ARIC Manuscript Proposal # 1176

PC Reviewed: _08_/_15_/06 Status: __D___ Priority: ____

SC Reviewed: _08_/_17_/06 Status: __D___ Priority: ___

1.a. Full Title:

Lower LDL-Cholesterol is associated with Parkinson's disease: results from ARIC study participants

b. Abbreviated Title (Length 26 characters): Lipids in Parkinson's disease

2. Writing Group:

(Currently in alphabetical order): Chen, Honglei ; Huang, Xuemei; Mailman, Richard; Mosley, Thomas H; Poole Charlie; Rosamond, Wayne

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

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3. Timeline:

From approval to finish data analysis: 3 months.

From approval to submission of manuscript (6 months or less).

4. Rationale:

Parkinson's disease (PD) is a common age-related neurodegenerative disorder. Whereas some circumscribed etiological mechanisms are known (e.g., several genes), PD is largely idiopathic, and likely involves interactions of the genome and the environment. We recently demonstrated that apolipoprotein (APOE) ε2 allele, an allele associated with lower LDL-cholesterol, (Volcik et al., 2006) is positively associated with higher prevalence of sporadic PD). (Huang et al., 2004) In addition, PD is also associated with lower frequency of cardiovascular events (Kessler, 1972a; Kessler, 1972b; Nataraj and Rajput, 2005; Paganini-Hill, 2001; Struck et al., 1990). Interestingly, smoking, a factor known to be associated with cardiovascular diseases and adverse lipid profiles (Craig et al., 1989), is consistently associated with decreased risk of PD.(Benedetti et al., 2000; Grandinetti et al., 1994; Tanner et al., 2002)

These data led to our central hypothesis: that lower serum cholesterol (especially LDL-C) is associated with increased occurrence of PD. We have tested the hypothesis both in a case control study (UNC Movement Disorders Clinic) and a prospective study (Honolulu Aging Study). We would, however, like to follow up the finding with additional prospective cohort data.

The existing data and study structure of ARIC project provide an ideal opportunity to explore our hypothesis further.

5. Main Hypothesis/Study Questions:

The current proposal is based on the hypothesis that low LDL-C increases the susceptibility to PD. The main study question is to determine the relationship between the occurrence of PD and pre-morbid fasting lipid profiles.

6. Design and analysis

Study Design:

Study participants will be selected from ARIC study, a prospective investigation of ARIC involving 15,792 persons aged 45-64 years at recruitment of 1987-1989 from four US communities: Forsyth County, NC; Jackson, MI, the northwestern suburb of Minneapolis, MN; and Washington County, MD. At baseline clinical examination in 1987-1989, fasting lipid profiles and APOE genotype information were collected. The cohort was followed up with clinical exams every three years, and an annual phone interview. All subjects with hospital discharge code of PD between 1987 to 2004 will be identified as potential PD cases. In addition, potential PD cases will be identified though clinical interview at visit 4 (1996 -1998) by answering "yes" to question "Have you ever been told by an MD that you have PD?" The relation of LDL-cholesterol and occurrences of PD will be studied

Inclusion criteria:

1) All ARIC cohort members with documented fasting cholesterol profiles at 1987-1989 and without the diagnosis of PD at the first visit at 1987-1989.
2) All ARIC cohort members with documented APOE information.

Exclusion criteria:

1) Any ARIC participant with documented diagnosis of PD prior to 1990 (within one year of documented fasting cholesterol profiles).

Outcome.

1). Primary outcome is discharge (determined through cohort surveillance) or self-reported (assessed at V4) diagnosis of PD.

Possible effect modifiers"

Many factors that have been known to associate with either PD or LDL-cholesterol: such as *age, smoking history and coffee use*, *APOE status, BMI, the use of statins, NSAID, and exercise.* They may modify the association between LDL-cholesterol and PD, so we will treat them as potential effect modifiers for our study.

Summary of Data analysis

Crude and age-adjusted occurrence rates of PD in the cohort will be estimated by Poisson regression in each subgroup categorized according to their baseline fasting LDL-C level: < 80, 80-99, 100-119, 120-139, 140-159 and ≥ 160 mg/dL. In addition to a test for trend of association between lower LDL-C and increased risk of PD, RR for PD [and associated confidence intervals (CIs)]) will also be estimated for each LDL-C 40 mg/dL drop, and for the increment between the 80^{th} and 20^{th} percentiles of LDL-C. The categorical and continuous trend will be estimated after adjusting for several possible effect modifiers including age, gender, pack-years of cigarette

smoking, daily intake of coffee, APOE genotypes, use of cholesterol lowering drugs (statins and non-statins together and separately), BMI, physical activity and NSAIDs use.

Limitations/Challenges:

The biggest of the challenges for this study is the ascertainment of incident PD cases using hospital discharge records self report of clinician diagnosis at visit 4 (1996-1998). This case-finding procedure may not be as sensitive and specific as conducting clinical PD diagnostic examinations on all participants Nevertheless, PD cases have been identified by hospital discharge records and self-report of clinical diagnosis in other studies (Kamel and Hoppin, 2004). In addition, we will attempt to compare occurrence rates of PD as ascertained in the current study with those from other prospective cohorts.

1). *Sensitivity*: As PD has a long and gradual period of symptom onset, early PD may be missed by many physicians without specific training. Hospitalization data may only capture a subgroup of severe and prevalent cases, and self-reports may not be complete.

Potential solution: A cross-tabulation of cases from these two sources up to visit 4 may be helpful. Ideally, PD cases will be identified more systematically in future studies.

2). *Lack of dates of PD onset*. This limitation will create inflation in the apparent person-time at risk and consequent deflation of the occurrence rates. Nevertheless, because the person-time inflation will occur only among cases, the rarity of PD should limit the magnitude of any resulting bias. Some canceling may also occur in the estimation of rate ratios. Although we do not expect bias from this source of error to be appreciable, it will be the subject of sensitivity analyses.

3). *False positive cases*. Many conditions may mimic PD [e.g., side effects of antipsychotic drugs, PD due to stroke (vascular Parkinsonism), progressive supernuclear palsy (PSP), multisystem atrophy (MSA), and normal pressure hydrocephalous]. Clinically all those Parkinson and parkinsonism syndromes are given the same code of 332.0. (IN ICD10, it is G20, ICD code is also changed in late 1990s). If ARIC used the same code to identify PD through hospital records, there will be some false positive cases.

Potential solutions for current study: Although many of the Parkinson-like disease may mimic PD, many of them do not respond to PD pharmacotherapy. We could review the medication lists of the PD cases to eliminate some of the false positive cases. The drugs commonly and **uniquely** used by PD patients are: selegiline (Eldepryl), Mirapex (pramipexole), Requip (ropinirole), amantidine, Permax (pergolide). Sinemet (carbidopa/levodopa) and Comtan (entacapone) are commonly used in PD, but also for parkinsonism. If the above information can not be obtained with querying the database, this and the other issues described above will be discussed as limitations in the discussion section of manuscript.

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

[Dr. Huang has not seen this file ICTDER02, but will adhere to these guidelines.]

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)?

We are aware of no other manuscripts on this topic in ARIC.

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 (list number* _____)

___ 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.cscc.unc.edu/aric/forms/

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.

Understand

References:

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