

ARIC Manuscript Proposal # 754 (REVISED)

"The primary modification is that the analysis has been changed to include a prospective analysis instead of the previous cross-sectional relationship that was indicated in the title of the proposal." (Carnethon email 1/8/01)

PC Reviewed: 01/ 16/ 01

Status: A

Priority: 2

SC Reviewed: 01/ 30/01

Status: A

Priority: 2

1.a. Full Title:

The Association between Menopausal Status, the Menopausal Transition, Hormone Replacement Therapy and Cardiac Autonomic Balance

b. Abbreviated Title (Length 26 characters):

Menopause and Autonomic Tone

2. Writing Group (list individual with lead responsibility first):

Lead: Mercedes Carnethon

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3. Timeline:

Data preparation and analysis (1 month), Manuscript preparation (3 months)

4. Rationale:

Research has demonstrated that low heart rate variability (HRV), a measure of cardiac autonomic balance, predicts clinical coronary heart disease (CHD) events and all-cause mortality in the population (1-4). Women have higher HRV as compared to men, indicating better autonomic balance (5-9), and variation in HRV among young women in different menstrual phases suggests that autonomic balance may be hormonally mediated (10, 11). Given this, differences in HRV by menopausal status in older women may be detectable, and changes in autonomic balance may be one mechanism by which the menopause is associated with an increase in CHD risk.

Previous research has correlated menopausal status and hormone replacement therapy with autonomic balance, but the direction of this association is not consistent. These inconclusive findings may be due to a combination of factors including small sample sizes ($n < 80$), cross-sectional designs, limited measures of autonomic balance, and the use of non-randomized trials with short follow-up times (12-14). A study of the relationship between the menopause and autonomic balance, measured by HRV, in ARIC could overcome many of the limitations of prior research. Most importantly, the direction of the proposed association could be identified using the prospective design in ARIC and approximately 9-12 years of longitudinal data among participants. Further, effect estimates based on the large number of women in ARIC are likely to be robust. Equally important, members of this writing group designed the HRV Ancillary Study that collected and processed HRV measures in this cohort, and these investigators are experienced using these

measures to estimate autonomic balance. Finally, using comprehensive information on medication use and CHD risk factors in the cohort, the investigators can study the effects of these covariates on the relationship between the menopause and autonomic balance.

5. Main Hypothesis/Study Questions:

This study will address the following questions:

- 1) Is there a cross-sectional association between menopause status and autonomic balance (as measured by HRV)?
- 2) Does HRV differ as the result of menopause status and changes in menopause status (prospective design)?
- 3) Is there a relationship between the duration spent post-menopausal and HRV?
- 4) Among post-menopausal women, does HRV differ between women using hormone replacement therapy and those who are not?
- 5) Among hormone replacement therapy users, does HRV differ by the type therapy, estrogen only or combined estrogen plus progestin?
- 6) Is there a relationship between the type of menopause (natural or surgical) and HRV?

We hypothesize that pre-menopausal women will have higher HRV (better autonomic balance) than post-menopausal women, and that the duration of time spent post menopausal will be inversely associated with HRV. We expect hormone replacement therapy to modify this relationship; hormone users will have higher HRV than their non-using counterparts. Further, estrogen therapy may be better at modifying HRV than combined estrogen plus progestin therapy. We do not expect to observe differences in HRV between naturally and surgically post-menopausal women once important covariates and age have been accounted for.

6. Data (variables, time window, source, inclusions/exclusions):

This study will include cross-sectional and prospective components. The study will be restricted to women in ARIC who are free of prevalent CHD, with complete information on menopausal status, medication use, and HRV. Women with available baseline HRV data will be included in the cross-sectional analysis, but HRV data must be available at the baseline and visit 4 examination in order for women to be included in the prospective analysis.

The following variables will be included:

Visit 1	Visits 2 and 3	Visit 4
Menopause Status	Menopause Status	Menopause status
Age	Age	Age
Medication Use	Medication Use	Medication use
Supine HRV		HRV
Diabetes		Diabetes
Prevalent CHD		Incident CHD
Cigarette Smoking		Cigarette Smoking
Hypertension		Hypertension
Cholesterol (Total, HDL, LDL, TG)		Cholesterol (Total, HDL, LDL, TG)
Race		Physical Activity
Physical Activity		

Additional covariates may be later added as the study question develops.

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 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? ☐ 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? ☐ 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 ICTDER01 must be used to exclude those with value RES_DNA = “No use/storage DNA”? ☐ Yes ☐ No

References

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