. Evidence of recent positive selection (~8000 years ago) appears to coincide with dairy farming, and reflects reproductive advantages associated with lifelong dairy consumption (*Bersaglieri, 2004*). Although the strongest selection signal appears near the lactase locus, additional genetic loci were probably affected. Reproductive advantages provided by lifelong dairy consumption may have affected growth, development, body size and body composition, implicating a wide range of biological and genetic pathways. In spite of the large number of potential loci that may have been shaped by the introduction of dairy foods to the human diet, only a few studies so far have examined dairy intake in conjunction with genetic variability (*Dedoussis, 2010; Corella, 2011*).

Identifying the dairy constituents and genetic modulators that interact to influence health outcomes is challenging because of the chemical complexity and multiple forms of dairy foods. Key nutrients supplied by dairy foods (calcium, magnesium, vitamin D (if fortified), and good quality proteins) are well-recognized. However, additional unique and potentially bioactive components (phytanic acid (3,7,11,15-tetramethyl hexadecanoic acid) , palmitoleic acid (C16:1n-7), oligosaccharides, branched chain amino acids and others) may interact with genetic regulators of energy homeostasis, including satiety mechanisms, to modulate obesity risk in unanticipated ways (*Shah, 2000; Ward, 2004; German, 2008; Astrup, 2010; Gilbert, 2011*). A genome-wide analysis of dairy x SNP interactions (GWIS) may detect novel loci and pathways through which this important food group may be acting to optimize health,

and enable identification of those who stand to benefit most from additional consumption. At the same time, these analyses will pave the way for functional studies that increase biological understanding of dairy benefits.

5. Main Hypotheses/Study Questions:

Aim: To combine into a meta-analysis of data from CHARGE cohorts with genome-wide arrays, including Cardio-MetaboChip, we will test interactions in the ARIC between genotype and i) **total dairy foods** ii) **low-fat dairy foods** and iii) **high-fat dairy foods** for the outcomes of BMI, fasting glucose and fasting insulin. We will also report associations between total dairy foods, high-fat dairy foods and low-fat dairy foods for the same outcomes, without considering genotypes. **We will consider all European American and African American ARIC participants that have both GWAS Array data and also the dairy dietary data.**

6. Design and Analysis:

Methods

Dependent Variables

1. BMI (kg/m^2)
2. Fasting glucose (SI units: mmol/L)
3. Fasting insulin (SI units: ln-pmol/L) (following natural-log transformation)

Exclusions

- Implausible dietary data
  ->Women > 5500kcal or < 500kcal;Men > 6000kcal or <600 kcal.
- Non-white and non-African American (whites and African Americans will be analyzed separately)
- Missing genotype data
- Missing dependent variables
- Type 1 diabetes or type 2 diabetes (self-reported, anti-glycemic medication use, or fasting glucose ≥7 mmol/L (≥126 mg/dL))
- Filters to exclude SNPs based on low quality imputation, low MAF, etc., will be applied centrally.

Independent Dietary Variables

1. Total dairy (servings/day, evaluated continuously)
2. Low fat dairy (servings/day, evaluated continuously)
3. High fat dairy (servings/day, evaluated continuously)

Defining high and low fat dairy

Estimates of total, high-fat and low-fat dairy will be harmonized to the greatest extent possible given the number of questionnaires and differences in the food supply across countries. Proposed definitions of high and low fat dairy, serving size and milk equivalents are below:
High-fat dairy foods include whole milk, 2% milk, cheese, butter, and ice cream.
Low-fat dairy foods include 1% milk, skim milk, cottage cheese, and yogurt.

Definitions of high-fat and low-fat are based on:

- Mozaffarian D, Cao H, King IB, Lemaitre RN, Song X, Siscovick DS, Hotamisligil GS. Trans-palmitoleic acid, metabolic risk factors, and new-onset diabetes in U.S. adults: a cohort study. Ann Intern Med. 153(12):790-9,2010.
- Hu FB, Stampfer MJ, Manson JE, Ascherio A, Colditz GA, Speizer FE,Hennekens CH, Willett WC. Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women. Am J Clin Nutr 1999;70:1001–8.

Milk serving = 240 ml (1 cup or 8 fluid oz)
Milk serving equivalents*:

- 43 g (1½ oz) hard cheese (cheddar, mozzarella, Swiss, Parmesan)
- 480 ml (2 cups) cottage cheese, 57 g (2 oz) processed cheese
- 360 ml (1½ cups) ice cream
- Butter : 1 pat (1" sq, 1/3 " high) or 1 teaspoon or 5 grams

Non-dairy milks (soy, nut, rice, coconut) are not included as dairy foods.
*from United States Department of Agriculture (USDA) food groups
http://www.choosemyplate.gov/food-groups/dairy.html# (*Note t*hat the dairy group is based on calcium but the genetic impact involves *lactose*).

Genetic Variables

We will include genome-wide (via GWAS array) genetic data that has been imputed to cover 2.5M SNPs based on Phase II HapMap. All non-autosomal SNPs will be excluded. SNPs are coded as dosages, ranging between 0 and 2.

MODELS

Phase 1 – BMI

Model 1 = Age, Sex, Field Center (as needed), Principal components (as needed to adjust for population substructure), Family structure (as needed)

Model 2 = Model 1 + total energy (kcal/day) + physical activity (sedentary vs. non-sedentary, if available) + CHARGE diet score

Phase 2 – Fasting glucose and fasting insulin

Model 3: Fasting Glucose = Age, Sex, Field center (as needed), Principal components (as needed for population substructure), Family structure (as needed) + total energy (kcal/day)

Model 4: Fasting Insulin = Same model as for Fasting Glucose **+ BMI**

Note : When the trait of interest is **insulin**, analysis should also be adjusted for **BMI.**

ANALYSES

For the models above conduct genome-wide linear regression analyses or linear mixed effects models with indicated metabolic traits (BMI, fasting glucose or fasting insulin) as outcomes.

1. Association analyses

MODEL: METABOLIC TRAIT = Dietary exposure + covariates

2. Interaction analyses

The primary independent variables of interest will be the main effect of each SNP and its interaction with a dietary exposure. Output from analyses will include regression parameters, their standard errors and p values, and also covariance estimates. The covariance estimate will be used to conduct 2 df tests of the association of a SNP, taking possible interaction into account. The Model can be stated as follows:

MODEL: METABOLIC TRAIT = SNP + Dietary exposure + SNP*Dietary exposure + covariates

Genome-wide significance threshold will be results with p value < 5 x 10-8. Each study will conduct analyses of its data and results will be meta analyzed with fixed effects inverse variance weighting of the regression coefficients.

Obtain robust standard errors and covariance estimate between the SNP beta and the Interaction beta. These will be run using ProbABEL version 0.1-3 (http://mga.bionet.nsc.ru/~yurii/ABEL/)

REFERENCES

Abargouei AS, Janghorbani M, Salehi-Marzijarani M et. al. Effect of dairy consumption on weight and body composition in adults: a systematic review and meta-analysis of randomized controlled clinical trials. Int J Obes. 36(12):1485-93, 2012.

Arnberg K. Molgaard C. Michaelsen KF et. al. Skim milk, whey, and casein increase body weight and whey and casein increase the plasma C-peptide concentration in overweight adolescents. J Nutr. 142(12):2083-90, 2012.

Astrup A, Chaput JP, Gilbert JA et. al. Dairy beverages and energy balance. Physiology & Behavior 100(1):67-75, 2010.

Berkey CS, Rockett HR, Willett WC et. al. Milk, dairy fat, dietary calcium, and weight gain: a longitudinal study of adolescents. Arch Pediatr Adolesc Med. 159:543-550, 2005. .

Bersaglieri T**,** Sabeti PC**,** Patterson N et. al. Signatures of strong recent positive selection at the lactase gene. Am J Hum Genet. 74(6):1111-20, 2004. PMC1182075.

Beydoun MA, Gary TL, Caballero BH et. al. Ethnic differences in dairy and related nutrient consumption among US adults and their association with obesity, central obesity, and the metabolic syndrome. Am J Clin Nutr. 87(6):1914-25, 2008. PMC2585752

Bowen J, Noakes M, Clifton PM. Effect of calcium and dairy foods in high protein, energy-restricted diets on weight loss and metabolic parameters in overweight adults. Int J Obes (Lond). 29(8):957-65, 2005.

Chen M. Pan A. Malik VS. Hu FB. Effects of dairy intake on body weight and fat**:** a meta-analysis of randomized controlled trials. Am J Clin Nutr. 96(4):735-47, 2012.

Choi HK, Willett WC, Stampfer MJ et. al. Dairy consumption and risk of type 2 diabetes mellitus in men: a prospective study. Arch Intern Med. 165(9):997-1003, 2005.

Corella D, Arregui M, Coltell O et. al. Association of the LCT-13910C>T Polymorphism With Obesity and Its Modulation by Dairy Products in a Mediterranean Population. Obesity (Silver Spring). 19(8):1707-14, 2011.

Dedoussis GV, Louizou E, Papoutsakis C et. al. Dairy intake associates with the IGF rs680 polymorphism to height variation in periadolescent children. Eur J Clin Nutr 64: 253-258, 2010.

Dove ER, Hodgson JM, Puddey IB et. al. Skim milk compared with a fruit drink acutely reduces appetite and energy intake in overweight men and women. Am J Clin Nutr. 90(1):70-5, 2009.

Drouillet P, Balkau B, Charles MA et. al. Calcium consumption and insulin resistance syndrome parameters. Data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR). Nutr Metab Cardiovasc Dis.17(7):486-92, 2007.

Faghih Sh, Abadi AR, Hedayati M et. al. Comparison of the effects of cows' milk, fortified soy milk, and calcium supplement on weight and fat loss in premenopausal overweight and obese women. Nutr Metab Cardiovasc Dis. 21(7):499-503, 2011.
German JB, Dillard CJ. Composition, structure and absorption of milk lipids: a source of energy, fat-soluble nutrients and bioactive molecules. Crit Rev Food Sci Nutr 46:57–92, 2008
Gilbert JA, Joanisse DR, Chaput JP et. al. Milk supplementation facilitates appetite control in obese women during weight loss: a randomised, single-blind, placebo-controlled trial. Br J Nutr. 105:133-43, 2011.
Grantham NM. Magliano DJ. Hodge A et. al. The association between dairy food intake and the incidence of diabetes in Australia: the Australian Diabetes Obesity and Lifestyle Study (AusDiab).Public Health Nutrition. 16(2):339-45, 2013.
Gunther CW, Legowski PA, Lyle RM et. al. Dairy products do not lead to alterations in body weight or fat mass in young women in a 1-y intervention. Am J Clin Nutr. 2005;81:751-756, 2005.
Hollis JD, Mattes RD**.** Effect of increased dairy consumption on appetitive ratings and food intake. Obesity 15:1520–1526, 2007.
Hoyt G, Hickey MS, Cordain L. Dissociation of the glycaemic and insulinaemic responses to whole and skimmed milk. Br J Nutr 93:175-17, 2005.

Josse AR, Atkinson SA, Tarnopolsky MA et. al. Increased consumption of dairy foods and protein during diet- and exercise-induced weight loss promotes fat mass loss and lean mass gain in overweight and obese premenopausal women. J Nutr. 141(9):1626-34, 2011.
Kratz M. Baars T. Guyenet S. The relationship between high-fat dairy consumption and obesity, cardiovascular, and metabolic disease. Eur J Nutr. 52(1):1-24, 2013.
Lamri A, Poli A, Emery N et. al. The lactase persistence genotype is associated with body mass index and dairy consumption in the D.E.S.I.R. study. Metabolism. 62(9):1323-9, 2013
Lawlor DA, Ebrahim S, Timpson N et. al. Avoiding milk is associated with a reduced risk of insulin resistance and the metabolic syndrome: findings from the British Women's Heart and Health Study. Diabetic Medicine. 22(6):808-11, 2005 PMID: 16911634
Liu E, McKeown NM, Newby PK et. al. Cross-sectional association of dietary patterns with insulin-resistant phenotypes among adults without diabetes in the Framingham Offspring Study. Br J Nutr. 102(4):576-83, 2009.
Liu S, Choi HK, Ford E et. al. A Prospective Study of Dairy Intake and the Risk of Type 2 Diabetes in Women. Diabetes Care 29(7):1579-84, 2006.
Louie JC. Flood VM. Hector DJ et. al. Dairy consumption and overweight and obesity: a systematic review of prospective cohort studies. [Review] Obesity Reviews. 12(7):e582-92, 2011.
Mozaffarian D, de Oliveira Otto MC, Lemaitre RN et. al. Trans-Palmitoleic acid, other dairy fat biomarkers, and incident diabetes: the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr. 97(4):854-61,2013.
Mozaffarian D. Cao H. King IB. Lemaitre RN. Song X. Siscovick DS. Hotamisligil GS. Trans-palmitoleic acid, metabolic risk factors, and new-onset diabetes in U.S. adults: a cohort study. Ann Intern Med. 153(12):790-9,2010.
Ostman EM, Liljeberg Elmstahl HG et. al. Inconsistency between glycemic and insulinemic responses to regular and fermented milk products. Am J Clin Nutr 74:96-100, 2001.

Rajpathak SN, Rimm EB, Rosner B, Willett WC, Hu FB. Calcium and dairy intakes in relation to long-term weight gain in US men. Am J Clin Nutr 2006;83:559–66, 2006.
Shah NP. Effects of milk-derived bioactives: an overview. Br J Nutr. 84 Suppl 1:S3-10, 2000.
Sluijs I. Forouhi NG. Beulens JW et. al. The amount and type of dairy product intake and incident type 2 diabetes: results from the EPIC-InterAct Study. Am J Clin Nutr 96(2):382-90, 2012.

Snijder MB, van Dam RM, Stehouwer CD, Hiddink GJ, Heine RJ, Dekker JM. A prospective study of dairy consumption in relation to changes in metabolic risk factors: the Hoorn Study. Obesity. 16(3):706-9, 2008.

Thompson WG, Rostad Holdman N, Janzow DJ, Slezak JM, Morris KL. Zemel MB. Effect of energy-reduced diets high in dairy products and fiber on weight loss in obese adults. Obesity Research 13(8):1344-53, 2005.

van Meijl LE. Mensink RP. Low-fat dairy consumption reduces systolic blood pressure, but does not improve other metabolic risk parameters in overweight and obese subjects. Nutr Metab & Cardiovasc Dis. 21(5):355-61, 2011

Ward RE, German, JB. Understanding milk's bioactive components: a goal for the genomics toolbox. J Nutr. 134(4):962S-7S, 2004.

Weaver CM, Campbell WW, Teegarden D et. al. Calcium, dairy products, and energy balance in overweight adolescents: a controlled trial. Am J Clin Nutr. 94(5):1163-70, 2011.

Werner LB. Hellgren LI. Raff M. Jensen SK. Petersen RA. Drachmann T. Tholstrup T. Effects of butter from mountain-pasture grazing cows on risk markers of the metabolic syndrome compared with conventional Danish butter: a randomized controlled study. Lipids health dis. 12:99, 2013.
Zemel MB, Richards J, Milstead A et. al. Effects of calcium and dairy on body composition and weight loss in African-American adults. Obes Res. 13:1218-25, 2005.

7.a. Will the data be used for non-CVD analysis in this manuscript?

_ Yes

__X_ No

b. If Yes, is the author aware that the file ICTDER02 must be used to exclude

persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and

for DNA analysis RES_DNA = "CVD Research" would be used?

_X_Yes

___ No

(This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?

_X_ Yes

____ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"?

_X_ Yes

____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

_X_ Yes

____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?

_____ Yes

_X_ No

11.b. If yes, is the proposal

__ A. primarily the result of an ancillary study (AS #2006.03 & 2007.02)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____)

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.