

**ARIC Manuscript Proposal # 3171**

**PC Reviewed:** 6/12/18  
**SC Reviewed:** \_\_\_\_\_

**Status:** \_\_\_\_\_  
**Status:** \_\_\_\_\_

**Priority: 2**  
**Priority:** \_\_\_\_\_

**1.a. Full Title:** Association of Metformin, Sulfonylurea and Insulin Use with Brain Structure and Function and Risk of Dementia and Alzheimer's Disease: Pooled Analysis from 6 Cohorts

**b. Abbreviated Title (Length 26 characters):** diabetes meds, dementia, 5 cohorts

**2. Writing Group:**

Writing group members: Galit Weinstein, Kendra L. Davis-Plourde, Sarah Conner, Jayandra J Himali, Alexa S. Beiser, Ann Lee, Andreea M. Rawlings, Sanaz Sedaghat, Jie Ding, Erin Moshier, Cornelia M. van Duijn, Michal S. Beeri, Elizabeth Selvin, M Arfan Ikram, Lenore J. Launer, Marry Haan, and Sudha Seshadri

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. \_\_\_\_ **[please confirm with your initials electronically or in writing]**

**First author:** Galit Weinstein / Andreea Rawlings (Dr. Rawlings will lead the analyses for ARIC)

**ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator):

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**3. Timeline:** All data are currently available.

#### **4. Rationale:**

*This proposal is part of a larger pooled analysis project that aims to pool data from 6 cohorts: The Original and Offspring cohorts of the Framingham Heart Study (FHS), the Rotterdam Study (RS), the Aging Gene-Environment Susceptibility-Reykjavik Study (AGES), the Atherosclerosis Risk in Communities (ARIC) Study, the Sacramento Area Latino Study on Aging (SALSA) and The Israel Diabetes and Cognitive Decline study (IDCD).*

*This proposal focuses on assessing the efficacy of specific diabetes interventions (i.e. life-style change only, exogenous insulin, metformin, sulfonylureas, gliptins) in mid- and late-life, in reducing Alzheimer's Disease risk, independently of their efficacy in glucose control.*

Dementia is a devastating clinical diagnosis that has physical, financial and social consequences for patients, their care-givers and families including increased mortality and a greater need for medical services [1]. It is increasingly recognized that dementia is a life-course illness, preceded by years and even decades of subclinical brain changes, [2-4] which could explain why disease-modifying treatments are lacking for most people who already have dementia [5, 6]. While it is postulated that delaying disease onset by 5 years could reduce lifetime risk by 50% [7], there are currently no confirmed prevention strategies. Therefore, in order to reduce the burden of dementia and Alzheimer's disease (AD), there is an urgent need to find effective strategies for prevention. Considering the expected increase in number of AD cases worldwide, from 30.8 million in 2010 to over 106.2 million in 2050, it is assumed that a 20% reduction per decade in each of the modifiable risk factors would result in a reduction of 15.3% (16.2 million) in AD prevalence by 2050 [8]. Yet, unlike other common aging related diseases which have efficient preventive strategies such as control of hypertension and hyperlipidemia to prevent stroke and coronary artery disease, smoking cessation to prevent lung cancer, and screening procedures for early detection and removal of precancerous lesions, there are no known preventive interventions for dementia and AD.

Type 2 diabetes (T2D) is a well-established risk factor for dementia and AD [9-12]. Nevertheless, it is yet unclear whether cognitive decline may be prevented by an adequate metabolic control. The proposed research aims to enhance the development of dementia-prevention strategies, through better understanding the relationships between impaired glucose homeostasis and cognitive outcomes.

The specific aim for this paper is:

To assess the efficacy of specific diabetes interventions (i.e. life-style change only, exogenous insulin, metformin, sulfonylureas, gliptins) in mid- and late-life, in reducing AD risk, independently of their efficacy in glucose control.

## 5. Main Study Questions:

### Aim

We will assess the efficacy of specific diabetes interventions (i.e. life-style change only, exogenous insulin, metformin, sulfonylureas, gliptins) in mid- and late-life, in reducing AD risk, independently of their efficiency in controlling blood glucose levels

Current considerations for choosing the type of diabetes management include the disease severity as well as the patient's age, health status and risk from possible adverse drug events. Identifying specific diabetes interventions which are more effective in reducing cognitive decline and AD risk, and the time in the patient's lifespan during which use of these interventions is most effective, could result in new guidelines addressing individuals at high risk for AD, and hence will have a tremendous impact on reducing dementia burden. By adjusting for glucose control, we will focus on the benefits of the intervention per se, and therefore will be also able to draw conclusions regarding AD pathophysiology, based on the drug mechanism of action.

Our approach is novel. Very little data exists to date on whether intensive glucose control (achieved by any means) is associated with reduced progression of AD. Even less is known on the effect of specific T2D medications. It has been previously suggested that peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) agonists may have specific benefits in AD, perhaps by anti-inflammatory effects, however randomized clinical trials among AD patients have failed to confirm this assumption [20, 21], and this drug class has been withdrawn from the market due to induction of hepatotoxicity. In a post-hoc analysis of the ACCORD-MIND study, an association of insulin and thiazolidinediones with cognitive performance was assessed, with no significant results [22]. Although Randomized clinical trials (RCTs) are considered the highest-quality scientific evidence, they are limited in the duration of follow-up and in the number and types of treatments tested in each trial as well as in the baseline characteristics of the participants. Here, we are proposing a novel approach to study a possible effect of T2D treatments on AD risk as well as on cognitive performance and brain integrity among non-demented individuals. The information obtained prospectively on a large number of individuals, the observational rather than intervention design, and the long duration of follow-up, will enable a comprehensive evaluation of various T2D drug classes, in two different time points in one's life-span, and on several cognitive outcomes. This information, in turn, will lay the foundation for future well- designed RCTs. Findings from the proposed research will have immense and immediate impact on public health, because T2D interventions, if shown effective to reduce dementia burden, are already available and inexpensive.

**6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).**

Study Design

- Cross-sectional using data from visit 5
- Prospective analyses using data from visit 4

Exposures

- Diabetes
- Diabetes medication use/type (insulin, sulfonylureas, etc)
- Fasting blood glucose (FBG), fasting insulin levels, Hemoglobin A1C (HbA1C), homeostatic model assessment of insulin resistance (HOMA-IR), T2D, and T2D treatments: life-style change, exogenous insulin, metformin, sulfonylurea and gliptins. For the purpose of the proposed analyses, life-style change will be defined as anyone with T2D who do is not prescribed any glucose control medication.

Outcomes

- Incident dementia (yes/no) after visit 5: Incident dementia and AD will be the primary outcome. In all of the samples there are more diagnoses of AD than other, less common types of dementia. Our general statistical approach is to consider first all types of dementia as one outcome, but we recognize that analyses focused on “all dementia” are likely to be driven largely by effects associated with AD, which we verify with a separate analysis of AD only. If there is a dissociation of results between the “all dementias” versus “AD only” analyses, this would suggest that significant associations may be linked to other types of dementia, the most probable of which is vascular dementia, the second most commonly diagnosed dementia.
- Change in cognitive function from visits 4 to 5: We will first test associations with general cognitive performance. Subsequently, we will include outcomes of memory and executive function performance, the first is linked more to hippocampal neurodegeneration, and the latter reflects the integrity of the frontal lobe which is more prone to subclinical vascular injury [38, 39].
- Findings on MRI at visit 5 (total brain volume, white matter hyperintensity volume, hippocampal volume): hippocampal volume: Atrophy in the hippocampus has been shown to be one of the first areas affected by T2D [40, 41] and is highly correlated with future risk of dementia [42, 43]. One disadvantage of using incident dementia/AD as an outcome is that persons with a propensity to develop the disease may not yet have done so when examined and some may die of competing causes prior to onset of clinical disease. However, persons who later develop clinical AD show differences in brain volumes and cognitive functions

10-20 years before the onset of clinical AD [44]. Therefore, we propose to conduct separate analyses with structural brain measures and cognitive function scores as outcomes. These outcomes will serve as endophenotypic early risk markers, which are quantitative, can be measured in all individuals and hence improve power to detect associations and to understand underlying pathophysiology. As a result, each aim will include a prospective analysis of disease outcomes as well as cross-sectional analysis of endophenotype outcomes. In addition, all the participating studies have extensive information on the sample's health behavior, demographic and clinical data, hence a proper stratified analyses and as well as adjustment for potential confounders using multivariate models will be undertaken.

### Data analysis

Cox-proportional regression models using age as the time-scale will be used to assess risk of dementia and AD with each of the following exposure variables included in the regression models: life-style change only (assessed as persons with T2D who are not prescribed any glucose-control medication), exogenous insulin, metformin, sulfonylureas and gliptins, as well as common treatment combinations. In each of these models, mean HbA1C from all available measurements during the follow-up period will be entered together with other covariates, to adjust for level of glucose control. The models will be adjusted for participant-level and study-level potential confounders and individuals will be able to contribute observations to more than one treatment group. We will consider the number of individuals in the different treatment groups, and will merge groups in case numbers are small. The same approach will be taken with cognitive and structural brain measures at the last available examination as the outcome, using linear regression models. Significant results for each of the intervention will suggest a role for this intervention in prevention of AD, independently of its effect in improving glycemic control. For this analysis, we will exclude participants who do not have information at baseline (midlife: 40 to 60 or late-life: 65-80) assessment for the variable of interest and persons who were demented or had a history of stroke at baseline. In addition, in sensitivity analyses, we will exclude persons with interim strokes.

### Challenges/Limitations

Our approach of harmonizing and combining data from 6 prospective studies will decrease the variation caused by random error and will result in an increased statistical power that will allow evaluation of relationships that could not be done in smaller samples. However, pooling the data does not eliminate any systematic errors, and therefore the proposed study's findings will be subjected to the same biases and limitations that may be present in each of the studies:

Selective attrition: This is an unavoidable limitation of large epidemiological cohort studies. However, each of the studies participating in the proposal minimizes attrition through a careful surveillance for endpoints which includes integration of participants' data from different sources (e.g. home assessments, off-site, medical records). We will compare the baseline characteristics of study-specific participants vs. those who were lost to follow-up or excluded to assess the magnitude of potential selection bias. In addition,

we will use an adaptation of a marginal structural model (MSM) applying inverse probability weights (IPW), and compare the results of analysis using this method with analysis that did not take the above potential bias into account.

Confounding by indication/ severity: The threat of confounding by indication, and /or by severity may exist because T2D treatment decision (whether to prescribe medications at all, or the type of medication) is influenced by the disease severity, and hence may be related to the study outcomes (e.g. incident dementia/AD). We will minimize this threat by controlling for HbA1C, a marker of T2D severity, as well as for education and occupation as markers of socioeconomic status and microalbuminuria as a marker of end-organ damage, and for other potential risk factors for dementia and AD. If a residual bias remains, we expect it to result in underestimation of the association if a drug class for a more advanced disease (e.g. exogenous insulin) is compared to a milder disease treatment (e.g. life-style change). Confounders: We will adjust for potential confounders. The first model will include adjustments for age, sex, education and cohort, the second will include further adjustments for vascular risk factors.

Missing data: In some analyses, not all 7 cohorts will be able to contribute data, and statistical models will be conducted among subgroups of participants. For example, there is no information on insulin levels in AGES and the IDCD, and blood biomarkers in SALSA are available only in late-life. Similarly, because the IDCD have only small numbers of incident dementia cases, it will contribute mainly to the cross-sectional analyses. Yet, considering the large numbers of participants, we will have sufficient statistical power, and at least 5 cohorts will participate in all analyses. The nature of the missing values will be explored, and in case data are not missing completely at random we will conduct a sensitivity analysis omitting the study from the analyses.

Measurement error/ misclassification: The use of multiple measurements of the exposure variables, together with the prospective design of the study, reduces the probability that a differential bias of the exposure will occur. Similarly, misclassification of dementia or other related outcome is not expected to differ according to exposure level/category. Therefore, while random measurement errors may result in a weaker association, a bias with unknown implications is less likely.

Differences in follow-up durations: Will be dealt by using age, rather than time-to-event, as the time-scale. In addition, our test for heterogeneity will include a random-effect meta-regression to estimate the extent to which variation in follow-up durations affects heterogeneity.

Generalizability of observations to other ethnic minorities: Individuals from the participating cohorts are predominantly of European ancestry, which may hamper the generalizability of the study results. We are, however, able to confirm the findings from this sample, in other, multi-ethnic cohorts: the Omni cohorts from generations 1 and 2 of the Framingham study include African-American, Hispanic, Asian, Indian, Pacific Islander and Native American origins. The Atherosclerosis Risk in the Community (ARIC) studies include African-American participants, and SALSA consists of Mexican

American participants. Hence, findings from the current study can be studied in other ethnic groups.

**7.a. Will the data be used for non-CVD analysis in this manuscript?**  Yes  No

**b. If Yes, is the author aware that the file ICTDER03 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?**  Yes  No  
(This file ICTDER03 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?**  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 ICTDER03 must be used to exclude those with value RES\_DNA = “No use/storage DNA”?**  
 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.csc.unc.edu/ARIC/search.php>  
 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)?**

MP #1553: Associations between vascular risk factors and longitudinal changes in ventricular size: a 14-Year longitudinal study (Knopman)

MP #1771: Cognitive, Vascular Risk Factors, and APOE Genotype Predictors of Hippocampal Volume (Knopman)

MP #1899: Troponin T, NT-proBNP and stroke incidence (Folsom)

MP #2288: Associations of brain imaging with cognitive change over 20 years (Knopman)

MP #2002: Association of High-Sensitivity Cardiac Troponin T (hs-cTnT) with Cognitive Function: the Atherosclerosis Risk in Communities Study (Schneider/Rawlings)

MP #2227: Relationship of cardiac structure and function with cognitive performance: as study of the Atherosclerosis Risk in Communities (ARIC) study (Jhund)

MP #2315: Association of diabetes with brain magnetic resonance imaging (Schneider)

MP #2334: Troponin T and N-terminal pro-B-type Natriuretic Peptide and Cognitive Decline and Dementia in the ARIC study (Pokharel)

MP #2351: Association of blood pressure with neurodegenerative and cerebrovascular changes on brain MRI (Power)

MP #3018: Evaluation of novel circulating biomarkers in the prediction of adverse cardiovascular events including heart failure (Nambi)

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?**  Yes  No

ARIC NCS

**11.b. If yes, is the proposal**

**A. primarily the result of an ancillary study (list number\* 2008.06)**

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

\*ancillary studies are listed by number at <http://www.cscce.unc.edu/aric/forms/>

**12a. 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.**

**12b. The NIH instituted a Public Access Policy in April, 2008** which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from <http://publicaccess.nih.gov/> are posted in <http://www.cscce.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.



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