1.a. Full Title: Anthropometric cut-points and risk of diabetes, cardiovascular disease and mortality

b. Abbreviated Title (Length 26 characters): Obesity cut-points and disease risk

2. Writing Group:
   Writing group members: The manuscript will be published under “The Obesity, Diabetes and Cardiovascular Disease Collaboration”. A writing committee will be formed when data collection is complete.
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   2. Mark Woodward, The George Institute for Global Health, Australia, markw@georgeinstitute.org.au

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

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3. Timeline:

October 2016 – Finalize data collection
4. **Rationale:**
Type 2 diabetes is a costly yet preventable chronic disease. Studies have shown that lifestyle modification interventions can prevent or delay the onset of diabetes in people at high risk of diabetes (1). Non-invasive diabetes risk assessment tools are available in countries such as Australia, Finland and the UK (2-4). Clinical guidelines in Australia recommend general practitioners (GPs) to screen patients for diabetes with the Australian diabetes risk assessment tool every three years from age 40 years or from age 18 years for Aboriginal and Torres Strait Islander people (5). However, evidence suggests that the diabetes risk assessment tool is underutilized by GPs (6). Only 14% of the GPs surveyed applied the risk assessment tool and most GPs surveyed considered they had little to offer to patients detected as high risk. Another possible explanation for the low uptake of the risk assessment tool (which takes approximately 5 minutes to complete per patient) is the time constraint during clinical visits. Thus, although most health care professionals would agree that performing a fasting glucose test on all patients would be a substantial waste of resources, there is an urgent need to identify patients at especially high risk of diabetes for further testing and early intervention.

Apart from age, excess adiposity is the strongest risk factor for type 2 diabetes. Simple anthropometric measures such as body mass index (BMI; calculated as weight in kilograms divided by height in metres squared) and waist circumference (WC) are widely used to assess adiposity in epidemiological studies. The BMI cut-points recommended by the World Health Organization (WHO) to define overweight (≥25 kg/m$^2$) and obesity (≥30 kg/m$^2$) were developed from studies on mortality in Caucasian populations. Likewise, the WHO recommended WC cut-points were developed based on their statistical equivalence to the existing BMI cut-points (BMI ≥25 kg/m$^2$: WC ≥94 cm for men and ≥80 cm for women; BMI ≥30 kg/m$^2$: WC ≥102 cm for men and ≥88 cm for women) (7).

Analyses by the Obesity in Asia Collaboration on cardiovascular risk factors (diabetes, hypertension and dyslipidemia) and anthropometric cut-points, which included over 150,000 individuals from ten countries in the Asia-Pacific region, suggested that the optimal cut-points for the discrimination of diabetes, hypertension and dyslipidemia were lower in Asians than Caucasians and that the WC cut-points should be lower than those recommended by the WHO (8-10). However, this collaboration only obtained cross-sectional data, which makes the results susceptible to bias.

The most common method used to derive optimal cut-points is the receiver operating characteristic curve method, in combination with the Youden index. Cut-points derived from this method, however, have been shown to be affected by background obesity prevalence (11). Therefore, simply using the existing WHO cut-points for overweight and obesity to identify people at high risk of diabetes may not even be appropriate for Caucasians. Moreover, a recent Japanese study reported different WC cut-points for the prediction of incident diabetes and cardiovascular disease (12). The WHO cut-points were originally defined in 1995 since which time the prevalence of overweight and obesity have increased in many countries including
Australia and USA where more than two thirds of the adult population fall into this category. Finally, most previous studies have relied upon cross-sectional data rather than relating present anthropometry to future hard events, such as type 2 diabetes.

5. Main Hypothesis/Study Questions:

Main study questions:
1. What are the optimal anthropometric cut-points for the identification of people at high risk of developing diabetes at 5, 10, and 15 years?
2. Are sex- and/or race/ethnic-specific anthropometric cut-points warranted?
3. Do anthropometric cut-points for the prediction of diabetes, cardiovascular disease and all-cause mortality differ?

Hypotheses:
1. The anthropometric cut-points for the identification of people at high risk of diabetes will be different to the obesity cut-points recommended by WHO.
2. Optimal anthropometric cut-points will differ between sex and/or race/ethnic subgroups.
3. Optimal anthropometric cut-points for the prediction of diabetes will be different to those for the prediction of cardiovascular disease and/or all-cause mortality.

Specific research aims:
1. To determine optimal anthropometric cut-points for the identification of people at high risk of developing diabetes at 5, 10 and 15 years using data from an international data pooling collaboration of longitudinal studies.
2. To investigate the need for sex- and/or race/ethnic-specific anthropometric cut-points for the identification of people at high risk of developing diabetes.
3. To compare anthropometric cut-points developed for the prediction of diabetes risk to those developed for the prediction of cardiovascular disease risk and mortality using the same dataset.

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
Individual participant data analysis of longitudinal studies included in an international data pooling collaboration

Data source
This study will utilize data from the Obesity, Diabetes and Cardiovascular Disease Collaboration (ODCDC). The ODCDC, based at Curtin University, Australia, is an international data pooling collaboration of longitudinal studies established to address outstanding issues of epidemiological and clinical importance regarding obesity, diabetes and cardiovascular disease in diverse populations. The ODCDC database was developed from a cleaned and coded dataset provided by
investigators of the Collaborative Study of Obesity and Diabetes in Adults (CODA) after obtaining permission of data use from investigators of each of the prospective studies included in CODA (13). With funding available through a National Health and Medical Research Council project grant (2016-2018), we have begun contacting investigators of existing and potential studies to provide data for all available study visits in order to develop a more comprehensive and informative dataset for the Collaboration. To date, 23 studies with more than 150,000 individuals from 11 countries have either provided or agreed to provide data to the Collaboration.

The updated ODCDC dataset will be the perfect data source for the re-examination of existing obesity cut-points as few studies have examined optimal cut-points with longitudinal data or compared cut-points for the prediction of future risk of diabetes, cardiovascular disease and mortality. The ODCDC dataset will provide the opportunity to investigate the need for ethnic-specific obesity cut-points for the identification of people at high risk of diabetes, which has particular relevance for multi-ethnic societies, such as Australia, UK and USA. To date, most studies that support ethnic-specific cut-points have used methods to derive cut-points that could be influenced by background prevalence of obesity and diabetes. Therefore, the difference in optimal cut-points reported between ethnic groups may be due to the difference in prevalence of obesity rather than the difference in risk associated with excess adiposity.

**Variables of interest**

Baseline – subject ID, age, sex, date of birth, exam date, education, race, systolic blood pressure, diastolic blood pressure, antihypertensive medication, diabetes treatment type, triglycerides, total cholesterol, HDL cholesterol, fasting insulin, fasting time, fasting plasma glucose, 2 hour plasma glucose, height, weight, waist circumference, hip circumference, smoking status, physical activity, self-report/known diabetes, family history of diabetes, cigarettes smoked per day, coronary heart disease status, gestational diabetes, age when first diagnosed with diabetes.

All follow-up visits – variables that can be used to determine diabetes incidence, cardiovascular disease events, and mortality e.g. fasting plasma glucose, 2 hour plasma glucose, self-report/known diabetes, diabetes treatment type, exam date, follow up time for diabetes, age when first diagnosed with diabetes, coronary heart disease event, cardiovascular disease event, stroke event, time to event, mortality, date of death.

**Statistical analysis**

Co-author Woodward has previously explored statistical methods that are potentially useful in determining optimal cut-points (14). In this study, optimal cut-points for BMI, WC, waist-hip ratio and waist-height ratio will be determined by fractional polynomial models and by inverse polynomial models. Data will be analysed by sex and by race/ethnicity. Participants with known or newly diagnosed diabetes at baseline will be excluded from all analyses. Since there are currently a number of accepted diagnostic tests for diabetes (fasting plasma glucose, oral glucose tolerance test and glycated hemoglobin), optimal cut-points for the prediction of incident diabetes as defined by each of the accepted diagnostic tests will also be explored. For studies that have data on cardiovascular disease and mortality, optimal cut-points for predicting risk of diabetes, cardiovascular disease, and mortality will be compared.
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 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    _X___ No
(This file ICTDER 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    _X___ 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.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)?

According to the ARIC proposals on diabetes and body mass index, we have identified the following manuscript proposals to be partly related to our proposed manuscript.

1. MS1456 – Measures of obesity in predicting different CVD outcomes by race and sex in the ARIC study
2. MS proposal by Christina Parrinello – Associations of c-reactive protein over six years with incident diabetes, cardiovascular events and mortality
3. MS proposal by R. Chatterjee – Novel risk factors of diabetes and their impact on the racial disparity in risk of incident diabetes: The Atherosclerosis Risk in Communities study
4. MS784 – Heterogeneity in the relationship between race, adiposity, insulin and incident diabetes
5. MS1762 – Epidemiologic studies of type 2 diabetes in normal weight adults: cardiovascular and all cause mortality
6. MS 1589 – Ethnic differences in body composition given the same body mass index level

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/](http://www.cscc.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/](http://publicaccess.nih.gov/) are posted in [http://www.cscc.unc.edu/aric/index.php](http://www.cscc.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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript _X___ Yes _____ No.