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The Association of Area-based Deprivation and Cardiovascular Risk among Vietnam-Era Twins

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The Association of Area-based Deprivation and Cardiovascular Risk among Twins

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B.S.
University of Central Arkansas
2017

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An abstract of
A thesis submitted to the Faculty of the
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Abstract

The Association of Area-based Deprivation and Cardiovascular Risk among Vietnam-Era Twins

By Annam A. Ahmed

Objectives: The aim of this study was to examine the association of area-based deprivation and cardiovascular risk using a controlled twin design.

Background: Existing literature has highlighted the importance of considering both genetic and environmental influences on cardiovascular health. However, there is limited information on the influence of area-based deprivation on cardiovascular risk.

Methods: We conducted a secondary analysis of data from a study of middle-aged male twins recruited from the Vietnam Era Twin Registry. The area-deprivation index (ADI) scores were calculated using the 2013 Neighborhood Atlas developed by the University of Wisconsin, and Framingham risk scores for LDL cholesterol (FRS-LDL) were calculated. Analysis was conducted using linear mixed models.

Results: A total of 502 twins (251 pairs) with a mean age of 55.5 years were included in this study. The mean ADI score was 46 and the mean FRS-LDL score was 5.9. Considering twins as individuals, there was a significant unadjusted association between ADI and FRS-LDL: for each 10 points increment in ADI score, the FRS-LDL increased by 0.1 points. After adjusting for potential confounders (age, years of education, and history of coronary heart disease), the association was slightly weakened. In within twin pair-analyses, there was no association between ADI and FRS-LDL comparing twins discordant for ADI (FRS-LDL: -0.02 per 10-point increment in ADI, 95% CI: -0.14, 0.01). Results remained consistent even when using the dichotomizing ADI score. When examined by zygosity, the within-pair association between ADI and FRS-LDL was larger in dizygotic than monozygotic twin pairs (p=0.05 for interaction).

Conclusions: Among Vietnam-era veterans, genetics and familial factors play a greater role in cardiovascular risk than environmental factors.

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List of Abbreviations and Acronyms

ABI	Ankle-brachial Index
BMI	Body Mass Index
CHD	Coronary Heart Disease
CVD	Cardiovascular Disease
DZ	Dizygotic
FRS	Framingham Risk Score
HDL	High-density Lipoprotein
IQ	Intelligence Quotient
LDL	Low-density Lipoprotein
MZ	Monozygotic
SES	Socioeconomic Status
SMSA	Standard Metropolitan Statistical Area
U.K.	United Kingdom
U.S.	United States of America

Background

I. Introduction

Cardiovascular disease (CVD) has long been studied using a variety of methods and perspectives. In particular, many studies have aimed to examine disparities with cardiovascular health and the associated environmental factors such as area-based deprivation and geographic influence on cardiovascular health. Additionally, there has been a plethora of literature examining the heritability of CVD in the context of twin studies. Despite these existing studies, much still needs to be understood about the environmental influences on health of different geographic areas where people live. The following literature review examines these influences on cardiovascular health.

II. Area-based Deprivation and Cardiovascular Disease

The link between cardiovascular health and socioeconomic status (SES) has long been established in the literature. Recently, studies have begun adopting area-based deprivation as a proxy measurement for SES. In particular, this measurement aims to quantify the socioeconomic state of geographic areas (i.e. neighborhood, state etc.) rather than of the individual. The area-based deprivation measurement allows investigators to consider environmental resources as a factor in individual health. A cross sectional study of adults in New Zealand aimed to compare different types of socioeconomic indicators with CVD and diabetes risk factors. The study found that risk factors were more strongly associated with area-based SES and household income than occupation-based SES (individual level) and education level (Metcalf et. al., 2008). These findings provide evidence of the importance of considering area-based deprivation as a measure of SES. As such there has been a

considerable body of literature published examining the association of area-based deprivation and cardiovascular health, as described below.

Much of the research regarding area-based deprivation and cardiovascular health has looked at mortality, cardiovascular risk factors, and even considered geographical differences. While there is evidence that area-based deprivation affects cardiovascular risk and mortality, the literature has not been consistent in the magnitude and robustness of these associations. Jackson et. al. (2012) conducted a study of twins in Scotland aimed at understanding the relationship between type II diabetes, area-based deprivation and cardiovascular-related death. They found that risk of cardiovascular-related death was more common in people with diabetes than those without diabetes, and that the risk increased with increasing deprivation, after adjusting for age and SES (RR (Risk Ratio): 1.71; 95% CI (95% Confidence Intervals): 1.57, 1.86). However, in other studies, associations were eliminated after adjusting for sociodemographic factors.

When considering general cardiovascular risk, researchers aimed to study whether the odds of CVD differ based on neighborhood differences in health-damaging and health-promoting resources. They found that among both men and women, there was a small increase in the odds of CVD due to neighborhood resources (RR_{MEN}: 1.39, 95% CI: 1.35, 1.42; RR_{WOMEN}: 1.60, 95% CI: 1.55, 1.66), although this association disappeared after adjusting for age, family income, and neighborhood-level deprivation (Calling et. al., 2016). Another study found strong correlations between infant mortality rates and cause-specific adult mortality. However, these correlations also diminished after adjusting for socioeconomic characteristics such as deprivation and social class, which suggests that early

childhood risks do not have a direct influence on adult coronary heart disease (CHD) mortality risk (Ben-Shlomo & Smith, 1991).

A prospective cohort study of adults in the United States of America (U.S.) examined the association of neighborhood deprivation and incidence of CHD. While there were major differences in CHD risk between races, living in a deprived neighborhood was associated with an increased risk of developing CHD, compared to those living in less deprived neighborhoods, in both white and black participants. This was true even after adjusting for personal indicators of socioeconomic status (HR_{White}: 3.1, 95% CI: 2.1, 4.8); HR_{Black}: 2.5, 95% CI: 1.4, 4.5) (Roux et. al., 2001). Lastly, a prospective cohort study of men and women in Scotland revealed that more deprivation was associated with more CVD risk factors and mortality. Additionally, the researchers found that geographical differences in mortality were independent of individual SES (Smith et. al., 1998).

The literature has consistently demonstrated that area-based deprivation is associated with cardiovascular risk and mortality. However, the possibility of residual confounding from social and behavioral factors, or other individual or family-related characteristics of people living in different areas remains in all these studies.

III. Geographic Variation and Cardiovascular Disease

There are plenty of studies that have been conducted examining the geographic variation of CVD. Studies have focused on CVD risk, prevalence, and mortality. However, the published data have not always been consistent in their findings.

In particular, there has been evidence about state-level differences in cardiovascular risk, which could be attributed to both individual and state-level environments (Gebreab et. al.,

2015). A cross-sectional analysis of CVD risk factors such as diabetes and hypertension found that there is geographic variation in these risk factors, with the highest prevalence being in the South and Midwest regions of the U.S. The researchers found that disparities exist both within states and within counties, with additional disparities seen across races (Loop et. al., 2017). Similarly, a study on cardiovascular inflammation among a cohort of adult women revealed state-level geographic differences in inflammatory biomarkers of cardiovascular risk including C-reactive protein and fibrinogen, that were not completely attributable to traditional cardiovascular risk factors such as cholesterol levels, body mass index (BMI), systolic blood pressure and diabetes or lifestyle characteristics including smoking, exercise and dietary habits. The study noted that although these differences were significant, the pathways of these disparities remain unknown (Clark et. al., 2011). Geographic variation in cardiovascular risk can also remain even after adjusting for race. A cross-sectional study based on the Behavioral Risk Factor Surveillance System data found a substantial geographic variation in CVD risk factors between black and white men, as well as between black and white women (Hahn, Heath, & Chang, 1998).

CVD prevalence and its associated mortality have also been examined for geographic variation. As touched upon above, prevalence studies have pointed to the southern regions of the U.S. as holding a high burden of CVD. A cross-sectional survey was conducted in the U.S., examining the geographic variations in CVD and pulmonary disease prevalence. The study compared three different levels of urbanization: standard metropolitan statistical area (SMSA) central city, SMSA non-central city, and non-SMSA. The study found that variation in prevalence concerning region and urbanization was not consistent across age and sex groups, apart from consistently high rates of disease in the South. Males were more

likely to have higher prevalence rates compared to women. In terms of age, individuals under the age of 65 had lower prevalence of CVD and pulmonary disease compared to individuals 65 and older. However, when comparing men and women 65 years and older, the regional differences in disease prevalence were not consistent, with higher differences being observed in men compared to women in this age category. Additionally, high rates of CVD and pulmonary disease prevalence found in the South were particularly seen among black people (Gillum, 1994). Results were similar when considering CVD-related mortality. Singh et al. (2017) found that mortality from CVD is higher in the South than other U.S. regions and is higher in areas with lower SES. Additionally, they found that risk factors associated with CVD have geographic variation and are related to both racial and socioeconomic disparities (Singh et. al., 2017).

In summary, the literature demonstrates a clear link between geographical region and cardiovascular health. However, these associations are complex, as they are also affected by race and individual socioeconomic status.

IV. Twins and Geographic Variation

The twin design has been used to understand the effects of geographic variation on health. The purpose of twin studies is generally to control for genetic differences between individuals and shared childhood environment. Comparing monozygotic and dizygotic twins allows researchers to consider differing genetics between twin pairs. Additionally, the shared childhood environment allows researchers to control for early childhood experiences and familial factors that may influence adult health outcomes. Thus, twin studies are useful for understanding genetic and environmental influences on geographic variation. The

breadth of literature covers a variety of perspectives on the topic of geographic variation, with studies examining SES, biological, and psychological/behavioral factors, often in combination.

Of the studies examining a combination of socioeconomic and biological factors, the main outcomes examined are BMI and height. One cross-sectional study of twins in the U.S. examined both micro- and macro-levels of SES and their association with BMI. The investigators found that lower SES was associated with having a higher BMI among participants. However, within twin-pairs, this association was non-significant suggesting that there may be an underlying familial or genetic link between SES and BMI. Nonetheless, they also found that the influence of genes lessens as SES increases (Dinescu et. al., 2016). In other twin studies, researchers found that genetics played a role in BMI variation, with heritability being similar across different geographic locations (Silventoinen et. al., 2016; Silventoinen et. al., 2017). Additionally, they found that shared environmental factors influenced BMI in childhood, but that this influence decreased as the twins got older (Silventoinen et. al., 2016). Researchers examined differences in height heritability on a global scale across birth cohorts from 1886 to 1994, as height heritability can be implicated in BMI heritability. They found that although there are substantial height variations in twin pairs across North America and Australia, there is no evidence to suggest that height heritability is lower in low SES populations compared to more affluent populations (Jelenkovic et. al., 2016).

Each of these studies demonstrates the impact that surrounding environment has on development among twins. While many of the studies acknowledge the role that genetics

plays in twin development, researchers also acknowledged the strong environmental link that also plays a role.

V. Twin Studies of Area Deprivation Index

There has been limited research examining neighborhood or area-based deprivation in using twin studies. The four studies available assessed area deprivation in the context of BMI, dietary patterns, and sleep duration.

In a study of twins in the United Kingdom (U.K.), researchers aimed to investigate the association of neighborhood deprivation on the genetic influence of BMI. They found that the genetic influence on BMI increases in more deprived neighborhoods, with heritability becoming stronger (Owen, Jones, & Harris, 2017).

In a separate cross-sectional study of female twin in the U.K., investigators examined the influence of both genetics and the environment on dietary choices and nutrient intake. They found that less deprived areas had higher scores for fruit and vegetable intake, and that the influence of the family home environment on dietary choices decreases with age (Teucher et. al., 2007).

Lastly, in a cross-sectional study of U.S. twins, conducted by the University of Washington, researchers analyzed the association of area-based deprivation and sleep duration. After controlling for familial factors such as shared environment and genetics, researchers found that as area-deprivation increased, sleep duration decreased. Additionally, they found evidence of gene and environment interaction, as well as a significant environmental pathway between the deprivation index score and sleep duration (Watson et. al., 2016).

In the aforementioned studies, researchers found a link between the environment, in particular area-based deprivation, and a variety of outcomes. All of the studies highlighted the importance of genetic influence on BMI, sleep duration, and dietary choices. While a link between area-based deprivation and these outcomes has been established, there are no data linking area deprivation with a whole set of cardiovascular risk factors using a twin design.

VI. Twins Studies of Cardiovascular Disease

There has been a plethora of twin studies examining various aspects of CVD and its associated risks. Some studies examined the effect of genetics on CVD-related mortality. Other studies looked at psychological risks such as stress and depression on CVD.

It is well documented that biological and genetic factors play a major role in mortality risk related to CVD. Cholesterol levels are one major risk factor for developing heart disease. In a study of adolescent twins, researchers found that twins in families with a history of early cardiovascular mortality had lower levels of high-density lipoprotein (HDL) cholesterol than those who did not share such a history. Additionally, twins born to mothers who smoked had lower HDL cholesterol than children whose mothers did not smoke (Bodurtha et. al., 1987). Alongside the biological impact on cardiac-related mortality, genetics have been shown to play a significant role. Two cohort studies of twins found that CHD-related mortality is influenced by genetics in both men and women. However, researchers in both of the studies found that although this genetic influence remained throughout the lifetime, its association with mortality decreased with age (Marenberg et. al., 1994; Zdravkovic et. al., 2002).

Alongside biological influences, environmental influences have been shown to influence CVD risk. In particular, both psychological stressors, as well as lifestyle habits demonstrate a strong influence on cardiovascular health. Carmelli et. al. (1985) conducted a study of adult twins examining cardiovascular reactivity to laboratory stressors. They found that cardiovascular reactivity may be heritable, demonstrating a genetic link among twins. Similarly, in a cohort study of U.S. male-male twin pairs from the Vietnam Era Twin Registry, researchers found that major depression symptoms were significantly associated with self-reported heart disease, but not hypertension. Individuals with four or more depressive symptoms were more likely to self-report having a history of heart disease compared to individuals with no depressive symptoms (Scherrer et. al., 2003). Both of these studies demonstrate the impact of psychological stressors on cardiovascular health and its related risk factors. Modifiable lifestyle habits have also been linked to cardiovascular health among twins. In a study of adult male twins in the U.S., researchers examined the role that environmental factors played on the concordance of hypertension between twin pairs. They noted that modifiable factors such as adulthood weight gain, physical activity, and even alcohol consumption had an effect on this concordance (Carmelli, Robinette, & Fabsitz, 1994). All of these studies demonstrated the impact of environmental factors on CVD and overall cardiovascular health, as demonstrated by comparing monozygotic twin pairs.

Genetic variation in CVD risk factors has also been examined among twin pairs. A study of CHD risk factors revealed that some risk factors such as height and blood pressure had significant genetic variation between twins, while other factors such as total cholesterol level did not show this variability. HDL and low-density lipoprotein (LDL) cholesterol

levels also showed very little genetic variability between twins (Feinleib et. al., 1977). Another cohort study examined the influence of genetic and environmental influences on ankle-brachial index (ABI) values - a measure of peripheral arterial disease - and showed that concordance of low ABI values in twins was higher than would be expected by chance, although zygosity did not have an effect on this association. Additionally, the researchers found that twins with low ABI values were less likely to be physically active and more likely to be smokers (Carmelli et. al., 2000). These study findings demonstrate the interplay between genetics and shared environmental influences on cardiovascular diseases such as peripheral arterial disease and other cardiovascular risk factors.

The impact of genetics and environment on cardiovascular health among twins has been consistently demonstrated in the existing literature. In particular, there studies have highlighted the need to take both genetics and environmental factors into account when assessing associations between different exposures and cardiovascular health. However, none of these studies have examined the link between area deprivation and CVD risk.

VII. Framingham Risk Score

The Framingham Risk Score (FRS) is often used to quantify and estimate CVD risk, using different models to predict risk. In these models, a variety of risk factors were used to predict CVD and incorporated in risk prediction algorithms, separately in men and women, including age, total cholesterol (or LDL-cholesterol), HDL cholesterol, blood pressure, diabetes mellitus and smoking status (Framingham Heart Study, 2019). The initial scoring system was developed as part of the Framingham Heart Study and continues to be widely used in the literature and clinical care today. There have been a number of studies

examining the efficacy of the FRS in predicting CVD risk. These studies will be discussed in relation to area deprivation, geographic variation and twin studies.

A prospective cohort study conducted in Scotland aimed to examine the accuracy of the FRS in different SES groups among a population with high rates of CVD. The researchers found that the FRS underestimates the risk in SES-deprived participants, suggesting that treatment options in these areas may be less likely (Brindle et. al., 2005). A similar prospective cohort study sought to examine if the FRS method of assessing CVD is deficient after omitting social deprivation. The researchers found that the FRS is not good at predicting CVD in different SES groups. Similar to the previous study, they concluded that risk is underestimated in more deprived populations (Tunstall-Pedoe & Woodward, 2006).

Alongside area-based deprivation, the FRS has also been examined in relation to geographical variation. Geldsetzer et.al (2018) conducted a cross-sectional study in India to determine how the CVD risk measured by the FRS differs by location and individual-level SES. The location differences measured in the study were urban and rural classifications. The researchers found that among both males and females, CVD risk was higher in urban areas after adjusting for covariates (RR in males: 7.35, 95% CI: 7.02-7.68); RR in females: 12.51, 95% CI: 12.14 – 12.88). Additionally, BMI was higher among wealthier than poorer individuals. However, high blood glucose and blood pressure were more common among poor individuals. Lastly, smoking was most prevalent among men in poor areas (Geldsetzer et. al., 2018). This study demonstrated that the FRS metric was successful in predicting CVD risks. However, these results have not always been consistent. In a longitudinal cohort study conducted in the U.S., researchers examined the association of geographic variation in risk scores and geographic variation in CVD-related mortality. They found that geographic

variations in risk factors contribute little to no association with geographic variation in mortality rates. They found slightly more moderate associations between CHD risk scores and CHD-related mortality, but these associations were not observed with stroke risk scores and stroke-related mortality (Howard et. al., 2009). This finding was similarly reflected in a systematic review of cardiovascular risk assessment tools among diabetic populations. The review concluded that the FRS performs well in U.S. populations, but absolute risk prediction had some problems when looking at populations different from the source cohort (Matheny et. al., 2011).

The FRS has also been examined in the context of twin studies. In a cohort study of twins conducted in Korea, researchers aimed to examine genetic heritability of the FRS and its association with adipose tissue. They concluded that both the FRS and traits associated with obesity and adiposity had common genetic and environmental influences (Song et. al., 2012). Another cohort study of twins in Amsterdam further highlighted the genetic influence of the vascular risk as measured by the FRS and white matter hyperintensities. When looking at within-pair differences, there was a high correlation between the FRS and the white matter (Ten Kate et. al., 2018). The study findings suggested that the FRS is influenced by both genetic and environmental factors.

Despite the numerous studies evaluating the FRS as a measure of overall CVD risk, no previous investigations have examined this metric in relation to area deprivation in the United States.

VIII. Conclusion

This literature review sought to examine environmental and genetic influences on CVD risk with a focus on area-based deprivation, geographic variation, and twin studies. One consistent finding throughout the studies has been the importance of the interplay between environmental and genetic factors in relation to the development, risk, and complications of CVD. Currently, no previous literature has examined if area-based deprivation is related to cardiovascular risk using a twin design to control for familial and genetic factors. This lack of knowledge warrants further exploration to better understand health disparities in CVD risk.

Introduction

Cardiovascular disease (CVD) is the leading cause of death among U.S. residents, with an estimated 900,000 deaths being attributed to the disease (Roth et. al., 2018). Diseases that fall under the CVD umbrella include coronary heart disease (CHD), stroke, and hypertension. CVD contributes to a major loss in individual productivity and is a significant financial burden on the American healthcare system costing about $100,000 - $120,000 dollars per heart procedure (Mensah & Brown, 2007). There are several risk factors associated with CVD such as genetics, family history, high blood pressure, and obesity (CDC, 2015). Additionally, many behavioral or psychological risk factors such as stress, smoking, and physical inactivity also contribute to the development of CVD (CDC, 2015) (Steptoe & Kivimaki, 2013).

Socioeconomic status (SES) has been consistently associated with disparities in health. SES is generally measured through a variety of factors including, occupation, education, and income. Additionally, researchers recognize that ecologic measures of SES can also help understand health disparities, especially when considering access to resources and community infrastructure (Shavers, 2007). SES is also linked to several determinants of health, including environmental exposure, lifestyle choices, and healthcare access (Adler & Newman, 2002). Furthermore, the underlying stress that is often associated with low SES is a likely contributing factor to the development of CVD (Pickering, 1999).

As highlighted above, geographic deprivation is often used by researchers as an ecological measurement of SES. Several studies have examined the impact of geographic deprivation and cardiovascular health, with varying results (Smith et. al., 1998) (Roux et. al., 2001). While these studies highlight the important effects of environment on cardiovascular health, the results may vary due to genetic and cultural differences of

populations residing in different areas, and provide the motivation to further investigate factors associated with these disparities.

Twin studies have been conducted for many years, investigating the interplay between genetics and the environment. Many of these studies have been conducted in relation to CVD risk and mortality (Zdravkovic et. al., 2002) (Marenberg et. al., 1994). There have also been twin studies exploring the connection between area-based deprivation and twin mental health and behavioral outcomes (Teucher et. al., 2007) (Watson et. al., 2016). Many of these studies highlight the need to consider both genetic and environmental influences when examining these risks. However, other than BMI, there has been no literature examining the association of area-based deprivation and cardiovascular disease risk or its related risk factors, using a twin design.

Adult twins discordant for their area of residence are ideal in exploring this question. Twins are naturally matched for family and cultural background, early familial influences, and genetic background, which is shared 100% in monozygotic (MZ) twins and 50%, on average, in dizygotic (DZ) twins. Thus, our study aims to quantify the association between area-based deprivation and cardiovascular health using a twin design. We hypothesize that within twin pairs, individuals living in more deprived areas will have higher cardiovascular risk scores, after accounting for familial and genetic similarities.

Methods

Participants

This study is a secondary data analysis of data collected from the Emory Twin Study Follow-Up, a prospective cohort study conducted by the Emory Program in Cardiovascular Outcomes Research and Epidemiology (EPICORE). The data collected for the Emory Twin Study Follow-Up was approved by the Emory IRB. Participants were recruited from the Vietnam Era Twin Registry and are monozygotic and dizygotic male-male twin pairs ranging in age from 47 to 63 years old. Zygosity of the twins was determined through genetic typing. All included participants had a history of active military service from all branches of the military. Pairs with at least one twin with a history of cardiovascular disease were excluded from the initial recruitment in the Emory Twin Study. In the current analysis, participants were also excluded if they had a missing Area Deprivation Index score or were not in a pair, totaling to a total of 32 twin pairs excluded (n=64) from the final analysis. There were 502 participants included in the final data analysis for a total of 251 twin pairs.

Area Deprivation Index Scores

The Area Deprivation Index Score (ADI) for each participant was calculated by mapping participants' addresses on the 2013 Neighborhood Atlas (University of Wisconsin, 2018). This public map was created by the Health Resources and Services Administration, and validated by a research team at the University of Wisconsin. The ADI score is used as proxy measurement of socioeconomic status across geographic areas of the United States, including income, education, employment, and housing quality as part of a 17-factor scoring

metric. In this study, we used national percentile scores ranging from 1 to 100 to indicate deprivation. A score of 1 indicated the least deprived area in the nation, while a score of 100 indicated the most deprived area in the nation. In the analysis, we considered the ADI score on both a continuous and a categorical scale. In the continuous scale, ADI scores remained as a numerical percentile score for each participant. In the categorical scale, participants were dichotomized into a high-advantage group and a low-advantage group. Participants with a score between 1 and 45 were placed in the high-advantage group. Participants with a score ranging from 46 to 100 were placed in the low-advantage group. These specified cutoffs were based on the median ADI percentile score of the sample, which was 45.

Framingham Risk Score

The Framingham Risk Score was calculated using an algorithm for predicting CHD risk in a middle-aged patient population. The algorithm included established risk factors: age, total cholesterol (or LDL-cholesterol), HDL cholesterol, blood pressure, diabetes, and smoking status (Wilson et. al., 1998). In this analysis, we used the Framingham risk score for low-density lipoprotein (FRS-LDL) cholesterol. The FRS-LDL cholesterol score ranged from -1 to 16 and was treated as a continuous outcome throughout the analysis.

Statistical Analysis

All statistical analyses was conducted using SAS 9.4. Univariate analysis of the data was conducted using frequency tables and mean calculations for variables such as age, ADI score, as well as established cardiovascular risk factors like smoking status and BMI. ADI as a continuous variable (score expressed as decile increment) was our main exposure of interest, but all analyses were repeated with ADI as a categorical variable. To ease

interpretation, the ADI percentile score was rescaled to express decile increments. Bivariate analyses were conducted using Pearson's correlation coefficients when testing ADI as a continuous variable, and t tests when testing ADI as a dichotomous variable. Multivariable analyses were conducted using linear mixed effects models adapted for twin studies (Vaccarino et. al., 2013) to assess relationships between ADI and FRS-LDL. All models included zygosity as a covariate. The initial model tested the unadjusted association between ADI and FRS-LDL. Next, we adjusted for potential confounding factors (age, years of education, and history of previous coronary heart disease) that were chosen *a priori*. The purpose of these two models was to examine associations while considering twins as independent individuals. After this initial analysis, we compared twins discordant for ADI percentile scores or ADI category. In the third model, we tested within and between-pair effects of the ADI score/category and FRS-LDL. In the fourth model, we expanded upon this analysis by including an interaction term between the within-pair ADI score/category effect and zygosity. This allowed for within-pair effects analysis, which controls for genetic influences, as well as shared familial and environmental experiences. In the final model, we conducted a stratified analysis comparing monozygotic twins to dizygotic twins. The results from this analysis allowed us to determine if genetic factors play a role in the association. Since MZ twins share 100% of their genes, while DZ twins only share on average 50%, a within-pair association that is stronger in the DZ than in the MZ twins suggests that genetic factors play a role ("genetic confounding"). A detailed description of the modeling process is documented elsewhere (Vaccarino et. al., 2013). A total of 12 models were run – 6 for each exposure level - with each model being built in successive progression.

Results

In this study, data were analyzed from 251 twin pairs (total n = 502). The mean age of the participants was 55.5 ± 3.1 years (mean ± SD). The mean ADI score for the cohort was 46 ± 23.4 (mean ± SD). After dichotomizing the ADI using the cut point of 45, there were 257 participants living in high-advantage areas and 245 participants in low advantage areas. There were 233 twin pairs that had discordant ADI percentile scores, and 93 twin pairs that were discordant for ADI category. Additionally, The FRS-LDL was 5.9 ± 2.4 (mean ± SD). Among the total cohort, 85.4% were classified as being overweight or obese. Participants diagnosed with diabetes comprised of 12.5% of the total cohort and 25.3% reported that they smoked. Lastly, 60.9% of the twins were classified as being monozygotic. A full summary of the participant demographics can be found in Table 1.

Results from the bivariate analyses showed a significant correlation between the ADI score and the FRS-LDL: Pearson's correlation coefficient $r = 0.13$, $p = 0.005$. When the ADI was dichotomized, the mean FRS-LDL was higher in twins living in low advantage areas (6.2 ± 2.3) than those living in high advantage areas (5.7 ± 2.4), $p=0.005$.

Results from the multivariable analyses of ADI scores and Framingham scores are shown through a series of models for FRS-LDL. The full model progression for the outcome are reported in Tables 2, 3, and 4 for the continuous ADI score and Tables 5, 6, and 7 for the dichotomized ADI categories.

Considering twins as individuals, there was a significant unadjusted association between ADI and FRS-LDL. For each 10 points increment in ADI score, the FRS-LDL increased by 0.1 points (Table 2). When potential confounding factors were included (age, years of education, and previous history of CHD), the association between ADI score and FRS-LDL

was weakened to 0.07 points (Table 2). When we examined within pair associations, however, we found no association between ADI and FRS-LDL comparing twins discordant for ADI (FRS-LDL: -0.02 per 10-point ADI increment, 95% CI: -0.14, 0.01) (Table 3). Next, we examined within pair associations separately in MZ and DZ pairs. The within-pair association between ADI score and FRS-LDL was more than two times larger in DZ twins than in MZ twins, although the effect was not significant in either group (MZ: -0.09 per 10-point ADI increment, 95% CI: -0.23, 0.06; DZ: 0.18 per 10-point ADI increment, 95% CI: -0.05, 0.42 (Table 4). The interaction effect between the within effect of ADI and zygosity was borderline significant (P=0.05).

When analyses were repeated using the categorical ADI variable, results remained similar, although there were no significant associations in all of the models (Table 5-7). Overall, twins living in low advantage areas had a 0.38-point higher FRS-LDL score compared with twins living in high advantage areas, although this association was not significant (Table 5). When potential confounding factors were included (age, years of education, and previous history of CHD), the association between ADI category and FRS-LDL was slightly weakened and FRS-LDL score was 0.32 points higher in the low advantage areas compared to the high advantage areas (Table 5). When we examined within pair associations, we found no significant association between ADI category and FRS-LDL comparing twins discordant for ADI category (FRS-LDL: 0.03, 95% CI: -0.50, 0.56) (Table 6). Next, we examined within pair associations separately in MZ and DZ pairs. For both MZ and DZ pairs, the within-pair association between ADI score and FRS-LDL was not statistically significant, although it was numerically larger among the DZ twins (MZ: -

0.08, 95% CI: -0.71, 0.55; DZ: 0.42, 95% CI: -0.55, 1.39) (Table 7). The interaction effect between the within effect of ADI and zygosity was not significant (P=0.38).

Discussion

This study aimed to quantify the association of area-based deprivation and cardiovascular risk using a twin design. We hypothesized that twins living in more deprived areas would have higher cardiovascular risk scores, after considering genetic and familial similarities in within-pair analysis. We found that the association between area deprivation and cardiovascular risk (as summarized by using the FRS-LDL) was entirely explained by familial and genetic confounding factors.

There was a significant unadjusted association between ADI percentile score and FRS-LDL. However, after adjusting for age, education in years, and previous history of CHD, the association between ADI score and FRS-LDL was diminished. In within-pair analysis, there was no association between ADI and FRS-LDL, suggesting an important role for familial factors. In the within-pair analysis of ADI score and FRS-LDL by zygosity, the within-pair association was larger in DZ than in MZ twin pairs ($p=0.05$ for interaction), suggesting that genetic factors play a role in the association between ADI and cardiovascular risk factors.

The analysis of a dichotomized ADI score comparing high advantage areas to low advantage areas and FRS-LDL provided similar results. In the unadjusted model, we found that there was an association between ADI category and FRS-LDL, although it did not reach statistical significance, and was weakened by adjusting for age, education in years, and previous history of CHD. In the within-pair analysis comparing twin pairs discordant for ADI category there was no association between ADI and FRS-LDL. The association was larger within DZ than MZ twin pairs, although the interaction was not significant.

Considering that the hypothesis was that twins with a higher area deprivation score would have a higher cardiovascular risk score than those with a lower deprivation score, the study fails to reject the null hypothesis. Considering twins as individuals, the association between ADI and cardiovascular risk factors was only slightly diminished by adjusting for the confounding factors of age, education in years, and previous history of CHD. However, in within-pair analysis, the association disappeared. Interestingly, there was a consistently significant association between ADI scores (both continuous and dichotomous) and FRS-LDL between twin pairs. These differences suggest that early childhood exposures, and genetic and other familial factors of people living in different communities influence FRS-LDL more than environmental exposures in adulthood. The study therefore concludes that although there were observed risk differences among twin pairs, these differences were not due to area-based deprivation.

The main strength of this study is the twin design that allowed us to account for genetic and familial factors, since twins are naturally matched for these influences. Secondly, by using two different approaches to the analysis of the ADI score (continuous and dichotomous), the study was able to analyze the association between the exposure and the outcomes in two different ways which provided similar results.

This study, however, has a number of limitations. A few participants and their twin pairs were excluded due to missing ADI scores, which may have had an impact on the final results. While there was limited discordance for ADI category for the twin pairs, almost half of the pairs were discordant for ADI percentile. Furthermore, there has been literature suggesting that Framingham risk scores underestimate cardiovascular risk in participants with lower SES. Considering that our exposure had to do with area-based SES, the risk

scores may not have accurately reflected the disparities within the sample population. Alongside this, our twin sample was mostly comprised of white men, which limits the generalizability of the study to the wider population.

The findings of this study suggest that genetic factors and early childhood familial exposures, rather than environmental exposures in adulthood, influence cardiovascular risk associated with geographic area deprivation. As such, future cardiovascular research and medical care should take into consideration these influences when recommending prevention and treatment strategies for cardiovascular health problems.

Appendices

Table 1. Descriptive Statistics of Sample

	Total (n=502)	High Advantage (n= 257)	Low Advantage (n=245)
	Mean ± SD	**Mean ± SD**	**Mean ± SD**
Age (Years)	55.5 ± 3.1	55.5 ± 3.1	55.4 ± 3.2
Area Deprivation Score	46 ± 23.4	27.1 ± 12.0	65.9 ± 14.1
Framingham Risk Score			
LDL Cholesterol	5.9 ± 2.4	5.7 ± 2.4	6.2 ± 2.3
Education (Years)	14.1 ± 2.2	14.5 ± 2.3	13.7 ± 2.1
Framingham Risk Factors	**n (%)**	**n (%)**	**n (%)**
Diabetes			
Yes	63 (12.5)	24 (9.3)	39 (15.9)
No	439 (87.5)	233 (90.7)	206 (84.1)
HDL Cholesterol (mg/dL)			
Less than 35	207 (41.2)	92 (35.8)	115 (46.9)
35 - 44	170 (33.9)	87 (33.9)	83 (33.9)
45 - 49	52 (10.4)	32 (12.4)	20 (8.2)
50 - 59	47 (9.4)	30 (11.7)	17 (6.9)
60 and above	26 (5.1)	16 (6.2)	10 (4.1)
LDL Cholesterol (mg/dL)			
Less than 100	130 (25.9)	61 (23.7)	69 (28.2)
100 - 129	187 (37.3)	101 (39.3)	86 (35.1)
130 - 159	112 (22.3)	58 (22.6)	54 (22.0)
160 - 189	57 (11.3)	28 (10.9)	29 (11.8)
190 and above	16 (3.2)	9 (3.5)	7 (2.9)
Total Cholesterol (mg/dL)			
Less than 160	114 (22.7)	54 (21.0)	60 (24.5)
160 - 199	211 (42.0)	106 (41.3)	105 (42.9)
200 - 239	138 (27.5)	77 (29.9)	61 (24.9)
240 - 279	30 (6.0)	14 (5.5)	16 (6.5)
280 and above	9 (1.8)	6 (2.3)	3 (1.2)

Smoking			
Yes	127 (25.3)	47 (18.3)	80 (32.6)
No	375 (74.7)	210 (81.7)	165 (67.4)
Other Risk Factors	**n (%)**	**n (%)**	**n (%)**
BMI Classification			
Normal	71 (14.2)	27 (10.5)	44 (18.0)
Overweight	218 (43.4)	120 (46.7)	98 (40.0)
Obese	211 (42.0)	110 (42.8)	101 (41.2)
Missing	2 (0.4)	0 (0)	2 (0.8)
Previous history of CHD			
Yes	52 (10.4)	27 (10.5)	25 (10.2)
No	450 (89.6)	230 (84.5)	220 (89.8)
Zygosity			
Monozygotic	306 (60.9)	155 (60.3)	151 (61.6)
Dizygotic	196 (39.1)	102 (39.7)	94 (38.4)

Table 2. Unadjusted and adjusted models of individual ADI percentile scores and FRS_LDL, considering twins as individuals.

	Model 1			Model 2		
	β Estimate	95% Confidence Levels	P-value	β Estimate	95% Confidence Levels	P-value
MAIN EXPOSURE						
ADI Percentile (per 10-point increment)*	0.10	(0.01, 0.19)	0.02	0.07	(-0.01, 0.16)	0.09
OTHER COVARIATES						
Dizygotic	-0.38	(-0.85, 0.09)	0.11	-0.40	(-0.84, 0.04)	0.07
Monozygotic (Ref)	0	.	.	0	.	.
POTENTIAL CONFOUNDERS						
Age				0.19	(0.12, 0.26)	<0.0001
Education (Years)				-0.15	(-0.24, -0.06)	0.001
History of CHD				-0.02	(-0.66, 0.62)	0.96

*ADI Percentile parameter estimate and confidence interval are shown for 10-point increment

Table 3. Within-pair analysis of ADI percentile scores and FRS_LDL			
	Model 3		
	β Estimate	95% Confidence Levels	P-value
MAIN EXPOSURE			
ADI Percentile (Between)(per 10-point increment)*	0.15	(0.03, 0.26)	0.01
ADI Percentile (Within)(per 10-point increment)*	-0.02	(-0.14, 0.01)	0.75
OTHER COVARIATES			
Dizygotic	-0.4	(-0.84, 0.03)	0.07
Monozygotic (Ref)	0	.	.
POTENTIAL CONFOUNDERS			
Age	0.19	(0.12, 0.26)	<0.0001
Education (Years)	-0.14	(-0.23, -0.05)	0.003
History of CHD	-0.02	(-0.66, 0.61)	0.94

*ADI Percentile parameter estimate and confidence interval are shown for 10-point increment

Table 4. Stratified within-pair analysis of ADI percentile and FRS_LDL by Zygosity							
	Monozygotic Twin Pairs			Dizygotic Twin Pairs			Interaction
	β Estimate	95% Confidence Levels	P-value	β Estimate	95% Confidence Levels	P-value	P-value
MAIN EXPOSURE							
ADI Percentile (Between)(per 10-point increment)*	0.11	(-0.06, 0.02)	0.21	0.17	(0.02, 0.32)	0.02	0.05
ADI Percentile (Within)(per 10-point increment)*	-0.09	(-0.23, 0.06)	0.24	0.18	(-0.05, 0.42)	0.13	
POTENTIAL CONFOUNDERS							
Age	0.13	(0.02, 0.23)	0.02	0.20	(0.15, 0.33)	<0.0001	
Education (Years)	-0.09	(-0.22, 0.04)	0.15	-0.18	(-0.30, -0.06)	0.005	
History of CHD	-0.49	(-1.40, 0.43)	0.30	0.53	(-0.35, 1.40)	0.24	

*ADI Percentile parameter estimate and confidence interval are shown for 10-point increment

Table 5. Unadjusted and adjusted models of individual ADI categories and FRS_LDL, considering twins as individuals.						
	Model 1			Model 2		
	β Estimate	95% Confidence Levels	P-value	β Estimate	95% Confidence Levels	P-value
MAIN EXPOSURE						
ADI Category*	0.38	(-0.01, 0.78)	0.06	0.31	(-0.07, 0.70)	0.11
OTHER COVARIATES						
Dizygotic	-0.38	(-0.85, 0.09)	0.12	-0.40	(-0.84, 0.04)	0.07
Monozygotic (Ref)	0	.	.	0	.	.
POTENTIAL CONFOUNDERS						
Age				0.20	(0.13, 0.27)	<0.0001
Education (Years)				-0.15	(-0.24, -0.06)	0.001
History of CHD				-0.004	(-0.64, 0.64)	0.99

*Estimate of the low advantage category vs. high advantage (reference)

Table 6. Within-pair analysis of ADI percentile scores and FRS_LDL			
	Model 3		
	β Estimate	95% Confidence Levels	P-value
MAIN EXPOSURE			
ADI Category (Between)	0.62	(0.07, 1.17)	0.03
ADI Category (Within)	0.03	(-0.50, 0.56)	0.91
OTHER COVARIATES			
Dizygotic	-0.4	(-0.84, 0.04)	0.07
Monozygotic (Ref)	0	.	.
POTENTIAL CONFOUNDERS			
Age	0.20	(0.13, 0.27)	<0.0001
Education (Years)	-0.15	(-0.23, -0.06)	0.002
History of CHD	0.002	(-0.64, 0.64)	0.99

*Estimate of the low advantage category vs. high advantage (reference)

Table 7. Stratified within-pair analysis of ADI percentile and FRS_LDL by Zygosity							
	Monozygotic Twin Pairs			Dizygotic Twin Pairs			Interaction
	β Estimate	95% Confidence Levels	P-value	β Estimate	95% Confidence Levels	P-value	P-value
MAIN EXPOSURE							
ADI Category (Between)	0.75	(-0.12, 1.61)	0.09	0.56	(-0.15, 1.26)	0.12	0.38
ADI Category (Within)	-0.08	(-0.71, 0.55)	0.80	0.42	(-0.55, 1.39)	0.40	
POTENTIAL CONFOUNDERS							
Age	0.13	(0.03, 0.24)	0.01	0.25	(0.16, 0.34)	<0.0001	
Education (Years)	-0.09	(-0.22, 0.04)	0.18	-0.20	(-0.32, -0.08)	0.001	
History of CHD	-0.54	(-1.45, 0.38)	0.25	0.54	(-0.36, 1.43)	0.24	

*Estimate of the low advantage category vs. high advantage (reference)

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