Ankle-brachial Index and Incident Diabetes Mellitus: The Atherosclerosis Risk in Communities (ARIC) Study.

By

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Abstract

Introduction: Individuals with peripheral artery disease (PAD) often have reduced physical function and activity, which may increase the future risk of diabetes. Although diabetes is a risk factor of PAD, whether low ankle-brachial index (ABI) predates diabetes has not been studied.

Methods: We examined the association of ABI with incident diabetes after accounting for potential confounders using Cox proportional hazards models in the ARIC Study. ABI was measured on a randomly selected leg in 12,247 black and white participants without prevalent diabetes at baseline (1987-1989). Incident diabetes cases were identified by glucose measurements (fasting ≥126 mg/dl or non-fasting ≥200 mg/dl) at subsequent three visits (1990-92, 1993-95, and 1996-98) and self-reported diagnosis or medication use at those visits or during annual phone interview through 2011.

Results: A total of 3,305 participants developed diabetes during a median of 21 years of follow-up. Participants with low (≤0.90) and borderline low (0.91-1.00) ABI had 30-40% higher risk of future diabetes as compared to those with ABI of 1.10-1.20 in the demographically adjusted model. The associations were attenuated after further adjustment for other potential confounders but remained significant for ABI 0.90-1.00 (HR=1.17, 95%CI 1.04-1.31) and marginally significant for ABI ≤0.90 (HR=1.19, 0.99-1.43). Although the association was largely consistent across demographic and clinical subgroups, we observed borderline significant interaction for hypertension

status and fasting glucose, with a stronger association between ABI and diabetes risk in participants without hypertension and those with normal fasting compared to their counterparts.

Conclusions: Low ABI was modestly but independently associated with increased risk of incident diabetes in the general population. Clinical attention should be paid to the glucose trajectory among people with low ABI.

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Preface

I'm interested in the biomarkers associated with diabetes, and the close relationship between cardiovascular diseases and diabetes motivated me to work on this topic about the association of ABI with incident diabetes. To our best knowledge, this is the first prospective cohort study on this topic and I hope my findings will provide insight to researchers in the field and contribute to the knowledge about the link between the two diseases. My thesis advisor, Dr. Matsushita, who leads several studies of PAD, supported and inspired me greatly throughout the whole project. I appreciated all the discussions and conversations with him, during which I benefited a lot. I would also like to thank my thesis reader, Dr. Selvin, who is an expert in both PAD and diabetes, for her contribution of in-depth thoughts to the proposal, abstract and manuscript. I'm really grateful for her comments and suggestions.

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Table of Contents

List of Tables

List of Figures

Introduction

Lower extremity peripheral arterial disease (PAD), typically defined by an ankle-brachial index (ABI) <0.9 [1], affects 8-10 million people in the United States [2]. PAD increases the risk of cardiovascular disease and reduces quality of life due to ischemic leg pain and intermittent claudication [1][3]-[5].

Regardless of leg symptoms, patients with PAD experience functional decline and impairment [6]-[9], which can result in reduced level of physical activity [7][10][11]. Since physically inactivity is an important risk factor of diabetes [12]-[14], it is possible that low ABI is associated with the development of diabetes. In addition, delayed insulin delivery due to endothelial dysfunction, an early condition of atherosclerosis, is considered to contribute to the development of insulin resistance [17]-[20]. Shared pathophysiology between atherosclerosis and insulin resistance, such as the involvement of inflammation, may also contribute to the link of ABI to diabetes risk [21][22]. However, to the best of our knowledge, the association of ABI with future risk of diabetes has not yet been studied although the opposite direction of association (i.e., diabetes as a risk factor of PAD) is well-known [2][15][16]. Therefore, we aimed to investigate whether ABI is independently associated with incident diabetes in a community-based cohort, the Atherosclerosis Risk in Communities (ARIC) Study.

Methods

Study population

The ARIC Study is a community-based prospective cohort study of 15,792 individuals aged 45-64 years at baseline. Participants were recruited at baseline examination (visit 1) during 1987-1989 from four US communities: Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland [23]. The participants were invited for follow-up examinations every three years (visits 2 [1990-1992], 3 [1993-1995], and 4 [1996-1998]). They also received annual telephone interview regarding their lifestyle and clinical conditions. The study was approved by the institutional review board at each field center, and informed consent was obtained from all participants.

Of 15,792 participants, we excluded 1,870 participants with prevalent diabetes (defined as self-reported diagnosis or treatment of diabetes, fasting blood glucose ≥126 mg/dl or random blood glucose ≥200 mg/dl at baseline) and 148 participants with no information about diabetes status. We also excluded 44 non-white and non-black participants as well as those with missing information on ABI (n=476), any covariates at baseline (n=575), and incident diabetes during follow-up (n=432), leaving 12,247 participants in our analysis.

Exposure assessment

ABI was defined as a ratio of systolic blood pressure of ankle to that of arm [24]. The ankle and brachial blood pressures were measured in a supine position by automated

oscillometric device Dinamap Model 1846 SX [25]. Ankle systolic blood pressure was measured four times in a randomly selected leg and the last non-missing value was used as numerator of ABI. Brachial systolic blood pressure was measured twice in the right arm and the first non-missing value was used as denominator of ABI [26].

Outcome assessment

The ascertainment of incident diabetes was based on two elements, self-reported physician diagnosis or treatment of diabetes during visits or phone interview through April 18, 2011 (interview-based definition) and fasting blood glucose ≥126 mg/dl, random blood glucose ≥200 mg/dl, or self-reported physician diagnosis or treatment of diabetes during visits 2 through 4 (visit-based definition), as previously done [27]. To maximize the statistical power, as the primary outcome, we combined these two definitions but also analyzed them separately as a secondary analysis.

Covariates of interest

Age, gender, race, parental history of diabetes, medical history of coronary heart disease (CHD) and stroke/transient ischemic attack (TIA), and smoking and alcohol drinking habits were self-reported at baseline. Medication use was assessed by self-report and examination of medication containers brought to the visit. Height, weight and sitting blood pressure were measured according to standardized protocols [28]. Hypertension was defined as a mean systolic blood pressure ≥140 mmHg or a mean diastolic blood pressure ≥90 mmHg, or use of antihypertensive drugs. Total cholesterol level, high-density lipoprotein cholesterol level and triglyceride level were measured using

enzymatic determination methods [29]. Glucose was measured using the hexokinase-glucose-6-phosphate dehydrogenase method [30].White blood cell count was measured by automated hematology analyzer [31]. Fibrinogen was measured using assay according to standard procedures [32]. Physical activity was assessed with the Baecke physical activity questionnaire, which recorded the duration, intensity and frequency of physical activity at work, in leisure time and during sports and produced an index score to represent level of physical activity [33].

Statistical Analyses

We categorized ABI into seven groups, ≤0.90, 0.91-1.00, 1.01-1.10, 1.11-1.20, 1.21-1.30, 1.31-1.40 and >1.40, consistent with prior literature [4]. Baseline characteristics were compared across these groups, according to chi-square test and ANOVA, as appropriate.

To visualize potentially non-linear associations, we used Poisson regression models with ABI modeled using linear spline terms (knots at 0.9, 1.0, 1.1, 1.2, 1.3 and 1.4) and estimated incidence rates of diabetes according to ABI. We subsequently quantified the adjusted risk of incident diabetes according to the seven ABI categories using Cox proportional hazards models. ABI 1.11-1.20 was used as the reference group since this is the group that is commonly thought to have "normal" ABI and had the largest number of participants [34][35]. To evaluate the impact of potential confounding, we constructed 3 models. Model 1 was adjusted for age, sex and race. Model 2 included all variables in Model 1 plus factors associated with atherosclerosis and diabetes, namely body mass index, total cholesterol, high-density lipoprotein cholesterol, and triglyceride, drinking and smoking status (current vs. never and former vs. never), systolic blood pressure,

hypertension medication use, history of coronary heart disease, stroke or transient ischemic attack (TIA), statin use, parental history of diabetes, white blood cell count, and physical activity index. Model 3 included all variables in Model 2 plus baseline fasting glucose. There was no major deviation from the proportional hazards assumption for ABI categories based on visual evaluation from log-log plot as well as from test on Schoenfeld residuals.

We tested for interaction and conducted subgroup analyses by age (≤ vs. >55 years), gender, race, smoking status (current vs. former/never), history of cardiovascular disease, history of stroke or TIA, hypertension status, baseline fasting glucose level (normal <100 vs. impaired 100-125 mg/dl) and exertional leg pain status. Interaction was tested by incorporating a production term of ABI categories and subgroups in Cox models.

As to sensitivity analysis, we repeated the analysis in visit-based definition and interview-based definition of diabetes separately. We also explored the model which replaced white blood cell count with fibrinogen (an alternative inflammatory marker) in Model 2. Finally, we treated physical activity, a potential mediator of ABI-diabetes association, as a time-varying covariate using data assessed at visit 3 in addition to Model 2 covariates.

All analyses were performed with Stata version 12.0. All p-values were two-sided, and $p < 0.05$ was considered statistically significant.

Results

The mean ABI of study population was 1.13 (SD 0.14). There were 455 individuals

(3.7%) with ABI ≤ 0.90 and 1,529 participants (12.5%) with borderline low ABI of 0.91-1.00. There was no significant correlation between ABI and baseline fasting glucose (r=0.002, p-value=0.81). Baseline characteristics of study participants by ABI categories are shown in Table 1. As compared to participants with ABI 1.11-1.20 (reference group), those with lower ABI were more likely to be older, female, and blacks. They also had worse cardiovascular risk profiles relative to the reference group, including higher prevalence of current smokers, hypertension, and cardiovascular diseases (CHD and stroke/TIA), higher levels of body mass index, total cholesterol, triglyceride, white blood cell count, and fibrinogen, and lower level of physical activity. Participants with ABI>1.40, indicative of arterial stiffness [34], also had worse cardiovascular risk profiles as compared to those with ABI 1.11-1.20.

A total of 3,305 cases of incident diabetes were identified during a median of 21 years of follow-up (incidence rate 16.8 [95%CI: 15.8-16.9] per 1,000 person-years). Figure 1 shows demographically adjusted incidence rates of diabetes according to ABI at baseline. The incidence rates of diabetes were lowest in ABI 1.10-1.30 and increased as ABI decreased below this range. The incidence rate of diabetes was similar or slightly higher in ABI >1.30 compared to ABI 1.10-1.30.

In a demographically adjusted Cox regression model with ABI 1.10-1.20 as the reference, low ABI categories were significantly associated with incident diabetes (hazard ratio [HR] 1.41 [95% CI 1.17-1.68] for ABI ≤0.90, 1.29 [1.15-1.45] for ABI 0.91-1.00, and 1.10 [1.00-1.22] for ABI 1.01-1.10, Model 1 in Table 2). When we further adjusted for other potential confounders including white blood cell count and physical activity (Model 2 in Table 2), the associations for all low ABI categories remained

significant although it was borderline significant for ABI ≤0.90. The replacement of white blood cell count with fibrinogen did not make material difference (data not shown). After accounting for baseline fasting glucose (Model 3), the association remained marginally significant only in participants with ABI 0.91-1.00 (p-value=0.051). However, when we combined ABI≤0.90 and 0.91-1.00 groups, the association was statistically significant even in Model 3 (HR=1.12 [95% CI 1.01-1.24], p-value=0.034). For participants with ABI>1.40, we observed slight but non-significant increase in the risk of incident diabetes compared to those with ABI 1.11-1.20 in Models 1 and 3. The association was largely consistent when we analyzed interview-based cases and visit-based cases separately (Table S1 and Table S2). The model with physical activity as a time-varying covariate using visit 3 data showed similar results (data not shown).

To obtain reliable estimates in subgroup analyses, we dichotomized ABI at below and above 1.00. Given slight increase in the risk of diabetes in some models, those with ABI >1.40 were excluded from this analysis. Overall, no significant interaction was observed between ABI and potential modifiers tested (Table 3). However, we observed borderline significant difference in the association of ABI with diabetes in participants with vs. without hypertension (HR 1.20 [95%CI 1.07-1.35] vs. 1.01 [0.88-1.15], p-value for interaction = 0.054) and those with normal vs. impaired fasting glucose (HR 1.20 [95% CI 1.04-1.39] vs.1.01 [0.90-1.14], p-value for interaction = 0.072). The higher risk of diabetes was confirmed for both ABI categories of ≤0.90 and 0.91-1.00 in participants with normal fasting glucose and in those without hypertension (Tables S3 and S4).

Discussion

This study, to our knowledge, is the first study to examine the association between ABI and the future risk of diabetes. We found that low ABI (≤1.0) was associated with a moderately increased risk of diabetes. The association was independent of other atherosclerotic cardiovascular diseases, physical activity, and other potential confounders. We did not observe any significantly different results in demographic and clinical subgroups. However, the association of ABI with diabetes risk was stronger in participants without hypertension and those with normal fasting compared to their counterparts, with a borderline significant interactions.

ABI is a marker of systematic atherosclerosis [36], and participants with low ABI indeed had worse cardiovascular risk profiles in our study. Several traditional cardiovascular risk factors such as hypertension, smoking, and dyslipidemia are known to be related to high risk of developing diabetes [37]-[41]. Thus, we rigorously adjusted for these traditional risk factors but still observed significant associations between ABI and risk of diabetes. Although chronic inflammation can be a common ground for development of both atherosclerosis and diabetes [21][22][42][43], our results were not altered with adjustment for white blood cell count or fibrinogen. Although ABI may be associated with diabetes through its impact on physical activity, the adjustment for physical activity as both time-fixed and time-varying covariates did not meaningfully attenuate the association. Nevertheless, we need to keep in mind that physical activity was self-reported in our study, which may misclassify true physical activity level [44].

We found that the association between low ABI (≤1.00) and risk of diabetes tended

to be stronger in participants without hypertension and those with normal fasting glucose as compared to their counterparts, with borderline significant interaction. We are not necessarily sure about mechanisms behind these suggestive interactions, but there may be a few potential explanations. Many of those with hypertension were treated with antihypertensive medications (72%), which might confound the ABI-diabetes association. Indeed, renin-angiotensin system inhibitors are reported to reduce the risk of diabetes [45][46], whereas diuretics and beta blockers may contribute to increased risk of developing diabetes [47][48]. People with impaired fasting glucose are known to already have reduced insulin sensitivity and β cell dysfunction [49] and thus already at high risk of diabetes. For these individuals, a mild single predictor such as ABI may not considerably contribute to discriminating their diabetes risk. Another possible explanation is that the performance of ABI as a diagnostic tool for PAD might be inferior in those with hypertension and impaired fasting glucose than in their counterparts. For example, low sensitivity of ABI to detect PAD (41%) has been reported in patients with diabetes due to high prevalence of arterial stiffness [34], and persons with impaired fasting glucose also were known to have higher prevalence of arterial stiffness compared to those with normal glucose [50].

Previous studies showed that people with PAD were at high risk of other cardiovascular diseases, such as coronary heart disease, stroke and heart failure [4][51]-[54]. In addition, these individuals are known to have increased risk of leg amputation and reduced quality of life (e.g., low physical functioning, bodily pain, and reduced vitality) [5][55]-[59]. Our study demonstrates elevated risk of future diabetes among persons with low ABI independent of other cardiovascular diseases and risk

factors. ABI is able to identify subclinical atherosclerosis, which may encourage early initiation or better compliance of cardiovascular risk factor control [36][59]. In addition to risk factor management, our results suggest that attentions should also be given to glucose trajectory in people with low or borderline low ABI even when their fasting glucose is within the normal range.

Our study has several limitations. First, ABI was measured once for a randomly selected leg at baseline. The prevalence of low ABI may be underestimated as a result of missing low ABI in the opposite leg in some participants. Second, there were 15 years of follow-up where incident diabetes cases were solely based on self-report (interview-based definition). However, as aforementioned, the association was largely consistent for visit-based and interview-based diabetes. Third, our study participants were 45-64 years old at baseline, and thus the generalization of our results to adults in other age ranges should be done with caution. Finally, like other observational studies, residual confounding cannot be denied.

In conclusion, low ABI (≤1.00) was modestly but independently associated with increased risk of future diabetes in community-based middle-aged populations. The association was more evident in people with fasting glucose and blood pressure in the normal range. Although future studies are needed to confirm our findings and investigate potential mechanisms, our study suggests that attentions should be given to glucose trajectory in people with low or borderline low ABI.

References

[1] Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation 2006;113:e463-654.

[2] Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation 2012;125:e2-220.

[3] O'Hare AM, Katz R, Shlipak MG, et al. Mortality and cardiovascular risk across the ankle-arm index spectrum: results from the Cardiovascular Health Study. Circulation 2006;113:388-93.

[4] Weatherley BD, Nelson JJ, Heiss G, et al. The association of the ankle-brachial index with incident coronary heart disease: the Atherosclerosis Risk In Communities (ARIC) study, 1987-2001. BMC Cardiovasc Disord 2007;7:3.

[5] Spronk S, White JV, Bosch JL, Hunink MG. Impact of claudication and its treatment on quality of life. Semin Vasc Surg. 2007;20(1):3-9.

[6] McDermott MM, Liu K, Greenland P, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. JAMA 2004;292:453-61.

[7] Nitta A, Hozawa A, Kuriyama S, et al. Relationship between peripheral arterial disease and incident disability among elderly Japanese: the Tsurugaya project. J Atheroscler Thromb 2010;17:1290-6.

[8] Widener JM. Peripheral arterial disease and disability from NHANES 2001-2004 data. J Vasc Nurs 2011;29:104-12.

[9] Selvin E, Hirsch AT. Contemporary risk factor control and walking dysfunction in individuals with peripheral arterial disease: NHANES 1999-2004. Atherosclerosis 2008;201:425-33.

[10] McDermott MM, Greenland P, Ferrucci L, et al. Lower extremity performance is associated with daily life physical activity in individuals with and without peripheral arterial disease. J Am Geriatr Soc 2002;50:247-55.

[11] Hawkins MS, Gabriel KP, Conroy MB, et al. Physical activity intensity and cardiovascular risk by ankle-brachial index. Vasc Med 2013;18:79-84.

[12] Gill JM, Cooper AR. Physical activity and prevention of type 2 diabetes mellitus. Sports Med 2008;38:807-24.
[13] Folsom AR, Kushi LH, Hong CP. Physical activity and incident diabetes mellitus in postmenopausal women. Am J Public Health 2000; 90(1):134-8.
[14] The InterAct Consortium. Physical activity reduces the risk of incident type 2 diabetes in general and in abdominally lean and obese men and women: the EPIC–InterAct Study. Diabetologia 2012; 55:1944–1952.
[15] Stohr R, Federici M. Insulin resistance and atherosclerosis: convergence between metabolic pathways and inflammatory nodes. Biochem J 2013;454:1-11.
[16] Rocha VZ, Libby P. Obesity, inflammation, and atherosclerosis. Nat Rev Cardiol 2009;6:399-409.
[17] Caballero AE. Endothelial dysfunction in obesity and insulin resistance: a road to diabetes and heart disease. Obes Res. 2003;11(11):1278-89.
[18] Meigs JB, Hu FB, Rifai N, Manson JE. Biomarkers of endothelial dysfunction and risk of type 2 diabetes mellitus. JAMA. 2004;291(16):1978-86.
[19] Thorand B, Baumert J, Chambless L et al. Elevated markers of endothelial dysfunction predict type 2 diabetes mellitus in middle-aged men and women from the general population. Arterioscler Thromb Vasc Biol. 2006;26(2):398-405.
[20] Song Y, Manson JE, Tinker L, et al. Circulating Levels of Endothelial Adhesion Molecules and Risk of Diabetes in an Ethnically Diverse Cohort of Women. Diabetes. 2007;56(7):1898-1904.
[21] Althouse AD, Abbott JD, Forker AD et al. Risk factors for incident peripheral arterial disease in type 2 diabetes: results from the Bypass Angioplasty Revascularization Investigation in type 2 Diabetes (BARI 2D) Trial. Diabetes Care 2014 ;37(5):1346-52.
[22] Tapp RJ, Balkau B, Shaw JE et al. Association of glucose metabolism, smoking and cardiovascular risk factors with incident peripheral arterial disease: the DESIR study. Atherosclerosis 2007;190(1):84-9.
[23] The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. Am J Epidemiol 1989;129(4):687-702.
[24] Murphy TP, Dhangana R, Pencina MJ et al. Ankle-brachial index and cardiovascular risk prediction: an analysis of 11,594 individuals with 10-year follow-up. Atherosclerosis 2012;220:160-7.
[25] ARIC Manual 6A Ultrasound scanning.
https://www2.cscc.unc.edu/aric/cohort-manuals
[26] ARIC Data Book: Ankle Brachial Index Data.
https://www2.cscc.unc.edu/aric/cohort-forms-forms
[27] Selvin E, Steffes MW, Zhu H et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010;362:800-11.
[28] ARIC Protocol Manual 11. Sitting Blood Pressure and Postural Changes.

https://www2.cscc.unc.edu/aric/cohort-manuals.
[29] ARIC Protocol Manual 8. Lipid and Lipoprotein Determinations Version 1.0. https://www2.cscc.unc.edu/aric/cohort-manuals.
[30] ARIC Protocol Manual 10. Clinical Chemistry Determinations Version 1.0. https://www2.cscc.unc.edu/aric/cohort-manuals.
[31] ARIC Protocol Manual 7. Blood Collection and Processing Version 1.1. https://www2.cscc.unc.edu/aric/cohort-manuals.
[32] ARIC Protocol Manual 9. Hemostasis Determinations. https://www2.cscc.unc.edu/aric/cohort-manuals.
[33] Pols MA, Peeters PH, Bueno-De-Mesquita HB et al. Validity and repeatability of a modified Baecke questionnaire on physical activity. Int J Epidemiol 1995;24:381-8.
[34] Al-Qaisi M, Nott DM, King DH, Kaddoura S. Ankle Brachial Pressure Index (ABPI): An update for practitioners. Vascular Health and Risk Management. 2009;5:833-841.
[35] Niblo J, Coull A. Ankle brachial pressure index of normal, healthy, younger adults. Br J Nurs. 2013;22(12):S16, S18-21.
[36] Paraskevas KI, Kotsikoris I, Koupidis SA et al. Ankle--brachial index: a marker of both peripheral arterial disease and systemic atherosclerosis as well as a predictor of vascular events. Angiology. 2010;61(6):521-3.
[37] Stahl CH, Novak M, Lappas G, et al. High-normal blood pressure and long-term risk of type 2 diabetes: 35-year prospective population based cohort study of men. BMC Cardiovascular Disorders. 2012;12:89.
[38] Wei GS, Coady SA, Goff DC, et al. Blood Pressure and the Risk of Developing Diabetes in African Americans and Whites: ARIC, CARDIA, and the Framingham Heart Study. Diabetes Care. 2011;34(4):873-879.
[39] Sharma MD, Pavlik VN. Dyslipidaemia in African Americans, Hispanics and whites with type 2 diabetes mellitus and hypertension. Diabetes Obes Metab. 2001;3(1):41-5.
[40] Wannamethee SG, Shaper AG, Perry IJ; British Regional Heart Study. Smoking as a modifiable risk factor for type 2 diabetes in middle-aged men. Diabetes Care. 2001;24(9):1590-5.
[41] Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC. Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. BMJ : British Medical Journal. 1995;310(6979):555-559.
[42] Gkrania-Klotsas E, Ye Z, Cooper AJ et al. Differential White Blood Cell Count and Type 2 Diabetes: Systematic Review and Meta-Analysis of Cross-Sectional and Prospective Studies. Fadini GP, ed. PLoS ONE. 2010;5(10):e13405.
[43] Doronina AM, Lipinskiĭ B, Bokarev IN. Fibrinogens and their role in atherogenesis in diabetes mellitus. Klin Med (Mosk). 2007;85(7):52-5.
[44] Prince SA, Adamo KB, Hamel ME et al. A comparison of direct versus self-report

measures for assessing physical activity in adults: a systematic review. Int J Behav Nutr Phys Act 2008;5:56.
[45] Tikellis C, Cooper ME, Thomas MC. Role of the renin-angiotensin system in the endocrine pancreas: implications for the development of diabetes. Int J Biochem Cell Biol. 2006;38(5-6):737-51.
[46] Cooper ME, Tikellis C, Thomas MC. Preventing diabetes in patients with hypertension: one more reason to block the renin-angiotensin system. J Hypertens Suppl. 2006;24(1):S57-63.
[47] Faerch K, Borch-Johnsen K, Holst JJ, Vaag A. Pathophysiology and aetiology of impaired fasting glycaemia and impaired glucose tolerance: does it matter for prevention and treatment of type 2 diabetes? Diabetologia. 2009;52(9):1714-23.
[48] Shen L, Shah BR, Reyes EM et al. Role of diuretics, β blockers, and statins in increasing the risk of diabetes in patients with impaired glucose tolerance: reanalysis of data from the NAVIGATOR study. BMJ. 2013;347:f6745.
[49] Rizos CV, Elisaf MS. Antihypertensive drugs and glucose metabolism. World Journal of Cardiology. 2014;6(7):517-530.
[50] Shin JY, Lee HR, Lee DC. Increased arterial stiffness in healthy subjects with high-normal glucose levels and in subjects with pre-diabetes. Cardiovasc Diabetol. 2011;10:30.
[51] Zheng ZJ, Sharrett AR, Chambless LE et al. Associations of ankle-brachial index with clinical coronary heart disease, stroke and preclinical carotid and popliteal atherosclerosis: the Atherosclerosis Risk in Communities (ARIC) Study. Atherosclerosis. 1997;131(1):115-25.
[52] Gupta DK, Skali H, Claggett B et al. Heart failure risk across the spectrum of ankle-brachial index: the ARIC study (Atherosclerosis Risk In Communities). JACC Heart Fail. 2014;2(5):447-54.
[53] Fan H, Hu X, Yu W et al. Low ankle-brachial index and risk of stroke. Atherosclerosis. 2013;229(2):317-23.
[54] Criqui MH, McClelland RL, McDermott MM. The ankle-brachial index and incident cardiovascular events in the MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2010;56(18):1506-12.
[55] Amer MS, Alsadany MA, Tolba MF, Omar OH. Quality of life in elderly diabetic patients with peripheral arterial disease. Geriatr Gerontol Int. 2013;13(2):443-50.
[56] Korhonen PE, Seppälä T, Kautiainen H et al. Ankle-brachial index and health-related quality of life. Eur J Prev Cardiol. 2012;19(5):901-7.
[57] Sprengers RW, Teraa M, Moll FL et al. Quality of life in patients with no-option critical limb ischemia underlines the need for new effective treatment. J Vasc Surg. 2010;52(4):843-9, 849.e1.
[58] Regensteiner JG, Hiatt WR, Coll JR et al. The impact of peripheral arterial disease

on health-related quality of life in the Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) Program. Vasc Med. 2008;13(1):15-24.
[59] Kramer CK, Zinman B, Gross JL et al. Coronary artery calcium score prediction of all cause mortality and cardiovascular events in people with type 2 diabetes: systematic review and meta-analysis. BMJ. 2013;346:f1654.

Appendices

Table 1 Baseline Characteristics of Participants without Prevalent Diabetes by ABI Categories

Characteristics	ABI≤0.90	0.91-1.00	1.01-1.10	1.11-1.20	1.21-1.30	1.31-1.40	ABI>1.40
N (%)	455 (3.7)	1,529 (12.5)	2,894 (23.6)	3,633 (29.7)	2,509 (20.5)	924 (7.5)	303 (2.5)
Age, mean(SD),years*	54.9 (5.9)	53.7 (5.8)	53.4 (5.6)	53.9 (5.8)	53.9 (5.6)	54.6 (5.7)	55.1 (5.7)
Female, No. (%) *	321 (70.6)	1116 (73.0)	1867 (64.5)	1903 (52.4)	1104 (44.0)	373 (40.4)	125 (41.3)
Black, No. (%) *	121 (26.6)	357 (23.4)	700 (24.2)	867 (23.9)	542 (21.6)	177 (19.2)	47 (15.5)
BMI, mean(SD), kg/m^2 *	27.7 (6.0)	27.7 (5.8)	27.1 (5.2)	27.0 (4.7)	27.0 (4.6)	27.4 (4.8)	28.3 (5.5)
Current Drinker, No. (%)*	244 (53.6)	874 (57.2)	1698 (58.7)	2189 (60.3)	1525 (60.8)	550 (59.5)	163 (53.8)
Current Smoker, No. (%)*	167 (36.7)	440 (28.8)	798 (27.6)	855 (23.5)	602 (24.0)	195 (21.1)	63 (20.8)
Arm SBP, mean(SD),mmHg*	123.0 (19.7)	121.0 (19.2)	120.3 (18.8)	119.7 (17.5)	118.2 (16.6)	118.0 (15.8)	117.6 (15.3)
Hypertension Medication, No. (%)*	169 (37.1)	449 (29.4)	810 (28.0)	932 (25.7)	587 (23.4)	221 (23.9)	95 (31.4)
Prevalent CHD, No. (%)*	30 (6.6)	68 (4.5)	103 (3.6)	137 (3.8)	103 (4.1)	38 (4.1)	20 (6.6)
Stroke or TIA[a], No. (%)*	33 (7.3)	68 (4.5)	123 (4.3)	151 (4.2)	99 (4.0)	26 (2.8)	15 (5.0)
Total Cholesterol, mean(SD),mg/dl*	223.3 (43.3)	216.0 (40.0)	215.4 (42.2)	213.5 (41.0)	211.9 (39.4)	211.3 (39.8)	211.2 (41.1)
HDL,mean(SD),mg/dl*	53.3 (17.4)	54.2 (17.6)	54.3 (17.5)	52.3 (17.1)	51.2 (16.8)	50.3 (16.3)	49.4 (15.3)
Triglyceride,median(IQR),mg/dl *	113 (80-159)	105 (77-146)	103 (75-145)	106 (77-150)	108 (77-151)	106 (76-150.5)	112 (80-160)
Statin Use, No. (%)	5 (1.1)	13 (0.9)	16 (0.6)	12 (0.3)	9 (0.4)	5 (0.5)	2 (0.7)
Fasting Glucose,mean(SD),mg/dl	99.2 (9.5)	98.6 (9.3)	98.5 (9.4)	98.5 (9.1)	99.0 (9.2)	98.7 (9.0)	98.4 (9.0)
Parental History of Diabetes, No. (%)	104 (22.9)	363 (23.7)	633 (21.9)	809 (22.3)	580 (23.1)	190 (20.6)	76 (25.1)
White Blood Cell Count, median(IQR), 10^3 *	6.3 (5.1-7.5)	5.9 (4.9-7.2)	5.8 (4.8-7.0)	5.6 (4.7-6.9)	5.6 (4.7-6.9)	5.7 (4.7-6.8)	5.6 (4.7-6.9)
Fibrinogen, median(IQR),mg/dl *	314 (277-362)	295 (261-342)	295 (260-336)	288 (255-327)	285 (255-324)	286 (254-323)	294 (261-333)
Physical Activity Index, mean(SD)*	6.7 (1.5)	6.9 (1.5)	7.0 (1.4)	7.1 (1.4)	7.2 (1.4)	7.2 (1.4)	7.2 (1.5)

Abbreviations: ABI, ankle-brachial index; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TIA, transient ischemic attack; CHD, coronary heart disease; HDL, high density cholesterol.
* indicates statistically significant difference among ABI groups.

Table 2 Hazard Ratios of Diabetes in Different ABI Categories

	ABI	≤0.90	0.91-1.00	1.01-1.10	1.11-1.20	1.21-1.30	1.31-1.40	>1.40
N	**12,247**	455	1,529	2,894	3,633	2,509	924	303
Number of events	**3,305**	137	457	781	927	668	249	86
Model 1	**HR**	1.41	1.29	1.10	1.00	1.06	1.07	1.16
	95%CI	1.17-1.68	1.15-1.45	1.00-1.22	--	0.96-1.17	0.93-1.23	0.93-1.45
Model 2	**HR**	1.19	1.17	1.10	1.00	1.08	1.10	1.01
	95%CI	0.99-1.43	1.04-1.31	1.00-1.21	--	0.98-1.20	0.96-1.27	0.81-1.27
Model 3	**HR**	1.12	1.12	1.08	1.00	1.06	1.09	1.12
	95%CI	0.94-1.34	0.99-1.26	0.98-1.18	--	0.96-1.17	0.94-1.25	0.90-1.40

Model 1: adjusted for age, gender and race; Model 2: adjusted for age, gender, race, current and former drinking, current and former smoking, BMI, SBP, hypertension medication, HDL, total cholesterol, log(triglyceride), prevalent CHD, stroke or TIA, statin use, parental history of diabetes, log(white blood cell count) and Baecke physical activity index; Model 3: adjusted for baseline fasting glucose in addition to model 2.

Table 3 Hazard Ratios of Diabetes in Different Subgroups

Subgroup	HR and 95% CI ABI ≤1.00 vs 1.01-1.40	p-value for interaction	Subgroup	HR and 95% CI ABI ≤1.0 vs 1.01-1.40	p-value for interaction
Gender			**Stroke or TIA**		
Male (5,260)	1.19 (1.01-1.40)		No (11,444)	1.09 (0.99-1.19)	
Female (6,684)	1.07(0.96-1.19)	0.274	Yes (500)	1.43 (1.00-2.05)	0.141
Race			**Hypertension**		
White (9,180)	1.13 (1.02-1.26)		No (8,923)	1.20 (1.07-1.35)	
Black (2,764)	1.05 (0.89-1.23)	0.423	Yes (3,622)	1.01 (0.88-1.15)	0.054
Age			**Family history of diabetes**		
≤55 (7,193)	1.06(0.94-1.16)		No (9,625)	1.05 (0.94-1.18)	
>55 (4,751)	1.18 (1.03-1.36)	0.229	Yes (2,679)	1.23 (1.05-1.43)	0.119
Current Smoking			**Baseline FPG 100-126mg/dl**		
No (8,887)	1.09 (0.98-1.21)		No (6,895)	1.20 (1.04-1.39)	
Yes(3,057)	1.17 (0.99-1.38)	0.480	Yes (5,049)	1.02 (0.90-1.14)	0.072
Prevalent CHD			**Leg Pain While Walking**		
No (11,465)	1.11 (1.02-1.22)		No (9,606)	1.10 (0.99-1.23)	
Yes (479)	0.91 (0.59-1.42)	0.383	Yes (2,338)	1.10 (0.92-1.30)	0.958

N=11944. Excluded ABI>1.4 and adjusted for age, gender, race, current and former drinking, current and former smoking, BMI, SBP, hypertension medication, HDL, total cholesterol, log(triglyceride), prevalent CHD, stroke or TIA, statin use, parental history of diabetes, log(white blood cell count) and Baecke physical activity index.

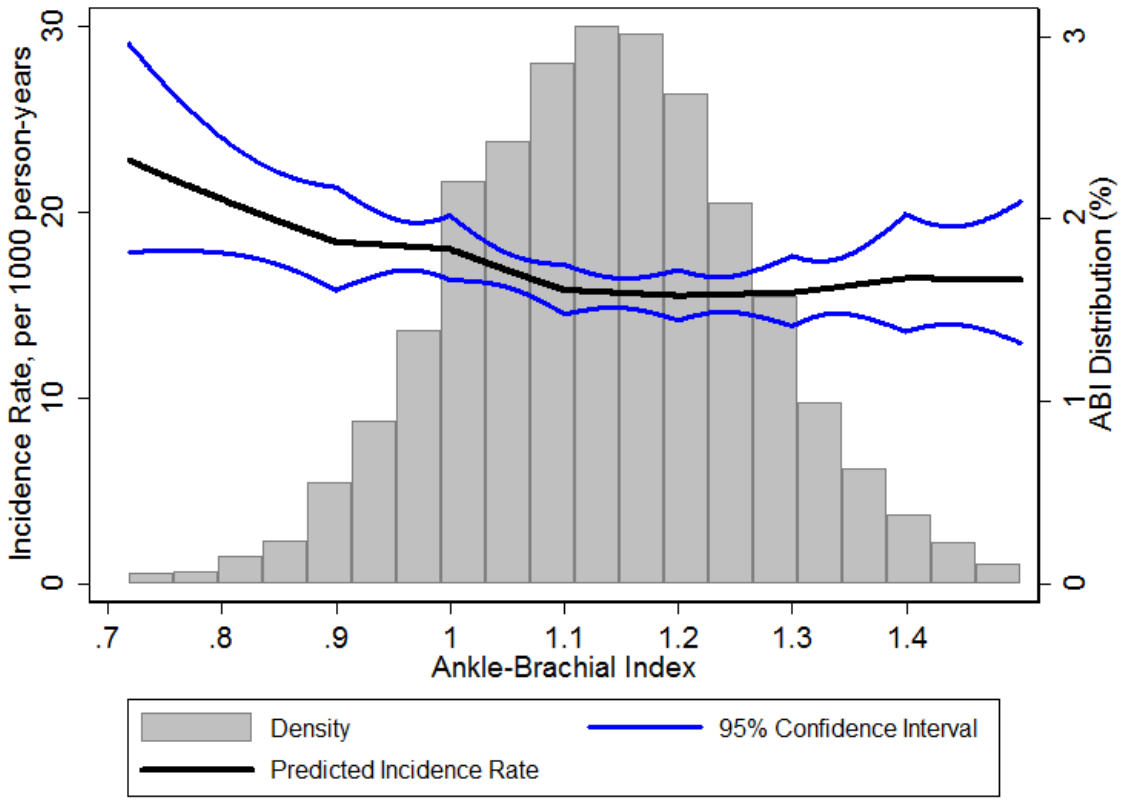

Figure 1 Demographically Adjusted Incidence Rates of Diabetes according to ABI and Distribution of ABI.
Note: Graphed for 0.5-99.5 percentile of ABI values. Adjusted to mean age, white and male.

Table 4 Hazard Ratios of Interview-based Definition of Diabetes in Different ABI Categories

	ABI	≤0.90	0.91-1.00	1.01-1.10	1.11-1.20	1.21-1.30	1.31-1.40	>1.40
N	**11,292**	390	1,397	2,668	3,373	2,320	861	283
Number of events	**2,959**	118	414	698	841	596	217	75
Model 1	**HR**	1.39	1.29	1. 08	1.00	1.05	1.02	1.12
	95%CI	1.15-1.69	1.14-1.45	0.98-1.20	--	0.94-1.16	0.88-1.18	0.88-1.42
Model 2	**HR**	1.21	1.16	1.08	1.00	1.06	1.04	0.98
	95%CI	1.00-1.47	1.03-1.30	0.97-1.19	--	0.95-1.18	0.89-1.20	0.77-1.24
Model 3	**HR**	1.16	1.12	1.05	1.00	1.04	1.03	1.07
	95%CI	0.96-1.41	0.99-1.26	0.95-1.16	--	0.94-1.16	0.88-1.19	0.84-1.35

Model 1: adjusted for age, gender and race; Model 2: adjusted for age, gender, race, current and former drinking, current and former smoking, BMI, SBP, hypertension medication, HDL, total cholesterol, log(triglyceride), prevalent CHD, stroke or TIA, statin use, parental history of diabetes, log(white blood cell count) and Baecke physical activity index; Model 3: adjusted for baseline fasting glucose in addition to model 2.

Table 5 Hazard Ratios of Visit-based Definition of Diabetes in Different ABI Categories

	ABI	≤0.90	0.91-1.00	1.01-1.10	1.11-1.20	1.21-1.30	1.31-1.40	>1.40
N	**11,858**	432	1,481	2,798	3,525	2,441	889	292
Number of events	**1,385**	59	185	332	378	287	110	34
Model 1	**HR**	1.51	1.26	1. 13	1.00	1.12	1.12	1.02
	95%CI	1.15-1.99	1.05-1.50	0.98-1.31	--	0.96-1.31	0.90-1.38	0.72-1.45
Model 2	**HR**	1.23	1.15	1.14	1.00	1.18	1.16	1.01
	95%CI	0.94-1.63	0.96-1.38	0.98-1.32	--	1.01-1.37	0.93-1.43	0.71-1.44
Model 3	**HR**	1.26	1.05	1.02	1.00	1.06	1.08	0.99
	95%CI	0.96-1.67	0.88-1.26	0.88-1.19	--	0.91-1.24	0.87-1.33	0.70-1.42

Model 1: adjusted for age, gender and race; Model 2: adjusted for age, gender, race, current and former drinking, current and former smoking, BMI, SBP, hypertension medication, HDL, total cholesterol, log(triglyceride), prevalent CHD, stroke or TIA, statin use, parental history of diabetes, log(white blood cell count) and Baecke physical activity index; Model 3: adjusted for baseline fasting glucose in addition to model 2.

Table 6 Hazard Ratios of Diabetes in Baseline Fasting Glucose<100 mg/dl and 100-125 mg/dl population

	ABI	≤0.90	0.91-1.00	1.01-1.10	1.11-1.20	1.21-1.30	1.31-1.40	>1.40
N	**7,080**	257	880	1,707	2,093	1,419	539	185
Number of events	**1,242**	53	178	297	349	241	88	36
<100 mg/dl	**HR**	1.33	1.27	1.06	1.00	1.06	1.03	1.03
	95%CI	0.99-1.79	1.06-1.53	0.90-1.23	--	0.90-1.25	0.82-1.31	0.73-1.45
N	**5,167**	198	649	1,187	1,540	1,090	385	118
Number of events	**2,063**	84	279	484	578	427	161	50
100-125 mg/dl	**HR**	1.09	1.07	1.13	1.00	1.09	1.17	1.14
	95%CI	0.87-1.38	0.93-1.24	1.00-1.28	--	0.96-1.23	0.98-1.40	0.85-1.53

Adjusted for age, gender, race, current and former drinking, current and former smoking, BMI, SBP, hypertension medication, HDL, total cholesterol, log(triglyceride), prevalent CHD, stroke or TIA, statin use, parental history of diabetes, log(white blood cell count) and Baecke physical activity index.

Table 7 Hazard Ratios of Diabetes in Study Participants with and without Hypertension at Baseline

	ABI	≤0.90	0.91-1.00	1.01-1.10	1.11-1.20	1.21-1.30	1.31-1.40	>1.40
N	**8,539**	265	1,023	1,961	2,556	1,837	680	217
Number of events	**1,954**	77	259	423	568	425	154	48
No hypertension	**HR**	1.41	1.17	1.00	1.00	1.05	1.06	0.89
	95%CI	1.11-1.79	1.00-1.35	0.88-1.14	--	0.92-1.19	0.88-1.26	0.66-1.19
N	**3,708**	190	506	933	1,077	672	244	86
Number of events	**1,351**	60	198	358	359	243	95	38
hypertension	**HR**	1.02	1.19	1.26	1.00	1.13	1.17	1.25
	95%CI	0.78-1.35	0.99-1.41	1.09-1.46	--	0.96-1.33	0.93-1.47	0.89-1.75

Adjusted for age, gender, race, current and former drinking, current and former smoking, BMI, HDL, total cholesterol, log(triglyceride), prevalent CHD, stroke or TIA, statin use, parental history of diabetes, log(white blood cell count) and Baecke physical activity index.

Bibliography

Simin Hua is a Master of Health Science candidate in Department of Epidemiology. She studied Cardiovascular Disease Epidemiology in Johns Hopkins University School of Public Health during 2013 and 2015. She received her undergraduate degree in Preventive Medicine from Fudan University in 2013. She has a strong passion for public health and she is particularly interested in the prevention of diabetes and cardiovascular diseases, tobacco control, primary care and economic evaluation. She actively engaged in several research projects and also served as volunteer and teaching assistant in college and graduate school. She presented her thesis project in poster session in 2015 American Heart Association EPI/Lifestyle Scientific Sessions. She was inducted to Delta Omega Public Health Honor Society upon graduation.

Curriculum Vitae

Name: Simin Hua (Stephanie) **Contact**: hsm121989@gmail.com

Education

Master of Health Science (MHS) September 2013 - May 2015

Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Concentration: Cardiovascular Disease Epidemiology

Bachelor of Medicine (BM) September 2008 - July 2013

Fudan University, Shanghai, China

Major: Preventive Medicine

Research Experience

Data Analyst July 2014-May 2105

Johns Hopkins Center to Eliminate Cardiovascular Health Disparities, Baltimore, MD

- Worked on large survey data and a clinical trial data-Achieving Blood Pressure Control Together.
- Performed data cleaning, created analysis datasets and generated descriptive statistics and reports with SAS statistical package.
- Created codebooks for datasets with SAS macro.

Graduate Researcher April 2014-March 2015

Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Master Thesis Research "Ankle-brachial Index and Future Diabetes-the Atherosclerosis Risk in Communities (ARIC) Study."

- Performed survival analysis on a cohort study data with 16,000 individuals and 4 follow-up examinations for 20 years using Stata statistical package.
- Wrote a proposal and a manuscript for the study.
- Presented in the poster session in 2015 American Heart Association EPI/Lifestyle Scientific Sessions.

Undergraduate Researcher April-June 2013.

Fudan University

Undergraduate Thesis Research "Change of Blood Serum CYP1A1 mRNA in Residents Living Near a Waste Incineration Plant".

- Analyzed cross-sectional data to assess the potential impact of a waste incineration plant on the health of surrounding residents using SPSS statistical package.

Undergraduate Researcher May 2010-May 2011

Fudan University Undergraduate Research Opportunities Program

"Patients' Satisfaction with Chronic Disease Management in Community Health Centers and Associated Factors."

- Designed a survey, collected data in community health centers, analyzed data and published the results in Journal of Chinese General Practice in 2012.

Internship and Volunteer Experience

Intern February-March 2013

Dept. of Immunization Planning and Management, Huangpu District Center for Disease Control and Prevention, Shanghai, China

- Assisted routine work such as vaccines management and adverse events monitoring and analyzed data on adverse effect of DPT vaccine.

Intern August-December 2011

The Fifth People's Hospital Affiliated to Fudan University, Shanghai, China

- Assisted superiors in diagnosing and treating patients in 11 departments by recording medical history and performing physical examination.

Teaching Assistant February 2015-Present

Johns Hopkins Undergraduate Course Fundamentals of Epidemiology

- Held discussion section and TA office hour. Assisted proctoring and grading.

Volunteer March 2014

The Students Teaching and Reaching Students (STARS) program in JHU

- Introduced Epidemiology to high school students by case studies in Baltimore Polytechnic Institute

Volunteer March 2010-February2011

Fudan University No-smoking Association

- Prepared materials and advocated for smoking ban policy in public areas and collected data of attitude and awareness of smokers in summer social practice program.
- Collected data from 200 visitors on the Expo site regarding the implementation of smoking ban policy.

Publications/Presentations

- **Hua Si-min**, Zheng Yi-ling, Dai Jun-ming. Community Management of Patients with Hypertension and/or Diabetes. Journal of Chinese General Practice.2012, 15(7).
- Zheng Yi-ling, **Hua Si-min**, Dai Jun-ming. Satisfaction of Community Patients with Chronic Disease to Treatment and Their Utilization of Medical Services. Journal of Chinese General Practice.2012, 15(19).
- Poster Presentation "Ankle-brachial Index and Future Diabetes-the Atherosclerosis Risk in Communities (ARIC) Study." in 2015 American Heart Association EPI/Lifestyle Scientific Sessions.

Honors and Awards

- Member of Delta Omega Public Health Honor Society, Alpha Chapter
- Third Award twice and Minor Award once of People's Scholarship in Fudan University
- Fudan University Excellent Summer Social Practice Team Award