Associations of Arsenic Exposure, Arsenic Metabolism, and Cadmium Exposure with Body Composition: Evidence from the Multi-Ethnic Study of Atherosclerosis

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Heng Bai, Ph.D.

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Exposures to arsenic (As) and cadmium (Cd) in drinking water and food pose significant environmental health problems with increased risk of cardiovascular and metabolic (cardiometabolic) diseases worldwide. However, pathogenic mechanisms that underlie these disease burden from environmental contaminants remain unresolved. Body composition changes have been associated with elevated cardiometabolic disease risks. Thus, there is a need to investigate whether exposure to environmental metals is associated with altered body composition and subsequent cardiometabolic health risks. We hypothesized that As and Cd exposure are associated with lower abdominal skeletal muscle quality with greater fat infiltration, and greater abdominal fat. We designed a cross-sectional study using urinary metals and body composition measures in 283 participants (age 45-80) enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA). Body composition was measured with abdominal CT scan. Body mass index (BMI) and waist circumference were also included as anthropometric measurements. We evaluated the health effects of total urinary Cd, total urinary arsenicals (ΣAs), and the proportion of each As metabolite [monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA)] over ΣAs separately. We built linear regression models for each body composition indicator with urinary As and Cd adjusted for age, sex, race, exam region, and urinary creatinine. We found that when treated as categorical variable, ΣAs was positively associated with BMI. In continuous As metabolite models, urinary MMA% was inversely associated with abdominal fat area and abdominal muscle area, but not with

muscle density. In contrast to MMA%, urinary DMA% was positively associated with all studied body composition endpoints. Categorical urinary Cd was only observed to be associated with decreased density and increased fat accumulation in abdominal stabilization muscles. The data suggest that poor As metabolism (high MMA% and low DMA% in the urine) may underlie a trend in altered body composition that can consequently increase the risk of cardiometabolic diseases. The effects of Cd's impacts on body composition appear to be more subtle and might limit to specific muscle groups. This study provides evidence for further investigating that changes in muscle and body composition might be an underlying mechanism for cardiometabolic disease risk from environmental exposures.

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List of Abbreviations

Abd: Abdominal

As: Arsenic

As3MT: Arsenite Methyltransferase

BMI: Body Mass Index

Cd: Cadmium

CT: Computed Tomography

CVD: Cardiovascular Disease

DM2: Type 2 Diabetes

DMA: Dimethylarsinic Acid

iAs: Inorganic Arsenic

IMAT: Intermuscular Adipose Tissue

IR: Insulin Resistance

MESA: the Multi-Ethnic Study of Atherosclerosis

MMA: Monomethylarsonic Acid

SAT: Subcutaneous Adipose Tissue

VAT: Visceral Adipose Tissue

1.0 Introduction

1.1 Overview of Cardiometabolic Diseases

Cardiometabolic diseases are a group of diseases including cardiovascular diseases (CVDs) and metabolic disorders such as Type 2 diabetes (DM2). CVDs include but not limited to heart failure, ischemic heart disease, stroke, atherosclerosis and peripheral arterial disease (Mensah et al., 2019). DM2 is a metabolic disorder characterized by hyperglycemia caused by impaired insulin secretion, insulin action, or both. Cardiometabolic diseases burden is a public health concern in both developing and developed countries. In the year 2017, CVD caused about 17.8 million deaths worldwide (Mensah et al., 2019). In 2019, global CVD mortality increased to 18.5 million, with 9.6 million among men and 8.9 million among women (Roth et al., 2020). According to the World Health Organization (WHO), the worldwide prevalence of DM2 among people 18 years and older increased from 4.7% to 8.5% during the year 1980 to 2014 (WHO), and is estimated to be 10.2% (578 million individuals) by 2030 (Saeedi et al., 2019).

It is widely accepted that lifestyle and behavior factors, such as lack of physical activity and sedentary behavior (Ahmad et al., 2017; Lavie et al., 2019; Lechner et al., 2020), smoking and alcohol consumption (Clawson et al., 2021; Piano, 2017), high fat diet and excessive energy intake (Chiavaroli et al., 2018; Tindall et al., 2018), are risk factors that lead to the development of

cardiometabolic diseases. However, environmental exposures, such as to metals, might be overlooked risk factors.

1.2 Overview of Arsenic

Arsenic (As, atomic number 33; relative atomic mass 74.92) is a toxic metalloid that occurs naturally, and is the 20th most abundant element comprising the earth's crust (Mandal & Suzuki, 2002). Human activities such as metal smelting, pigment production, extraction of underground aquifers, glass and electronic device production, are sources of As contamination (ATSDR, 2016). Arsenic is mostly found in three major forms: organic, inorganic, and arsine gas (ATSDR, 2016) with various chemical states, including "trivalent", "pentavalent", and "organoarsenical" ("fish arsenic") (Hall, 2002). In general, organic As species have been confirmed to be much less toxic than inorganic species (Farkhondeh et al., 2019).

1.2.1 Routes of Arsenic Exposure

More than 140 million people worldwide are exposed to As through contaminated drinking water (States et al., 2011). Humans can be exposed to As and arsenicals through food, drinking water and even air (Chou & Harper, 2007). Rice and mushrooms (Braeuer & Goessler, 2019) tend to accumulate As from the soil. Poultry products could contain As-based antimicrobial drugs even though several of these drugs have been banned from the market in recent years (Nigra et al., 2017). Seafoods are potentially high in As concentration due to bio-accumulation, but the main As species in seafood, arsenobetaine, is not considered to be toxic to humans (Jomova et al., 2011;

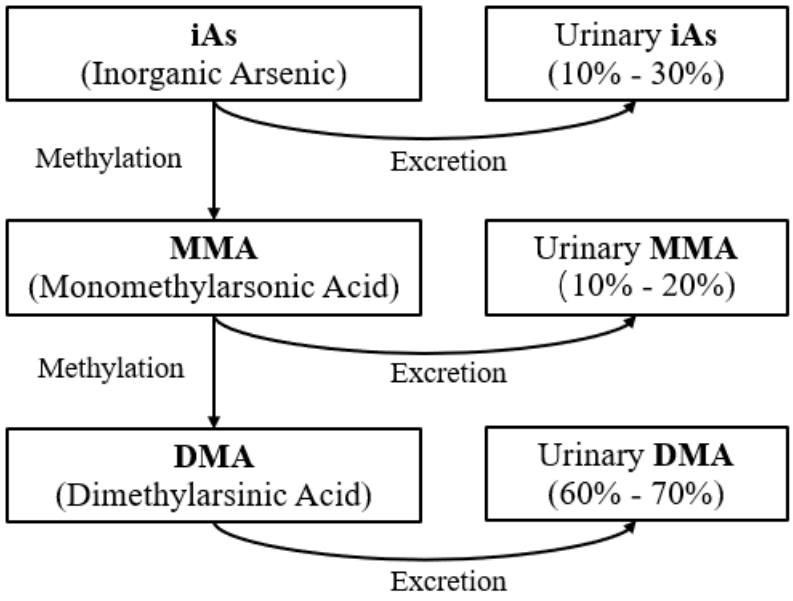
Nigra et al., 2017). The World Health Organization (WHO) recommended that the maximum tolerable daily intake of inorganic As is 0.0002 mg/kg body weight; the Food and Agriculture Organization (FAO) regulated that the maximum allowed As in rice is 0.2 mg/kg (Dani & Walter, 2018); but as a recognized carcinogen (Cohen et al., 2016), As has no minimum level of exposure that is considered to be safe.

1.2.2 Arsenic Metabolism

In general, two types of As, organic and inorganic As (iAs), can be found naturally. Organic As species have been confirmed to be less toxic than iAs due to more rapid elimination from the body (Abshire et al., 2017; Farkhondeh et al., 2019). When consumed, iAs is absorbed through the gastrointestinal tract and then methylated into monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) via two methylation steps catalyzed by the enzyme Arsenic Methyltransferase (As3MT) (Thomas, 2021; Wei et al., 2016) and excreted in urine (Ratnaike, 2003). **Figure 1** shows the general metabolism of As. Six major As species have been identified in human urine, including higher cytotoxic species iAs^{III}, MMA^{III} and DMA^{III}, and lower-cytotoxic species iAs^{V}, MMA^{V} and DMA^{V} (Ellinsworth, 2015; Smeester et al., 2017). Among all urinary As metabolites, DMA is usually the most abundant (60% to 70%), with MMA being approximately 10% to 20% and iAs contributing 10% to 30% (Abuawad et al., 2021; Spratlen et al., 2018). The ratios of As species in the urine are influenced by nutritional status, as well as genetics and methylation capacity of As3MT and can be used as predictors of diseases and metabolic status (Abuawad et al., 2021; Delgado et al., 2021; Pace et al., 2018; Stýblo et al., 2021; Wu et al., 2021). Arsenic has a biological half-life of 30 to 60 hours in the blood (Crecelius, 1977); both blood and

urinary arsenicals are widely used biomarkers that reflects recent As exposures (Zhang et al., 2018).

Figure 1. Arsenic Metabolism



1.2.3 Health Effects of Arsenic

Arsenic in the human body acts as a cause of inflammation, oxidative stress, and apoptosis at the cellular level (Farkhondeh et al., 2019). Systematic health effects of As include neurological and cognitive damages (Jahanbazi Jahan-Abad et al., 2017) (ATSDR, 2016; Engstrom et al., 2013), skin lesions (Weinmuellner et al., 2018), immunologic toxicities (ATSDR, 2016; Engstrom et al., 2013) and cancers in lung, skin, kidney, bladder and leukemia (Hong et al., 2014; Hughes, 2002). In addition, a growing body of evidence showed that As exposure is associated with elevated risk of developing cardiometabolic diseases, including CVDs (Kuo et al., 2017; Moon et al., 2017; Stea et al., 2014), hypertension (Hall et al., 2017; Yu et al., 2017), insulin resistance (IR) (Peng et al., 2015), DM2 (Castriota et al., 2018; Grau-Perez et al., 2017; Islam et al., 2012; Kim & Lee,

2011; Maull et al., 2012; Navas-Acien et al., 2008; Wang et al., 2014) and metabolic syndrome (Spratlen et al., 2018). These increased risks have been observed globally, among populations with a variety of exposure levels (Gribble et al., 2012; James et al., 2015; James et al., 2013; Moon et al., 2017; Spratlen et al., 2018).

1.2.4 Arsenic and Body Composition

Large numbers of epidemiological studies from different regions of the world show that As has an inverse association with BMI (Gomez-Rubio et al., 2011; Grashow et al., 2014b; Milton et al., 2010; Su et al., 2012), indicating the potential link between As and "lean" body shape.

A study of 74 U.S. welders showed that log-transformed toenail As was negatively associated with BMI with or without adjusting for age (Grashow et al., 2014a). A case-control study among 708 Bangladesh women found that chronic drinking water As exposure was positively associated with increasing risk of malnutrition (BMI<18.5) (Milton et al., 2010). A study among 303 Taiwanese adolescents found a significant negative association between urinary total As and BMI as well as a trend that children with obesity or higher insulin levels had higher MMA^V% and lower DMA^V% than those without obesity and low insulin levels, indicating a lower As methylation capability (Su et al., 2012). A study among 624 U.S. and northwest Mexican women showed a significant negative association between BMI and urinary MMA%, and a positive association between BMI with urinary DMA/MMA ratio (Gomez-Rubio et al., 2011). A study among 1166 Mexican adults showed a negative association between BMI and both urinary iAs% and MMA%, but a positive association between BMI with urinary DMA%. Studies above suggest that methylation capacity may be growth promoting and increases BMI (Bommarito et al., 2019). These results are consistent with findings of other studies (Jansen et al., 2016), including a

study of 3663 U.S. adults that found that increased BMI was associated with decreased urinary iAs% and MMA%, but an increased DMA%. The same trend was observed on body fat percentage but also fat free mass (Gribble et al., 2013). In general, it seems that poor As metabolism (i.e. increased urinary MMA%) has been negatively associated with BMI and efficient metabolism (i.e. increased urinary DMA%) has been positively associated with BMI (Abuawad et al., 2021; Bommarito et al., 2019; Gomez-Rubio et al., 2011; Jansen et al., 2016).

Animal models and lab experiments also provided evidence that As impacts both fat and muscle tissues. For example, one study observed adipose tissue As accumulation after As exposure (Farkhondeh et al., 2019), Arsenic is involved in adipose tissue signaling pathways such as peroxisome proliferator-activator receptor gamma (PPARγ) (Yadav et al., 2013). A rodent and human cell culture study found As decreases adipose lipid storage by specific adipocyte G-protein-coupled receptors (GPCRs) (Garciafigueroa et al., 2013), which is in consistency with the findings of inverse association between As and BMI. Arsenic decreases muscle quality by impairing the regenerative capacity of muscle progenitor cells and increasing intermuscular adipose tissue (IMAT) deposition (Ambrosio et al., 2014; Garciafigueroa et al., 2013). In addition, As decreases muscular mitochondrial function (Wang, Zhao, et al., 2018) and increases the level of IR among mouse adipocytes and myotubes (Padmaja Divya et al., 2015). Arsenic-promoted IR in muscle has also been suggested by epidemiological studies in both the US and Bangladesh (Gribble et al., 2012; Mondal et al., 2020).

In conclusion, it seems that both As exposure and As metabolites are associated with body composition. There is a tendency that As lowers BMI in population level studies. The mechanism could be impaired metabolism of both fat and muscle tissues.

1.3 Overview of Cadmium

Cadmium (Cd, atomic number 48; relative atomic mass 112.41) is a toxic transition metal that exists naturally in the environment, mainly found in the earth's crust. Cd can be released by human activities such as fossil fuel burning, metal ore combustion, metal refinery and waste burning, and agricultural phosphate fertilization (ATSDR, 2012; Rafati Rahimzadeh et al., 2017). The mobility of Cd is relatively high compared to other heavy metals (Cd > Ni > Zn > Mn > Cu > Pb=Cr > Hg), therefore, Cd can be bioaccumulated and retained in the ecosystem (Kim et al., 2015; Mortensen et al., 2018). Cd is considered highly toxic to both terrestrial and aquatic organisms, including humans (Haider et al., 2021). Cd ranks seventh on the Agency for Toxic Substances and Disease Registry (ATSDR) priority list (ATSDR). Cd and Cd compounds have been classified as Group 1 carcinogens in the IARC (International Agency for Research on Cancer) monographs, and as "Known to be human carcinogens" in the NTP (National Toxicology Program) classification (WHO).

1.3.1 Routes of Cadmium Exposure

The major routes of occupational Cd exposure are inhalation of dust and fumes (Chen et al., 2016). For the general population, people can be exposed to Cd via inhalation, consumption of contaminated water and food, such as vegetables and rice growing on the Cd-polluted soil (Nordberg, 2009; Rafati Rahimzadeh et al., 2017). Tobacco and cigarette smoke, even from involuntary exposure, are also important sources of Cd exposure (Jung et al., 2017; Li et al., 2020; Richter et al., 2017). Total daily Cd intake from all sources in North America and Europe ranges from 10 to 30 μg per day, although only about 10% or less is retained (ATSDR, 2012). Cadmium

chloride ($CdCl_2$) is the primary form of oral exposure due to its water solubility, while cadmium oxide (CdO) is the common form of inhalation exposure (Zalups & Ahmad, 2003).

1.3.2 Health Effects of Cadmium

Cadmium causes multiple health problems including renal damage, CVDs, endocrine disruption and immune disorders (Bernhoft, 2013). In the 1950s to 1970s, there was an outbreak of "Itai-Itai diseases" in Japan. Major symptoms were osteomalaecia, severe pain in the bones and kidney dysfunction. The disease was later confirmed to be caused by Cd poisoning due to mining contamination (Nishijo et al., 2017; Tsuchiya, 1969).

The relationship between Cd exposure and cardiometabolic diseases has been well studied. A study of 1171 adults in Spain found that the hazard ratio (HR, comparing the 80th to the 20th percentile of urinary Cd) for Cd in the incidence of CVD is 1.46 (95% confidence interval = 1.13-1.88) (Domingo-Relloso et al., 2019). A study of 3348 adults in the Strong Heart study of U.S. American-Indian communities found that urinary Cd was associated with elevated mortality caused by CVD (HR=1.43, 95% CI 1.32-1.70) and coronary heart disease (HR=1.34, 95% CI1.10–1.63) (Tellez-Plaza, Guallar, Howard, et al., 2013). In another study of 3047 participants in the Strong Heart Study, urinary Cd was positively associated with higher hypertension risk and faster yearly increase of diastolic and systolic blood pressure level (Oliver-Williams et al., 2018). It was also found that higher urinary Cd was associated with increased incidence of peripheral arterial disease (PAD) with a HR of 1.41 (95% CI = 1.05-1.81) (Tellez-Plaza, Guallar, Fabsitz, et al., 2013). A similar study on 1359 senior women in Australia showed that urinary Cd was associated with increased risk of heart failure (HR = 1.17, 95% CI 1.01-1.35) and heart failure related death (HR = 1.36, 95% CI 1.11-1.67) (Deering et al., 2018). A recent study of NHANES data based

examined the relationship of urinary Cd and CVD in 38,223 participants and found a positive relationship to both the overall risk of CVD and the risks of its subtypes, including congestive heart failure, coronary heart disease, heart attack, and stroke (Ma, Zhang, et al., 2021). Another study of 8722 NHANES participants found that when urinary Cd level elevated from 1-1.99 to > 2 μg/g creatinine, the odds ratio (OR) for DM2 increased from 1.24 to 1.45, and the OR for impaired fasting blood glucose increased from 1.48 to 2.05 (Schwartz et al., 2003). A study in Korea among 719 residents living near abandoned metal mines observed an OR of 1.81(95% CI = 1.05-3.12) for the effects of urinary Cd on DM2 prevalence (Son et al., 2015).

1.3.3 Cadmium and Body Composition

The association between Cd and body composition is controversial. A report from Canada showed that people with class II and III obesity had significantly lower blood Cd than people with normal BMI, meanwhile underweight people had significantly higher urinary Cd than people with normal BMI (Garner & Levallois, 2016). Similarly, a Spanish study found that BMI was inversely associated with fat tissue Cd (Echeverría et al., 2019). A study from the U.S. found that mean BMI significantly decreased with the increasing of urinary Cd concentration (Tellez-Plaza, Guallar, Howard, et al., 2013). However, another U.S. study showed the opposite trend (Jiang et al., 2018). A Korean study found no associations between body fat percentage and blood Cd (Park & Lee, 2013), while a study in rodents observed that Cd reduced adipocyte size (Kawakami et al., 2010).

1.4 Overview of Body Composition

Body composition describes the mass and percentage of bone and soft tissues in the human body (Shepherd et al., 2017). Soft tissues can be further classified as "lean" (muscle) and "fat" (adipose) mass. Body composition is a recognized factor that associates with cardiometabolic diseases. Overweight and obesity are risk factors of developing atherosclerosis, CVDs, hypertension and DM2 (Albrecht et al., 2017; Lu et al., 2015). According to the U.S. Centers for Disease Control and Prevention (CDC), 39.8% of U.S. adults were obese in the year 2015 to 2016 (Hales et al., 2017). Altered body composition increases the risk of multiple chronic diseases burden.

1.4.1 Muscle Tissue

Skeletal muscle, or "lean tissue" in our study, comprises approximately 40% of total body weight and contains half to two-thirds of total body proteins. Skeletal muscle is important for body protein metabolism (Frontera & Ochala, 2015) and is the largest insulin sensitive and glucose consuming organ in the body (Scott et al., 2016). Muscle quality is usually determined by the abundance of muscle mass or area and muscle density (Stretch et al., 2018). A variety of factors such as disease, malnutrition and aging can lower muscle quality (Aoyagi & Shephard, 1992). Myosteatosis, or excessive muscle fat infiltration, as one of these factors, leads to myofibrosis (Zoico et al., 2013), decreased muscle strength and physical function (Khoja et al., 2018; Reinders et al., 2015) and higher risk of bone fracture (Schafer et al., 2010). According to the position of fat depots within skeletal muscle, muscle fat infiltration can be classified as intramyocellular fat (fat within myocytes) and intermuscular fat (fat within fascia) (Miljkovic & Zmuda, 2010).

Unfortunately, despite of aging, there is no perfect explanation of the mechanism of myosteatosis (Correa-de-Araujo et al., 2020). There is currently no available treatment either.

1.4.2 Fat Tissue

In humans, subcutaneous fat (or subcutaneous adipose tissue, SAT) is fat deposit between the dermis and muscles (Miljkovic et al., 2021). SAT is the major form of fat in the body, comprising 80-90% of total fat. Visceral fat (or visceral adipose tissue, VAT) is abdominal cavity fat tissues that surrounds the organs. VAT accounts for another 5-15% of total fat and the final 2-3% is perivascular fat (Le Jemtel et al., 2018). It has been shown that fat distribution is more important for diseases risk than the quantity of fat in human body. For example, SAT is the natural storage of energy intake, but excess energy intake leads to fat accumulation in VAT instead of SAT (Ibrahim, 2010). VAT accumulation, or "visceral obesity", increases the risk of inflammation, CVDs, impaired glucose metabolism, and metabolic syndrome (Alexopoulos et al., 2014; Tchernof & Després, 2013). In addition, altered total abdominal fat has been found to be associated with increased VAT and increased risk of cardiometabolic diseases (Vispute et al., 2011).

1.4.3 The Association of Body Composition and Cardiometabolic Diseases

Studies found that loss of skeletal muscle mass promotes CVD development and mortality (Heo et al., 2018; Li et al., 2018; Prado et al., 2018; Rodriguez et al., 2017; Tikkanen et al., 1998), increases the risk of hypertension (Zhao et al., 2016), leads to abnormal blood glucose control and DM2 (Hickey et al., 1995; Ingram et al., 2012; Miljkovic et al., 2013; Son et al., 2017). Muscle density, rather than muscle volume or area, appear to be the more sensitive measure of disease risk

(Correa-de-Araujo et al., 2020). Myosteatosis has also been recognized as a risk factor of CVD and all-cause mortality (Larsen et al., 2020; Miljkovic et al., 2015; Reinders et al., 2016).

It is widely accepted that being overweight and obese (i.e., higher BMI) significantly increases the risk of cardiometabolic diseases (Alpert et al., 2016; Ha & Bauer, 2018; Lavie et al., 2016; Lu et al., 2015; Patel et al., 2016; Seravalle & Grassi, 2017). However, India and Bangladesh have the second highest number of people with DM2 in the world, but the average BMI of the populations is relatively low (Paul et al., 2019; Unnikrishnan et al., 2016). Epidemiological studies also showed that for some populations, people with lower BMI may have a higher risk of arterial stiffness (Huisman et al., 2015) and incidence of severe strokes (Funada et al., 2008; Hagii et al., 2018). Being underweight is also associated with developing DM2 (Chilunga et al., 2019; Katanoda et al., 2019) and CVDs (Gao et al., 2016; Katanoda et al., 2019), as well as higher CVD mortality (Senda et al., 2018). Unlike being overweight or obese, the pathophysiology of cardiometabolic diseases among non-obese population is unclear, and body composition, such as loss of lean body mass may be more import determinants of disease risk.

1.4.4 Body Composition Measurements

BMI is a widely used body composition approximative measurement. It roughly reflects body shape, but not distribution of lean and fat tissues. Several factors such as the amount of muscle and bones will easily alter BMI, as taller or heavier individuals have more muscle mass (Janssen et al., 2000). On the other hand, people with higher BMI may have lower adipose tissue mass but higher muscle mass.

Since BMI alone does not convey enough information for body composition information, advanced techniques that distinguish between “lean mass” and “fat mass” are used (Correa-de-

Araujo et al., 2020; Larsen et al., 2020). Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) scans are commonly used methods for body composition measurements. While both distinguish between lean and fat body mass, CT scans are considered the gold standard and are best able to assess body composition changes that associate with risk of cardiometabolic diseases (Correa-de-Araujo et al., 2020; Miljkovic et al., 2021). A study from UK with 6021 participants that underwent abdominal Magnetic Resonance Imaging (MRI) scanning found that, both higher VAT and muscle fat infiltration significantly increased the risk of coronary heart disease and DM2. In the same study, different body composition patterns were observed among all BMI levels, indicating that BMI alone might not be a good predictor of cardiometabolic diseases risk (Linge et al., 2018). In the Multi-Ethnic Study of Atherosclerosis (MESA), CT scans were used to demonstrate muscle and muscle type related changes in area and density that correlated with all-cause mortality risk pathogenic, systemic change in lipids and lipoprotein cholesterol (Larsen et al., 2020).

1.5 Overview of MESA

The Multi-Ethnic Study of Atherosclerosis (MESA) is a population-based study investigating subclinical CVD characteristics, etiology, progression, and risk factors (Burke et al., 2016). MESA was initiated by the National Heart, Lung, and Blood Institute in the year 2000 and is an ongoing survey study. The cohort now includes 6814 participants aged 45 to 84 years-old who were recruited from multiple ethnic groups including White, Black, Hispanic, and Asian Americans residing in 6 urban regions in the US (Burke et al., 2016). The regions include Los Angeles County, California; Minneapolis–Saint Paul, Minnesota; Chicago, Illinois; Forsyth

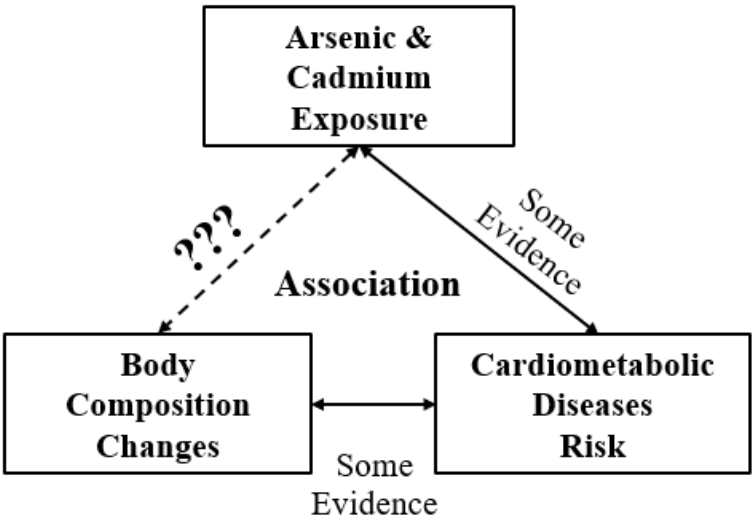
County, North Carolina; Baltimore City and Baltimore County, Maryland, and New York, New York (Burke et al., 2016). The participants completed a health questionnaire and, between years 2000 and 2018, received up to six clinical examinations (Bild et al., 2002; Burke et al., 2016; Olson et al., 2016). A total of 1970 participants from examinations 2 and 3 were randomly selected for abdominal computed tomography (CT) scanning (Shah et al., 2016). Urine samples at exam 1 from 910 randomly selected participants were selected for urinary metal measurements, including As, arsenicals and Cd.

1.6 Hypothesis and Aims

Since few studies of associations between metal exposure and body composition have used advanced, direct measures of body composition, we investigated health effects of Cd and As metabolism on body composition using direct CT measurements. We expected to measure health impacts of Cd and arsenicals in the etiology of cardiometabolic disease risks, therefore we included MESA participants with urinary measures of Cd and As, as well as a sub-cohort with abdominal CT measures (Larsen et al., 2020). It is important to note that these studies contrast greatly with those in Bangladesh (Abuawad et al., 2021; Raessler, 2018; Sarker et al., 2021) and Mexico (Gomez-Rubio et al., 2011), where As exposures were on average are much higher than the urban United States cohort. We hypothesized that higher urinary Cd, higher total urinary As and/or impaired As metabolism would be associated with body composition changes, such as decreased

muscle quality and quantity concomitant with increased intermuscular fat, harmful abdominal fat distribution and general (BMI) and central (waist) obesity (**Figure 2**).

Figure 2. Aim and Hypothesis

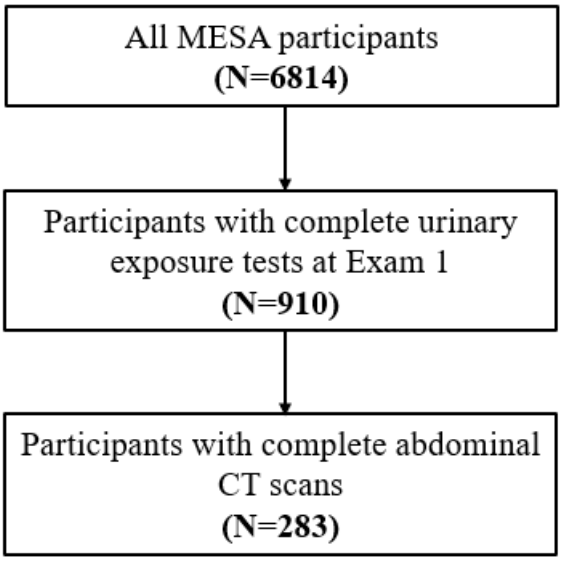


2.0 Materials and Methods

2.1 Study Sample

The Multi-Ethnic Study of Atherosclerosis (MESA) is a population-based study investigating subclinical CVD characteristics, etiology, progression, and risk factors (Burke et al., 2016). MESA was initiated by the National Heart, Lung, and Blood Institute in the year 2000 and the cohort now includes 6814 White, Black, Hispanic, and Asian Americans aged 45 to 84 years-old (Burke et al., 2016). Participants were recruited from 6 urban regions in the US including Los Angeles County, California; Minneapolis–Saint Paul, Minnesota; Chicago, Illinois; Forsyth County, North Carolina; Baltimore City and Baltimore County, Maryland, and New York, New York. Between 2000 and 2018, participants received up to six examinations (Bild et al., 2002; Burke et al., 2016; Olson et al., 2016). A total of 1970 participants from exams 2 and 3 were randomly selected for abdominal computed tomography (CT) scanning (Shah et al., 2016). For 32 participants where exam 2 and 3 scans were missing, we used substituted scans from exam 4. Urine samples at exam 1 from 910 randomly selected participants were selected for urinary As measurements. Participants were selected according to the criteria shown in **Figure 3**.

Figure 3. Selection Criteria



2.2 Urinary Arsenicals

Spot urine samples were collected in the morning after 12 hours of fasting and were stored at a temperature below -70°C (Balakrishnan et al., 2018). Baseline urinary As concentrations were measured using a standard protocol by inductively coupled plasma mass spectrometry (ICPMS, Agilent, Waldbronn, Germany). Arsenical speciation was conducted by anion-exchange high performance liquid chromatography (HPLC, Agilent Technologies, Waldbronn, Germany) coupled to ICPMS with 0.1 μg/L limit of detection (Balakrishnan et al., 2018; Pang et al., 2016; Sobel et al., 2020). Urinary iAs, MMA, and DMA were all measured and total urinary arsenic (ΣAs) was calculated as the sum of iAs, MMA and DMA. We also calculated the percentage of urinary As metabolites over ΣAs (iAs%= iAs / ΣAs × 100; MMA%= MMA / ΣAs × 100; DMA%= DMA / ΣAs × 100. ΣAs = iAs + MMA + DMA). The HPLC separation excludes arsenobetaine and other inert As metabolites found in food from the measurements and calculations.

2.3 Urinary Cadmium

Spot urine samples were collected in the morning after 12 hours of fasting and were stored at a temperature below -70°C (Balakrishnan et al., 2018). Baseline urinary Cd concentrations were measured by inductively coupled plasma mass spectrometry (ICPMS) at the Trace Metals Core laboratory in the NIEHS Center for Environmental Health at Columbia University, with a limit of detection of 0.015 μg/L. Among the 283 participants, no urinary Cd measurement was below LOD.

2.4 Body Composition

Areas of abdominal muscle, intermuscular fat, VAT and SAT were measured by CT scans at 6 levels of vertebral spaces (L2–L3, L3–L4, and L4–L5) (Shah et al., 2016). IMAT is defined as fat presented between muscle fascia and muscle groups, or "lightened areas" distributed in the skeletal muscle groups on the CT scan image. VAT is abdominal cavity fat tissues that surrounds the organs. SAT is fat deposit between the dermis and the fascia of abdominal muscles (Miljkovic et al., 2021). All CT scan images were read and evaluated by two trained analysts independently using the Medical Imaging Processing Analysis and Visualization software (MIPAV, version 4.1.2) (Remigio-Baker et al., 2015). We included only the L4-L5 slice to be consistent with previous studies (Larsen et al., 2020). Muscle and fat areas are the area of each group of muscle and fat tissue presented on the CT scan image. Muscle density is calculated from the value of Hounsfield Units (HU) of muscle tissue on the CT scan image. According to Mitsiopoulos et al (Mitsiopoulos et al., 1998), density ranges of fat tissue are -190 to -30 HU, skeletal muscle are -29 to +150 HU and bone are +152 to +1,000 HU. As previously described by Vella et al (Vella et

al., 2018), abdominal muscles were classified as locomotion (psoas) and stabilization/posture (rectus abdominus, obliques, paraspinal) according to their function. BMI [weight (kg) / height $(m)^2$] and waist circumference were also included. Due to the ongoing feature of the MESA cohort, each participant underwent multiple physical examinations at different time points after enrollment. Therefore, we used the BMI and waist circumference measurements that were closest to the CT scan time in order to be consistent with the timing of all body composition variables.

2.5 Other Variables

In MESA, standard questionnaires in different languages were used to collect basic information for each participant (Fliotsos et al., 2018). We assessed baseline sociodemographic variables including sex, gender, race/ethnicity, and exam region. Age at CT scan was calculated according to the time interval between baseline age and CT scan date. Smoking status was recorded by questionnaires with the classifications of "Never smoked", "Former smoker quit more than 1 year ago", "Former smoker quit less than 1 year ago", "Current smoker" and "Don't know" (Al Rifai et al., 2017). Physical activity status was expressed as "Total intentional exercise" described by Bapat et al (Bapat et al., 2015), which sums up all walking, sporting, dancing, and conditioning activities of each participant, then multiplied by metabolic equivalent (MET) level. Alcohol consumption status was categorized as "yes" and "no". Urine and kidney function variables were also assessed. Except for urinary creatinine, all urine and kidney function variables (serum creatinine, urine specific gravity and estimated glomerular filtration rate (eGFR) were baseline measurements.

2.6 Statistical Analysis

Natural-log transformation was applied to non-normal distributed variables, except for abdominal muscle density, which were left-skewed and were square transformed. Descriptive analysis of geometric mean, median, standard deviation and interquartile ranges were reported for continuous variables. Frequency and percentage were reported for categorical demographic variables (sex, race/ethnicity, exam region and smoking status). Correlations between urinary exposures and body composition measurements were evaluated by Spearman correlation tests.

In the first linear regression analysis, the association of each body composition measurement with categorical urinary Cd and urinary ΣAs were evaluated by multiple linear regression models. In these models, urinary Cd and ΣAs were categorized into four levels by quartiles. Differences between the reference level (the lowest quartile) and higher quartiles were estimated in the linear regression models. In the second linear analysis, the association of each body composition measurement with continuous urinary Cd and urinary ΣAs were evaluated. For both categorical and continuous approaches, Model 1 (basic model) was adjusted for age, sex, race/ethnicity, exam region, urinary creatinine and eGFR; Model 2 (advanced model) included all variables from Model 1 plus smoking status and exercise status.

The proportion of urinary As species (iAs%, MMA% and DMA%) were analyzed as continuous variables and the associations were expressed as a unit of 10% increase. As previously reported (Grau-Perez et al., 2017), two approaches were used for the As metabolite models. The "conventional approach" included only one As species in each regression model, while the "leave-one-out approach" included two in each model. The second As species variable in the leave-one-out approach was treated as a fixed adjustment, so that the non-included species was treated as a decrease of 10%. For example, if MMA% is the target species to be analyzed, and is adjusted for

iAs% in the leave-one-out model, DMA%, which is the species being left, is considered as a 10% decrease in this model, since MMA% + iAs% + DMA% = 100%. Both Model 1 (Basic Model) and Model 2 (Advanced Model) mentioned in the previous paragraph were used for both approaches, and were further adjusted for log-transformed ΣAs. All statistical analysis was conducted by SAS 9.4 (SAS Institute Inc., Cary, NC). The level of significance of all statistical tests was chosen as $p<0.05$.

3.0 Association of Arsenic Exposure and Metabolism with Body Composition: The Multi-Ethnic Study of Atherosclerosis (MESA)

In preparation for submission.

3.1 Introduction

Chronic As exposure is a global public health concern. There is substantial disease burden in large populations exposed to naturally occurring As in drinking water and food in many countries throughout the world (Chowdhury et al., 2018; D'Ippoliti et al., 2015; Gonzales et al., 2018; Kuo et al., 2017; Moon et al., 2017; Raessler, 2018; Spratlen et al., 2018). While environmental exposures have been linked to increased risk of cancers, there is a growing body of evidence that associates As exposure with increased risk of cardiometabolic diseases, such as CVDs (Kuo et al., 2017; Moon et al., 2017; Stea et al., 2014), IR (Peng et al., 2015) and DM2 (Castriota et al., 2018; Grau-Perez et al., 2017; Islam et al., 2012; Kim & Lee, 2011; Maull et al., 2012; Navas-Acien et al., 2008; Wang et al., 2014). These increased risks have been observed even in countries perceived to have relatively low levels of exposure and has been shown in several prospective cohort studies in diverse populations within the United States (Gribble et al., 2012; James et al., 2015; James et al., 2013; Moon et al., 2017; Spratlen et al., 2018). However, questions remain regarding the underlying pathogenic mechanisms through which As increases cardiometabolic disease risk.

It is widely accepted that being overweight and obese (i.e., higher BMI) significantly increases the risk of cardiometabolic diseases (Alpert et al., 2016; Ha & Bauer, 2018; Lavie et al., 2016; Lu et al., 2015; Patel et al., 2016; Seravalle & Grassi, 2017). However, India and Bangladesh have the second highest number of people with DM2 in the world, but the average BMI of the populations is relatively low (Paul et al., 2019; Unnikrishnan et al., 2016). Epidemiological studies also showed that for some populations, people with lower BMI may have a higher risk of arterial stiffness (Huisman et al., 2015) and incidence of severe strokes (Funada et al., 2008; Hagii et al., 2018). Being underweight is also associated with developing DM2 (Chilunga et al., 2019; Katanoda et al., 2019) and CVDs (Gao et al., 2016; Katanoda et al., 2019), as well as higher CVD mortality (Senda et al., 2018). Unlike being overweight or obese, the pathophysiology of cardiometabolic diseases among non-obese population is unclear, and body composition, such as loss of lean body mass may be more import determinants of disease risk.

Skeletal muscle comprises approximately 40% of body weight and contains half to two-thirds of total body proteins. As such, it is important for body protein metabolism (Frontera & Ochala, 2015) and is the largest insulin sensitive and glucose consuming organ (Scott et al., 2016). Over the past decade, loss of skeletal muscle area and increase in myosteatosis, ectopic fat infiltration in the muscle, have emerged as important factors predicting metabolic status and muscle function (Correa-de-Araujo et al., 2020; Larsen et al., 2020). Loss of muscle area and quality with an increase in muscle adiposity (e.g. myosteatosis) have broad clinical sequelae including accelerated aging and impaired longevity (Larsen et al., 2020; Santanasto et al., 2017; Vella et al., 2020).

Specifically, loss of muscle area and myosteatosis have been identified as a risk factor for cardiometabolic disorders (Correa-de-Araujo et al., 2020; Miljkovic et al., 2021), such as DM2

(Farsijani et al., 2021; Miljkovic et al., 2016; Miljkovic et al., 2020), hypertension (Zhao et al., 2016), CVDs (Ferreira et al., 2021; Lee et al., 2021; Ma, Levolger, et al., 2021; Miljkovic et al., 2015), increased risk of bone fractures (Lang et al., 2010; Lang et al., 2008), and increased mortality (Ferreira et al., 2021; Reinders et al., 2016) . Loss of muscle area (lean mass) has been found to be associated with IR and DM2 (DeFronzo & Tripathy, 2009; Hickey et al., 1995; Kelley & Goodpaster, 2001; Miljkovic et al., 2013; Son et al., 2017), probably due to the fact that skeletal muscle is the largest insulin-sensitive tissue in the body (Scott et al., 2016). Muscle density, rather than muscle volume/area, appears to be the more sensitive measure of disease risk (Correa-de-Araujo et al., 2020). Myosteatosis has also been recognized as a risk factor of CVD and all-cause mortality (Larsen et al., 2020; Miljkovic et al., 2015; Reinders et al., 2016). While the epidemiological support for a role of muscle loss and increased myosteatosis in aging and disease is growing, the mechanisms responsible for loss of skeletal muscle that is not age related remain largely unknown (Correa-de-Araujo et al., 2020; Miljkovic et al., 2021). Further, the contributions of environmental exposures are even less well known, although there is some evidence that loss of lean muscle mass in a non-obese cohort is associated with As-promoted IR (Mondal et al., 2020).

Measures of inorganic As and its metabolites in blood and urine, as well as total As in nails and hair, are common biomarkers of exposure. Arsenic has a biological half-life of 30 to 60 hours (Crecelius, 1977) in the blood, and both blood and urinary arsenicals are widely used biomarkers that reflects recent As exposures (Zhang et al., 2018). Inorganic As (iAs), which is usually the primary As species ingested, is methylated to MMA and DMA in the liver and excreted in urine (Ratnaike, 2003). Among all urinary As metabolites, DMA is usually the most abundant (60% to 70%), with MMA being approximately 10% to 20% and iAs contributing 10% to 30% (Abuawad

et al., 2021; Spratlen et al., 2018). The ratios of metabolites in the urine are influenced by nutritional status and genetics and methylation capacity can be used as predictors of diseases and metabolic status (Abuawad et al., 2021; Delgado et al., 2021; Pace et al., 2018; Stýblo et al., 2021; Wu et al., 2021).

Several epidemiological studies have reported that total urinary As and the profile of As metabolites are associated with BMI. In general, poor As metabolism (i.e. increased urinary MMA%) has been negatively associated with BMI and efficient metabolism (i.e. increased urinary DMA%) has been positively associated with BMI (Abuawad et al., 2021; Bommarito et al., 2019; Gomez-Rubio et al., 2011; Jansen et al., 2016). These relationships hold even in women in a non-obese population (Abuawad et al., 2021). In addition, A recent longitudinal study of the Strong Heart Study cohort concluded that there are contrasting and independent associations of As exposure and As metabolism with metabolic outcomes that may contribute to cardiometabolic disease risk (Spratlen et al., 2018). However, BMI alone does not convey sufficient information of body composition related to disease risk. Advances in techniques for accessing body composition have steadily improved design of studies that distinguish between “lean mass” and “fat mass” as they relate to cardiometabolic diseases risk (Correa-de-Araujo et al., 2020; Larsen et al., 2020). It has been shown that fat distribution is more important for diseases risk than the quantity of fat in human body. For example, SAT is the natural storage of energy intake, but excess energy intake leads to fat accumulation in VAT instead of SAT (Ibrahim, 2010). VAT accumulation, or “visceral obesity”, increases the risk of inflammation, CVDs, impaired glucose metabolism, and metabolic syndrome (Alexopoulos et al., 2014; Tchernof & Després, 2013). In addition, altered total abdominal fat has been found to be associated with increased VAT and increased risk of cardiometabolic diseases (Vispute et al., 2011).

3.2 Hypothesis and Aims

Since few studies of As effects on body composition have used advanced, direct measures of body composition, we investigated of the association between As metabolism and abdominal body composition using direct CT measurements, as well as anthropometrics. We expected to measure health impacts of As exposures and metabolism in the etiology of disease risks in the MESA cohort, therefore we included MESA participants with urinary measures of As and As metabolites, as well as identified a sub-cohort with CT measures of muscle area, muscle density and fat area (Larsen et al., 2020). It is important to note that these studies contrast greatly with those in Bangladesh (Abuawad et al., 2021; Raessler, 2018; Sarker et al., 2021) and Mexico (Gomez-Rubio et al., 2011), where As exposures were on average much higher than the urban United States cohort in MESA. We hypothesized that higher total urinary As and/or impaired As metabolism would be associated with decreased muscle quality and quantity and harmful abdominal fat distribution and general (BMI) and central (waist) obesity.

3.3 Results

3.3.1 Participant Characteristics (Tables 1 & 2)

In **Table 1** (see **Appendix A**), the mean age at the baseline exam of all participants was 61.11 years old, while the mean age at time of CT-scan was 64.14 years. For urinary arsenical content, means (SD) were iAs 0.51 (0.54) µg/L, MMA 1.06 (1.15) µg/L, DMA 11.21 (14.07) µg/L. Mean (SD) total ΣAs was 12.78 (15.17) µg/L. Mean (SD) percentages of urinary As metabolites

were 4.40 (3.36) for iAs%, 10.35 (4.79) for MMA%, and 85.25 (6.45) for DMA%. We observed that urinary iAs was higher among males than females (mean 0.61 ug/L vs 0.41 ug/L). Males also showed higher percentage of iAs and MMA, but lower DMA in the urine than females.

In **Table 2** (see **Appendix A**), among all participants, mean and standard deviation (SD) of locomotor muscle, stability muscle, and total abdominal muscle area were 28.20 (8.22) cm^2, 113.24 (26.95) cm^2 and 141.33 (32.47) cm^2, respectively. Mean (SD) locomotor muscle, stability muscle, and abdominal muscle density were 39.54 (11.65) cm^2, 13.65 (14.99) cm^2 and 20.16 (13.28) HU, respectively. Males had higher muscle area and muscle density but lower percentage of muscular fat than women. Males also showed significantly higher VAT area and lower SAT area than women. Total abdominal IMAT area was 25.35 (12.21) cm^2, while mean (SD) of VAT area was 146.01 (70.63) cm^2, SAT area was 268.52 (136.37) cm^2.

3.3.2 Correlation of Body Composition with ΣAs (Table 3)

In **Table 3** (see **Appendix A**), we did not observe any significant associations between urinary ΣAs and total abdominal muscle area. However, in the advanced model, participants in exposure quartile 2 had reduced stabilization (β: -4.65, 95% CI: -8.86, -0.44) and total abdominal (β: -3.76, 95% CI: -7.45, -0.07) muscle densities, relative to participants in quartile 1, which is the reference urinary As exposure level. However, in sex-specific models, the significance in muscle density, VAT and SAT partially remained among males, but ΣAs among females showed some significant associations with IMAT (**Supp Table S2** and **Figure 4,** see **Appendix B** and **C**). Conversely, VAT (β: 0.16, 95% CI: 0.00, 0.32) and SAT (β: 0.17, 95% CI: 0.01, 0.32) areas were slightly increased in quartile 2 relative to quartile 1. In addition, both BMI and Waist circumference were slightly increased in both quartiles 2 and 3, relative to quartile 1. Most

significant associations remained in female-only models but not in male-only models. We also built linear models for continuous urinary ΣAs, but no significant results were found **(Supp Table S1**, see **Appendix C).**

3.3.3 Correlation of Body Composition with As Metabolites (Tables 4 - 6)

Table 4 (see **Appendix A)** shows that a 10% increase of iAs% in the conventional model (linear regression model with iAs% as the only independent urinary As species) was associated with lower BMI (β: -0.07, 95% CI: -0.14, -0.01) and waist circumference (β: -0.05, 95% CI: -0.11, 0.00), but was not associated with changes in muscle or fat endpoints in the. However, in the leave-one-out model that adjusted for DMA% ((linear regression model with both iAs% and DMA% as independent urinary As species), iAs% was positively associated with locomotion muscle area (β: -0.07, 95% CI: -0.14, -0.01). The significance remained in male-only models (**Supp Table S3,** see **Appendix C**), and iAs% was positively associated with total abdominal muscle area among males.

In **Table 5** (see **Appendix A**), a 10% increase of MMA% in in the conventional model was associated with both reduced locomotion (β: -0.07, 95% CI: -0.12, -0.02) and stabilization (β: -0.08, 95% CI: -0.14, -0.03) muscle area, as well as reduced abdominal total muscle area (β: -0.08, 95% CI: -0.13, -0.03). In addition, MMA% was associated with lower VAT (β: -0.22, 95% CI: -0.35, -0.08) and SAT (β: -0.20, 95% CI: -0.34, -0.07) areas and with decreased BMI (β: -0.11, 95% CI: -0.17, -0.06) and waist circumference (β: -0.09, 95% CI: -0.13, -0.05). In the Leave-one-out models, when holding iAs% constant while urinary DMA% decreased for 10%, a 10% increase in MMA% was significantly associated with lower locomotion muscle area (β: -0.08, 95% CI -0.13, -0.03), stabilization muscle area (β: -0.08, 95% CI: -0.14, -0.02) and total abdominal muscle area (β: -0.08, 95% CI: -013, -0.03). In the same models, increased MMA% was also associated with

significantly decreased VAT (β: -0.20, 95% CI: -0.34, -0.06) and SAT (β: -0.20, 95% CI: -0.34, -0.06) areas, as well as lower BMI (β: -0.11, 95% CI: -0.16, -0.05) and waist circumference (β: -0.09, 95% CI: -0.13, -0.05).

In **Table 6** (see **Appendix A**), we observed that DMA% showed opposite effects relative to MMA% in the conventional models. Increased DMA% was associated with increased total abdominal muscle areas, total? abdominal fat areas, BMI and waist circumference. Even though no significant associations were found for any abdominal muscle density and intermuscular fat area models, there was a trend that the effects of MMA% and DMA% were opposite. In leave-one-out models, when MMA% was decreased by 10% and iAs% was held constant, a 10% increase in DMA% was associated with higher abdominal muscle area, higher SAT area, VAT area, BMI and waist circumference. We found no significant associations between either MMA% or DMA% with abdominal muscle density or intermuscular fat area.

In all models listed above, we observed no significant associations between As species and total abdominal intermuscular fat area. However, in female-only models (**Supp Tables S4 and S5,** see **Appendix C**), urinary MMA% was negatively, but DMA% was positively associated with total abdominal IMAT. In addition, both sexes presented significant associations of BMI and waist circumference with DMA% and MMA%.

3.4 Discussion

In our study, we found that males have significantly higher VAT area but lower SAT area than women, which was consistent with previous studies (Demerath et al., 2007; Onat et al., 2004; Tchoukalova et al., 2008; Wells, 2007). We also observed gender differences among the urinary

As species, which are also similar with previous reports (Jones et al., 2011; Lindberg et al., 2008). We found that urinary DMA% was positively and MMA% was negatively associated with abdominal muscle area, abdominal fat area (both VAT and SAT), BMI and waist circumference. However, there were only trending associations between total urinary As and body composition variables. These observations and recent reports (Abuawad et al., 2021; Sarker et al., 2021; Wu et al., 2021) suggest that compared to total As exposure levels, As methylation capacity might be an important factor that associates with a broad range of health effects. This is more likely true for low to moderate levels of As exposure and may relate to unknown roles for As3MT in the pathogenesis of cardiometabolic diseases. In contrast, in areas where As levels are high (>200 µg/L in drinking water) inorganic As can influence the metabolite formation (Mondal et al., 2020). Comparing with all-participants models, sex-specific models showed some shifting in significant associations. A previous study of 641 men and 597 women found that the association of body composition with inflammation markers was mostly explained by the proportion of fat-mass among women, but by waist-to-hip ratio among men (Thorand et al., 2006). Therefore, our results showed the possibility that the association between urinary As and body composition might be altered by sex.

After more than three decades of research, there is a consensus that As metabolism promotes elimination, but in the process generates MMA^{III}, commonly thought to be the most toxic As species [reviewed in (Thomas, 2021)]. An increase in MMA% may reflect inefficient elimination of the toxic metabolite, as well as iAs. Whereas, more complete methylation, indicated by increased DMA%, reflects both generation of a less toxic metabolite and more efficient elimination (Thomas, 2021). Incomplete As methylation has been shown to be associated with increased risk of cancers (Abuawad et al., 2021; López-Carrillo et al., 2020; Minatel et al., 2018)

and CVDs (Abuawad et al., 2021; Chen et al., 2013; Newman et al., 2016; Spratlen et al., 2018) Our findings are consistent with other reports of the US population exposed to As (DeFronzo & Tripathy, 2009; Spratlen et al., 2018; Wu et al., 2021) in that BMI, body fat, lean mass and waist circumference were positively associated with urinary DMA% and negatively with urinary MMA% (Gribble et al., 2013). A Similar trend was also reported by the Strong Heart study of DM2, where higher urinary MMA% was significantly associated with higher DM2 incidence, but no significant associations were found for total urinary arsenicals (Kuo et al., 2015). A Bangladesh cohort also showed that lower secondary As methylation capacity, or reduced DMA%, is associated with lower skeletal muscle loss and a higher risk of IR (Mondal et al., 2020; Sarker et al., 2021) . Our results suggest that reduced secondary methylation capacity is involved in the As-induced skeletal muscle loss that may be implicated in As-induced IR and cardiometabolic diseases.

Individual As methylation capacity can be modified by multiple factors, all of them could be cofounders of our study. Age and sex, for example, are the most recognized (Lindberg et al., 2008; Lindberg et al., 2007). Aging is not only a natural cause of As accumulation in the body, but also a risk factor of myosteatosis (Correa-de-Araujo et al., 2020). Studies with multiple populations from Italy, China, Chile and Mexico found significant gender differences on As metabolism, and most showed that women have better As methylation capacity than men. In humans, ingested arsenicals are methylated by arsenite methyltransferase encoded by the *AS3MT* gene (Abuawad et al., 2021; Thomas, 2021). Polymorphisms and epigenetic changes of *AS3MT* gene are associated with different As metabolism capacity (González-Martínez et al., 2020; Minatel et al., 2018; Thomas, 2021). However, individuals with “protective genetic patterns” might show adverse As health effects only at high levels of exposure (Minatel et al., 2018).

However, As exposure itself can be a cofounder, as several studies showed that drinking water quality and As concentration is inversely associated with As methylation capacity (Abuawad et al., 2021; De Loma et al., 2019; Hopenhayn-Rich et al., 1996; Huang et al., 2009; Kong et al., 2020). In the MESA cohort, we observed only weak associations between categorical urinary arsenicals and body composition, but no significant linear associations, reflecting a weak effect of As exposure.

Despite of the variations of As metabolism, factors that impact body composition might also bring uncertainties in this study. Dietary patterns, for example, are shown to be related with body fat and muscle proportion (Fernando et al., 2019; Hashimoto et al., 2016). Both high fat diet and arsenic exposure increase the risk of non-alcoholic fatty liver disease (Berná & Romero-Gomez, 2020; Canet et al., 2012; Frediani et al., 2018; Lian et al., 2020), while fatty liver disease in turn might alter arsenic metabolism and body composition (Milić et al., 2014). Unlike CT-scan measurements, BMI and waist circumference are widely used body composition markers, however, they do not distinguish fat body mass from lean body mass. It is well-accepted that lower BMI and smaller waist circumference are protective factors against cardiometabolic diseases (Khan et al., 2018; Messiah et al., 2012), but BMI itself increases with age until around 60 years old (Elia, 2001), and the association between BMI and amount of body fat is nonlinear (Rothman, 2008). The average age of our population is approximately 61 and with high BMI. Our results might contrast with results of studies in lower BMI populations (for example, in Bangladesh (Mondal et al., 2020; Sarker et al., 2021)). In our study, we did observe that urinary MMA was associated with lower abdominal fat area and lower waist circumference, and lower BMI. However, MMA was also associated with lower abdominal muscle area, suggesting that lower BMI may not be always protective. Adverse health effects brought by skeletal muscle loss might

overshadow the health benefits from of decreased adiposity. Further, the negative health effects of increased MMA% on body mass and composition, as well as skeletal muscle wasting, have been observed in populations with low BMI (Abuawad et al., 2021; Mondal et al., 2020).

In this study, urinary creatinine was used as a correction of metabolic variations. Creatinine is a waste product generated by muscle metabolism and is eliminated by glomerular filtration at a relatively stable rate. Almost all creatinine is stored within skeletal muscle (Barr et al., 2005; O'Brien et al., 2017). In healthy individuals, urinary creatinine is more correlated with lean body mass than fat mass (Bulka et al., 2017). However, conditions that lead to muscle loss could alter creatinine production. It has been reported that urinary creatinine could influence the causal pathway of As exposure to obesity (Bulka et al., 2017; Hall & Gamble, 2012). In contrast, in a population with very low BMI, serum creatinine levels were highly correlated with As exposure and IR, suggesting that negative effects of As on muscle metabolism greatly impact systemic metabolic dysfunction (Mondal et al., 2020).

Mechanisms for how As species affect muscle and fat composition have long been investigated, but the specifics for altering lean body mass are unresolved. Cell and animal experiments suggest that As disrupts signal transduction in both VAT (Ambrosio et al., 2014; Beezhold et al., 2017; Garciafigueroa et al., 2013; Yadav et al., 2013) and skeletal muscle progenitor cells (Ambrosio et al., 2014; Anguiano et al., 2020; Hong & Bain, 2012; Zhang et al., 2016) to impair tissue differentiation, maintenance and function. Interestingly, As impaired adipogenesis in mice VAT, at the same time it increased perivascular adiposity in skeletal muscle (Garciafigueroa et al., 2013). Arsenic species target fat tissue and skeletal muscle mitochondria to disrupt progenitor cell differentiation, tissue regeneration, and physiologic function (Ambrosio et al., 2014; Padmaja Divya et al., 2015). In addition, the mitochondrial dysfunction and resultant

dysfunctional redox biology underlies both functional changes in the tissues and longer-term epigenetic regulation of progenitor cell differentiation and behavior (Anguiano et al., 2020; Cheikhi et al., 2019; Hong & Bain, 2012), as well as IR (Padmaja Divya et al., 2015). Thus, future mechanistic studies on cellular and molecular levels are desired.

The strength of our study lies in directly determining body composition by gold standard CT measurements, and urinary As species in the same individuals along with measures of important confounders. The sensitivity of the As species measurements allowed analysis of the population that was exposed to low-to-moderate As levels. Our limitations include a small sample size and collection of only spot urine samples at baseline examination. Besides, As exposures were also measured at the baseline exam, but CT scans were taken in the later visits. The gap between exposure and health outcomes may impact our findings. What's more, due to limited sample size, we were not able to include dietary habits in our models. In addition, soft tissues move in the abdominal area, the change of their locations might cause bias in studies with only one CT slice (Shuster et al., 2012). Finally, the cross-sectional study design also lacks the ability to elucidate causal relationships. Future prospective studies with larger sample sizes are warranted.

3.5 Conclusion

In conclusion, our study shows that impaired As metabolism is associated with and may underlie abdominal muscle loss, abdominal VAT and VST changes that related to risk of cardiometabolic diseases. Poor metabolism with increased urinary MMA% may be a better correlate of decreased muscle quality at low level As exposure than total urinary As. More in depth, prospective studies are needed to determine interventional strategies to mitigate the effects of

impaired As metabolism on muscle loss and metabolism, as reducing total As exposure may not be a feasible means of protecting this population with low exposures.

4.0 The Association of Cadmium Exposure with Body Composition: Evidence from the Multi-Ethnic Study of Atherosclerosis (MESA)

In preparation for submission

4.1 Introduction

Cadmium (Cd) is a toxic transition metal element that exists naturally in the environment, mainly found in the earth's crust. Cd can be released by human activities such as fossil fuel burning, metal ore combustion, metal refinery and waste burning (Rafati Rahimzadeh et al., 2017). Exposure routes of Cd include inhalation, consumption of contaminated water and food, such as vegetables grown in Cd-polluted soil (Nordberg, 2009; Rafati Rahimzadeh et al., 2017). Tobacco and cigarette smoke, even from involuntary exposure, are also important sources of Cd exposure (Jung et al., 2017; Li et al., 2020; Richter et al., 2017). Total daily Cd intake from all sources in North America and Europe ranges from 30 to 50 μg Cd per day, although only about 10% or less is retained (ATSDR, 2012). This is primarily due to a low absorption rate as only 10% to 50% of inhaled Cd or 6% of orally ingested Cd is absorbed (ATSDR, 2012), Cadmium chloride ($CdCl_2$) is the primary form of oral exposure due to its water solubility, while cadmium oxide (CdO) is the common form of inhalation exposure (Zalups & Ahmad, 2003).

The small amount of Cd absorbed is very poorly excreted with only about 0.001% of the body burden being excreted per day. Cd binds to albumin and erythrocytes in the blood stream and is distributed to tissues and organs, such as liver, kidney and spleen (Diaz et al., 2021; Reyes-

Hinojosa et al., 2019). This is due to Cd binding to sulfur rich, low molecular mass intracellular proteins called metallothioneins (MT) to form a storage depot (Fatima et al., 2019). Released free Cd from Cd-MT complexes travels back into the circulation system and becomes a source of intracellular and systemic oxidative stress (Diaz et al., 2021; Fatima et al., 2019; Reyes-Hinojosa et al., 2019). Cd-MT complexes are mostly retained in the kidneys and liver (Friberg, 1984; Jain, 2020; Satarug, 2012; Satarug et al., 2017) and the complexes are extremely stable in the kidney with accumulation in proximal renal tubule cells and slow excretion in urine (Diaz et al., 2021; Reyes-Hinojosa et al., 2019). The biological half-life of Cd in human body can be 13 to 17 years and even longer (Diaz et al., 2021; Faroon et al., 2012; Fatima et al., 2019). Chronic Cd exposure has been reported to be associated with altered liver enzyme levels and liver diseases (Wang et al., 2021), osteoporosis (Genchi et al., 2020; Reyes-Hinojosa et al., 2019), kidney damage (Johri et al., 2010), endocrine disruption (Henson & Chedrese, 2004), immune disorders (Richter et al., 2017) and cancer (Genchi et al., 2020). Cadmium ranks seventh on the ATSDR priority list and is identified as a human carcinogen (ATSDR, 2012).

Cardiometabolic diseases have become a global public health concern. According to the World Health Organization (WHO), the worldwide prevalence of DM2 among people 18 years and older increased from 4.7% to 8.5% during the year 1980 to 2014 (WHO), and is estimated to be 10.2% (578 million individuals) by 2030 (Saeedi et al., 2019). Considerable evidence show that Cd exposure is related with increased CVD risk (Oliveira et al., 2019), including the development of atherosclerotic plaques, CVDs, coronary heart disease, stroke, and peripheral arterial disease as well as higher CVD related mortality (Bergström et al., 2015; Tellez-Plaza, Jones, et al., 2013; Tellez-Plaza et al., 2012). Cd exposure is also a possible risk factor for impaired blood glucose

uptake and DM2 development (Hansen et al., 2017; Schwartz et al., 2003; Treviño et al., 2015; Xiao et al., 2021).

Body composition, such as the proportion of fat and lean mass, is associated with cardiometabolic diseases (Alpert et al., 2016; Ha & Bauer, 2018; Lavie et al., 2016; Lu et al., 2015; Patel et al., 2016; Seravalle & Grassi, 2017). Human body fat consists of subcutaneous fat (or subcutaneous adipose tissue, SAT, 80-90%), visceral fat (or visceral adipose tissue, VAT, 5-10%) and perivascular fat (2-3%) (Le Jemtel et al., 2018). Excessive body fat accumulation is a risk factor of cardiometabolic diseases (Le Jemtel et al., 2018; Patel et al., 2016). BMI and waist circumference are anthropometric measurements commonly used to estimate overweight and obesity. It is widely reported that higher BMI and waist circumference are associated with higher risk of cardiometabolic diseases (Khan et al., 2018; Messiah et al., 2012). Reports of Cd impacts on BMI have been mixed. A report from Canada showed that people with class II and III obesity had significantly lower blood Cd than people with normal BMI, meanwhile underweight people had significantly higher urinary Cd than people with normal BMI (Garner & Levallois, 2016). Similarly, a Spanish study found that BMI was inversely associated with fat tissue Cd (Echeverría et al., 2019). A study from the U.S. found that mean BMI significantly decreased with the increasing of urinary Cd concentration (Tellez-Plaza, Guallar, Howard, et al., 2013). However, another U.S. study showed the opposite trend (Jiang et al., 2018). A Korean study found no associations between body fat percentage and blood Cd (Park & Lee, 2013), while a study in rodents observed that Cd reduced adipocyte size (Kawakami et al., 2010).

Skeletal muscle is a main part of total lean body mass. Skeletal muscle contains half to two thirds of total body proteins and is essential for body protein metabolism (Frontera & Ochala, 2015). Skeletal muscle is also the largest glucose consuming organ (Scott et al., 2016). Abnormal

fat tissue infiltration (e.g. myosteatosis) is one of the factors that cause muscle loss and lower muscle quality. Lower muscle quality and myosteatosis increase the risk of cardiometabolic diseases, such as DM2 (Farsijani et al., 2021; Miljkovic et al., 2016; Miljkovic et al., 2020) and CVDs (Farsijani et al., 2021; Ferreira et al., 2021; Lee et al., 2021; Ma, Levolger, et al., 2021). In cell culture experiments using C2C12 muscle cells, Cd exposure produced injury-like effects and decreased differentiation into myotubes (Papa et al., 2014). Another study in C2C12 cells found that Cd exposure was associated with altered cell morphology, adhesion, and decreased formation of vesicles, the result of oxidative damage (Yano & Marcondes, 2005). Epidemiological studies on the association of Cd and skeletal muscle are lacking.

Some studies showed that Cd exposure impacts both body composition and cardiometabolic diseases. A Korean study found that blood Cd increased the risk of osteoporosis among males with BMI≥25 kg/m^2, but not no significant association was found among males with BMI<25 kg/m^2 (Choi & Han, 2015). In a study in the United States, significantly negative association between urinary Cd and bone mineral density was observed among perimenopausal women with BMI≥27 kg/m^2, but not those with BMI<27 kg/m^2 (Gallagher et al., 2010). In addition, higher fat tissue Cd concentrations was observed to be associated with DM2 risk, especially for smokers, who showed higher hazard ratio of insulin levels and IR, comparing to non-smokers (Salcedo-Bellido et al., 2021).

4.2 Hypothesis and Aims

The aim of this study was to investigate the association between Cd and body composition using advanced measures of composition. We investigated a sub-cohort from MESA with urinary

Cd measurements and abdominal CT scans. We hypothesized that changes body composition, such as muscle area, density, and IMAT content, might be markers for cardiometabolic disease risk association of with Cd exposure.

4.3 Results

4.3.1 Participant Characteristics (Tables 1 & 2)

In **Table 1** (see **Appendix A**), the mean (SD) age at the baseline exam of all participants was 61.11 (9.85) years old and the mean (SD) age at CT scan was 64.14 (9.90) years old. Mean (SD) urinary Cd among all participants was 0.50 (0.59) μg/L. The 25% and 75% percentile of urinary Cd was 0.28 μg/L and 0.82 μg/L. Females had slightly higher urinary mean (SD) Cd levels than males, which was 0.55 (0.59) μg/L compared to 0.46 (0.45) μg/L. At baseline examination, 44.17% participants had hypertension, 26.15% participants had abnormal blood glucose or DM2. 48.06% participants were never smokers.

We observed sex differences in body composition in **Table 2** (see **Appendix A**). Among females, 38.57% were non-overweight, but the percentage was 29.37 for males. CT-scan analysis showed that among females, mean (SD) of area locomotor muscle, stability muscle, and total abdominal muscle were 22.08 (21.37) cm^2, 101.91 (98.74) cm^2 and 123.99 (121.64) cm2, respectively. For males, mean (SD) area of locomotor muscle, stability muscle, and total abdominal muscle were 34.19 (6.67) cm^2, 124.66 (27.77) cm^2 and 158.81 (31.38) cm^2, respectively. For muscle density, females' mean (SD) density of locomotor muscle, stability muscle, and abdominal muscle were 35.02 (37.30) cm^2, 7.86 (8.85) cm^2 and 14.65 (14.63) HU,

respectively; while the measurements for males were 43.97 (8.85) cm2, 19.32 (13.16) cm^2 and 25.55 (11.24) HU, respectively. No significant sex differences were observed for IMAT area, which was 25.35 (12.21) cm^2 for all participants. However, IMAT percentage was significantly higher among females than males. Mean (SD) of VAT area was 131.09 (114.68) cm^2 for females, 160.51.01 (73.12) cm^2 for males. Mean (SD) SAT area was 316.98 (283.43) cm^2 for females, 217.78 (109.69) cm^2 for males. BMI and waist circumferences showed no differences between females and males. Mean (SD) baseline BMI was 28.05 (5.81) kg/cm^2 and mean (SD) waist circumference was 97.96 (15.37) cm.

4.3.2 Correlation of Body Composition with Urinary Cd (Tables 7 & 8)

When urinary Cd was treated as a categorical variable (**Table 7,** see **Appendix A**), the were no statistically significant associations between urinary Cd and muscle area. However, when comparing quartiles of exposure, there were trends for association between Cd, muscle density, and IMAT when the second quartile (0.28-0.5 ug Cd /L) with the lowest quantile of urinary Cd (reference level, 0 - 0.28 μg Cd/L). The second quartile of exposure was associated with a 4.98 (95% CI -9.24, -0.72) log-transformed HU decrease of stabilization muscle density in the full model. Similarly, the second quantile of urinary Cd was associated with an of 0.18 (95% CI 0.03, 0.33) unit (log-transformed cm^2) increase of stabilization muscle fat area, and an increase of 0.17 (95% CI 0.02, 0.32) units of total abdominal muscle fat area. The trend of positive association with IMAT remained in the higher quantiles of urinary Cd, but no significant associations were observed. Significance was also lost when the same models were run by sex (**Supp Table S6,** see **Appendix C**). In models where urinary Cd were treated as a continuous variable, there were no significant associations (**Table 8,** see **Appendix A**). Sex-specific models (**Supp Table S7,** see

Appendix C) also showed no significant associations, but an opposite trend was observed for the association of urinary Cd with muscle density.

4.4 Discussion

The relationship between Cd exposure and cardiometabolic diseases has been well studied in diverse populations. A study of 1171 adults in Spain found that the hazard ratio (HR) of Cd for the incidence of CVD is 1.46 (95% confidence interval = 1.13-1.88) (Domingo-Relloso et al., 2019). For 3348 adults in the Strong Heart Study of U.S. American Indian communities, urinary Cd was associated with elevated CVD mortality (HR=1.43, 95% CI 1.32-1.70) and coronary heart disease (HR=1.34, 95% CI1.10–1.63) (Tellez-Plaza, Guallar, Howard, et al., 2013). Study of another cohort of 3047 individuals in the Strong Heart Study showed that urinary Cd was positively associated with higher hypertension risk and faster yearly increase of diastolic and systolic blood pressure level (Oliver-Williams et al., 2018). It was also found that higher urinary Cd was associated with increased incidence of peripheral arterial disease (PAD) with a HR of 1.41 (95% CI = 1.05-1.81) (Tellez-Plaza, Guallar, Fabsitz, et al., 2013). A similar study of 1359 senior women in Australia showed that urinary Cd was associated with increased risk of heart failure (HR = 1.17, 95% CI 1.01-1.35) and heart failure related death (HR = 1.36, 95% CI 1.11-1.67) (Deering et al., 2018). A recent study of NHANES data examined the relationship of urinary Cd and CVD in 38,223 participants and found a positive relationship to both the overall risk of CVD and the risks of its subtypes, including congestive heart failure, coronary heart disease, heart attack, and stroke (Ma, Zhang, et al., 2021). Another study of 8722 NHANES participants found that when urinary Cd level elevated from 1-1.99 to > 2 μg/g creatinine, the odds ratio (OR) for DM2 increased from

1.24 to 1.45, and the OR for impaired fasting blood glucose increased from 1.48 to 2.05 (Schwartz et al., 2003). A study in Korea of 719 residents living near abandoned metal mines observed an OR of 1.81(95% CI = 1.05-3.12) for the effects of urinary Cd on DM2 prevalence (Son et al., 2015). However, a recent review of systematic reviews found that associations of smoking-independent Cd exposures with cardiometabolic disease risks showed mixed results potentially complicated by non-linear dose-response relationships (Fagerberg & Barregard, 2021).

Since skeletal muscle quality and composition are important markers of cardiometabolic disease risk, the current study explored the association of changes in muscle composition with Cd exposures. The findings that males and females differ in body composition were not surprising, but it was interesting to observe that males had higher muscle area and muscle density, but lower percentage of IMAT, than women. As we previously reported (Demerath et al., 2007; Onat et al., 2004; Tchoukalova et al., 2008; Wells, 2007), we also observed that, male VAT areas were significantly higher than female, but male SAT areas were lower. However, we did not observe significant associations, or dose response relationships, of urinary Cd and body composition, unless we segregated the participants into quartiles of exposure and focused on specific measures of composition. The most significant changes were in Cd-associated decreased density in stabilization muscles concomitant with increased IMAT. The trends were similar in total abdominal muscle composition, but not locomotion muscles, which may reflect the different types of muscle fibers in the different muscles. The trends were similar in total abdominal muscle composition, but not locomotion muscles, which may reflect the different types of muscle fibers in the different muscle groups. Stabilization muscles have a predominance of glycolytic fibers, whereas locomotion muscles have more oxidative fibers. Thus, the differential response to Cd may reflect impacts on the different mechanisms of energy metabolism in the muscles.

In addition to our small sample size, there are several limitations to the study that might contribute to the findings of trends in the association with specific body composition measures. First, the health effects of Cd exposure level in our population might not be linear. According to previous studies, the mean level of urinary Cd among US adults is around 0.22 – 0.25 μg/L (Adams & Newcomb, 2014; Buser et al., 2016; Wang, Mukherjee, et al., 2018), or 0.28 – 0.52 μg/g creatinine (Hyder et al., 2013; Tellez-Plaza et al., 2012), but the range of standard deviation varies. In our population, mean urinary Cd was 0.50 μg/L (or 0.68 μg/g creatinine), slightly higher than the US average level. In our models of categorical Cd exposures, significant associations were mostly found with the second quartile levels of exposure, but disappeared at higher Cd exposures. These finding may be in line with a threshold effect that was suggested in systematic review of Cd effects on CVD (Fagerberg & Barregard, 2021), but the variation in muscle composition in the small sample size may have obscured the significance of the data. However, a Danish study, where a mean urinary Cd of 0.19 μg/g creatinine were measured, found a similar pattern of Cd associated CVD endpoints. The Cd exposures were shown to increase the risk of ischemic and hemorrhagic stroke, but the curve was not "smooth" at lower levels of Cd body burden (Poulsen et al., 2021).

A second limitation came from the lack of sufficient power to determine whether Cd associated changes in body composition was dependent on sex. Sex-specific differences in Cd body burden have been identified in many Cd studies; most of them showed that women have higher Cd body burden than men, for both blood and urinary Cd (Eom et al., 2018; Jain, 2017; Kim et al., 2017; Madrigal et al., 2019). We also observed higher Cd levels among females. The health impacts of Cd also show sex-specific trends. An US study found that Cd exposure was only associated with higher cardiovascular and coronary heart diseases mortalities among men, but not women (Menke et al., 2009). A study of NHANES that compared participants enrolled in

1988~1994 and 1999~2006 showed that urinary Cd level among males decreased significantly, but not among females (Ferraro et al., 2012). Another NHANES study of 3552 adults found that urinary Cd was associated with increased risk of prediabetes, but the association was more significant among males than females (Jiang et al., 2018). However, in our study, there were no significant differences in the associations among males and females. It was assumed that women of reproductive age have higher gastrointestinal and pulmonary Cd absorption rates than men (Barregard et al., 2013; Meltzer et al., 2010; Satarug et al., 2017; Sun et al., 2016). Hormone levels and the tendency of iron deficiency among women might also be contributors (Kim et al., 2014; Lee & Kim, 2012). Increased numbers of male and female participants in our population may have allowed better assessment of differences in Cd-associated trends.

With the low numbers of the MESA cohort with both CT scans and Cd exposure, we were not able to account for lifestyle factors that might be confounders to our study. We did not have the power of recent systematic reviews to focus on smoking-independent Cd exposures that might have better revealed dose-dependent effects (Fagerberg & Barregard, 2021). Cigarette smoking is a major, important route of Cd exposure (Domingo-Relloso et al., 2020). We included smoking status in our models, but there are trends in e-cigarette consumption that might not have been accounted for. It has been reported in multiple studies that e-cigarettes contain toxic metals including Cd, lead and nickel (Hess et al., 2017; Zhao et al., 2020). We could not exclude the possible impacts of e-cigarettes. Diet is also an important route of Cd exposure. Dietary supplements such as curcumin could reduce Cd toxicity (Mohajeri et al., 2017). Some vegetables, such as soybean, garlic and curry leaf, are found to contain vitamins and metals that help reduce the toxicity of Cd in human body (Pérez Díaz et al., 2019; Wang et al., 2021). However, leafy vegetables have higher chance of absorbing Cd from the soil and might lead to higher exposure

risk (Huang et al., 2020). A study of male adult mice found that, comparing with normal diet without Cd exposure, high fat diet combined with oral Cd exposure was associated with lower body weight, but higher blood glucose and higher total cholesterol level (Kawakami et al., 2013). In our study, we did not adjust for detailed dietary information due to the lack of power.

Due to the lack of power, we included region of recruitment as only one variable in the models, but could not adjust for more details. The distribution of Cd is different across the U.S. In **Figure 5** (**see Appendix B**), we compared the percentage of people distributed in each quartile among different testing regions of our population. It seems that regional difference of exposure patterns exists. What's more, co-exposures of other pollutants might also play a role. Like our previous As study, it has been found that As exposure is also associated with higher cardiometabolic diseases risk (Kuo et al., 2017; Moon et al., 2017; Stea et al., 2014), hypertension (Grau-Perez et al., 2017; Hall et al., 2017; Yu et al., 2017) and body composition changes (Gomez-Rubio et al., 2011; Gribble et al., 2013). In **Figure 6** (**see Appendix B**), we observed that As and Cd body burden in our population is highly correlated. It is possible that the significant results we observed were driven by As. On the other hand, if As works the opposite way to Cd, the effects of Cd might be weakened.

Finally, it is not clear that urinary Cd measures accurately reflect the burden of pathogenic Cd in different tissues. For example, like urinary Cd, blood Cd levels have been associated with both cardiometabolic diseases risk and body shape (Jeong et al., 2020; Madrigal et al., 2019). While blood and urinary Cd levels are correlated (Shimbo et al., 2000), the kinetics vary greatly. Cd is retained the circulation for only 75 to 128 days, reflecting only relatively recent exposures (Bernhoft, 2013). In contrast, urinary Cd, with a biological half-life of decades, is a more stable biomarker of Cd body burden (Grau-Perez et al., 2021; Nordberg et al., 2014). Further, Cd burden

is associated with glomerular filtration rate, in a sex-specific manner (Hwangbo et al., 2011; Madrigal et al., 2019). In our study, Cd was measured in a one-time spot urine, but due to the long half-life, the measurement is reliable but may not reflect longitudinal metal exposure to the muscles that drives compositional changes.

In summary, the strength of our study is that we used CT-scans to measure body composition. These measures can serve as a gold standard of distinguishing lean and fat body mass. Our major limitation is a small sample size. In addition, urinary Cd was measured at the baseline exam, but CT scans were taken in the later visits. However, due to the long half-life of Cd in human body, the time gap might not cause biased results. Finally, the cross-sectional study design lacks the ability to elucidate causal relationships.

4.5 Conclusion

Our results do not support a conclusion that urinary Cd is associated with body composition in general. However, it is unsafe to conclude that Cd exposure does cause pathogenic changes in body composition in our population. There may be specific changes in select muscle types, such as stabilization muscles, that correlate with Cd exposures. Future prospective studies with larger sample sizes will be needed to establish whether the trends in relationships are significant, dose-dependent, and demonstrate sexual dimorphisms.

5.0 Conclusion and Future Directions

5.1 Strengths and Limitations

The biggest strength of our studies lies in the fact that we used CT-scans to measure body composition. These measurements distinguish lean and fat body mass directly. CT-scan serves as a gold standard of body composition analysis. In the arsenic study, we included both total urinary arsenicals and As species in our models to reflected the impact of arsenic metabolism, rather than arsenic body burden alone, on body composition. Our arsenic study also provided evidence for low to moderate As exposure.

Our major limitation is the small sample size, which included only 283 participants. Due to the lack of power, we were not able to adjust for dietary habits or other potential confounders in our regression models. Another limitation is that, As and Cd exposures were generated from one spot urine sample without repeated measurements. In addition, urine samples were obtained at the baseline exam, probably years before abdominal CT scans were taken in the later visits. However, due to the stable metabolic status of As and long half-life of Cd in human body, the time gap might not cause biased results. Finally, the cross-sectional study design lacks the ability to elucidate causal relationships.

5.2 Conclusion

Our results do not support a conclusion that urinary Cd is associated with body composition in general. However, it is possible that there may be specific changes in select muscle types, such as stabilization muscles, that correlate with Cd exposures

Our results may not support that the total amount of urinary arsenicals is associated with body composition changes. However, we found that impaired As metabolism, such as higher MMA% and lower DMA% in urine, is associated with and may underlie abdominal muscle loss, abdominal VAT and SAT changes related to risk of cardiometabolic diseases. Arsenic metabolism may be a better correlate of body composition than total urinary arsenicals.

5.3 Future Directions

Our study provides evidence that environmental exposures may serve as hidden risk factors of cardiometabolic diseases. The findings suggest that maintaining a healthy body composition might be a main direction for cardiometabolic diseases prevention. Future prospective studies with larger sample sizes are desired to demonstrate whether the trends in relationships of metal exposures with body composition are significant, dose-dependent, and sexual-dimorphic.

Appendix A Tables

Table 1 Demographic Information

	All Participants		Females		Males		Sex Difference
	Mean (SD)	Frequency (%)	Mean (SD)	Frequency (%)	Mean (SD)	Frequency (%)	P-value
Age							
At Exam 1	61.11 (9.85)		61.64 (61.00)		60.59 (10.30)		0.3718
At CT-Exam	64.14 (9.90)		64.73 (63.82)		63.55 (10.26)		0.3161
Sex							
Female		140 (49.47)		140 (100.00)		0 (0.00)	N/A
Male		143 (50.53)		0 (0.00)		143 (100.00)	
Race							
White, Caucasian		116 (40.99)		54 (38.57)		62 (43.36)	0.0826
Chinese American		47 (16.61)		21 (15.00)		26 (18.18)	
Black, African-American		50 (17.67)		33 (23.57)		17 (11.89)	
Hispanic		70 (24.73)		32 (22.86)		38 (26.57)	
Region							
Wake Forest University, Winston Salem		54 (19.08)		29 (20.71)		25 (17.48)	0.0842
Columbia University, New York		65 (22.97)		40 (28.57)		25 (17.48)	
Johns Hopkins University, Baltimore		0 (0.00)		0 (0.00)		0 (0.00)	
University of Minnesota, Twin Cities		55 (19.43)		22 (15.71)		33 (23.08)	
Northwestern University, Chicago		56 (19.79)		28 (20.00)		28 (19.58)	
University of California, Los Angeles		53 (18.73)		21 (15.00)		32 (22.38)	
Smoking							
Never smoked		136 (48.06)		78 (55.71)		58 (40.56)	0.0621
Former smoker quit more than 1 year ago		103 (36.40)		43 (30.71)		60 (41.96)	
Former smoker quit less than 1 year ago		4 (1.41)		2 (1.43)		2 (1.40)	
Current smoker		37 (13.07)		17 (12.14)		20 (13.99)	
Don't know		3 (1.06)		0 (0)		3 (2.10)	
Alcohol Consumption							
Current use: No		112 (39.58)		61 (43.57)		51 (35.66)	0.1738
Current use: Yes		171 (60.42)		79 (56.43)		92 (64.34)	

	All Participants		Females		Males		Sex Difference
	Mean (SD)	**Frequency (%)**	**Mean (SD)**	**Frequency (%)**	**Mean (SD)**	**Frequency (%)**	**P-value**
Total Intentional Exercise	1348.30 (2092.26)		1141.27 (630.00)		1551.00 (2518.95)		0.0996
Diabetes Status							
Normal		209 (73.85)		109 (77.86)		100 (69.93)	0.3162
Impaired fasting glucose		51 (18.02)		23 (16.43)		28 (19.58)	
Untreated diabetes		5 (1.77)		1 (0.71)		4 (2.80)	
Treated diabetes		18 (6.36)		7 (5.00)		11 (7.69)	
Hypertension							
No		158 (55.83)		74 (52.86)		84 (58.74)	0.3190
Yes		125 (44.17)		66 (47.14)		59 (41.26)	
Overweight							
Normal weight		96 (33.92)		54 (38.57)		42 (29.37)	**0.0096**
Grade 1 overweight		92 (32.51)		34 (24.29)		58 (40.56)	
Grade 2 overweight		85 (30.04)		44 (31.43)		41 (28.67)	
Grade 3 overweight		10 (3.53)		8 (5.71)		2 (1.40)	
Arsenic Species (µg/L)							
Inorganic arsenic (iAs)	0.51 (0.54)		0.41 (0.29)		0.61 (0.59)		**0.0233**
Monomethylarsonate (MMA)	1.06 (1.15)		0.96 (0.60)		1.16 (1.25)		0.1010
Dimethylarsinate (DMA)	11.21 (14.07)		11.30 (5.55)		11.11 (15.64)		0.9080
Total As (iAs + MMA + DMA)	12.78 (15.17)		12.68 (6.76)		12.88 (16.81)		0.8328
Arsenic Species Percentage							
Inorganic arsenic (iAs%)	4.40 (3.36)		3.60 (3.54)		5.17 (3.50)		**0.0001**
Monomethylarsonate (MMA%)	10.35 (4.79)		9.44 (9.07)		11.21 (5.22)		**0.0022**
Dimethylarsinate (DMA%)	85.25 (6.45)		86.96 (87.52)		83.61 (6.80)		**<.0001**
Urinary Cadmium							
Original (µg/L)	0.50 (0.59)		0.55 (0.69)		0.46 (0.45)		**0.0137**
By creatinine (µg/g creatinine)	0.68 (0.75)		0.89 (0.93)		0.47 (0.42)		**<.0001**
Other Metabolite Variables							
Urinary creatinine	122.73 (68.89)		112.29 (101.20)		133.10 (65.08)		**0.0111**
Serum creatinine at baseline (Exam 1)	1.01 (0.25)		0.91 (0.88)		1.10 (0.27)		**<.0001**
eGFR at baseline (Exam 1)	70.57 (15.96)		67.85 (66.31)		73.18 (16.78)		**0.0055**
Urinary specific gravity	1.01 (0.07)		1.01 (1.02)		1.01 (0.10)		0.3474

Note: *eGFR: estimated glomerular filtration rate.*

Table 2 Body Composition and Anthropometric Measurements

	All Participants	Females	Males	Sex Difference
	Mean (SD)	Mean (SD)	Mean (SD)	P-value
CT Scan Measurements				
Muscle Area				
Locomotor Muscle Area (cm^2)	28.20 (8.22)	22.08 (21.37)	34.19 (6.67)	**<.0001**
Stability Muscle Area (cm^2)	113.24 (26.95)	101.91 (98.74)	124.66 (27.77)	**<.0001**
Total Abdominal Muscle Area (cm^2)	141.33 (32.47)	123.99 (121.64)	158.81 (31.38)	**<.0001**
Muscle Density				
Locomotor Muscle Density (HU)	39.54 (11.65)	35.02 (37.30)	43.97 (8.85)	**<.0001**
Stability Muscle Density (HU)	13.65 (14.99)	7.86 (8.85)	19.32 (13.16)	**<.0001**
Total Abdominal Muscle Density (HU)	20.16 (13.28)	14.65 (14.63)	25.55 (11.24)	**<.0001**
Fat Area				
Locomotor Muscle IMAT Area (cm^2)	2.02 (1.51)	2.17 (1.86)	1.88 (1.27)	0.2524
Stability Muscle IMAT Area (cm^2)	23.36 (11.52)	24.64 (22.40)	22.08 (10.70)	0.0674
Total Abd IMAT Area (cm^2)	25.35 (12.21)	26.80 (23.93)	23.89 (11.27)	0.0521
Visceral Fat Area (cm^2)	146.01 (70.63)	131.09 (114.68)	160.51 (73.12)	**0.0003**
Subcutaneous Fat Area (cm^2)	268.52 (136.37)	316.98 (283.43)	217.78 (109.69)	**<.0001**
Fat Percentage				
Locomotor Muscle IMAT %	7.62 (5.41)	9.71 (8.16)	5.57 (3.62)	**<.0001**
Stability Muscle IMAT %	20.60 (8.59)	23.74 (22.38)	17.44 (6.74)	**<.0001**
Total Abd IMAT %	18.09 (7.77)	21.28 (20.28)	14.87 (5.90)	**<.0001**
Anthropometrics				
BMI (kg/cm^2)	28.05 (5.81)	28.28 (26.67)	27.83 (4.75)	0.8697
Waist Circumference (cm)	97.96 (15.37)	97.50 (93.60)	98.41 (12.55)	0.3483

.

Table 3 Correlation of Body Composition with Categorical ΣAs

		Model 1 (Basic Model)		Model 2 (Advanced Model)	
		Beta (95% CI)	**p-value**	**Beta (95% CI)**	**p-value**
Muscle Area (cm^2)					
Locomotion Area	Q2	0.02 (-0.03, 0.08)	0.3711	0.03 (-0.03, 0.08)	0.3384
	Q3	0.03 (-0.03, 0.09)	0.3355	0.03 (-0.03, 0.09)	0.3062
	Q4	-0.02 (-0.08, 0.04)	0.5495	-0.02 (-0.08, 0.05)	0.5839
Stabilization Area	Q2	0.03 (-0.04, 0.10)	0.3957	0.04 (-0.03, 0.11)	0.2372
	Q3	0.03 (-0.04, 0.11)	0.3630	0.04 (-0.04, 0.11)	0.3102
	Q4	-0.02 (-0.10, 0.06)	0.6384	-0.01 (-0.09, 0.07)	0.8567
Total Abd Muscle Area	Q2	0.03 (-0.03, 0.09)	0.3277	0.04 (-0.02, 0.10)	0.1947
	Q3	0.04 (-0.03, 0.10)	0.2877	0.04 (-0.03, 0.10)	0.2390
	Q4	-0.02 (-0.09, 0.05)	0.5988	-0.01 (-0.08, 0.06)	0.8005
Muscle Density (HU)					
Locomotion Density	Q2	-70.97 (-305.05, 163.12)	0.5510	-75.34 (-310.01, 159.32)	0.5278
	Q3	125.62 (-130.6, 381.85)	0.3352	115.24 (-141.84, 372.32)	0.3782
	Q4	65.61 (-209.5, 340.71)	0.6390	39.77 (-236.58, 316.11)	0.7771
Stabilization Density	Q2	-4.43 (-8.62, -0.23)	**0.0386**	-4.65 (-8.86, -0.44)	**0.0306**
	Q3	2.84 (-1.75, 7.43)	0.2240	2.80 (-1.81, 7.42)	0.2324
	Q4	-0.35 (-5.28, 4.57)	0.8882	-0.70 (-5.66, 4.26)	0.7805
Total Abd Muscle Density	Q2	-3.56 (-7.24, 0.11)	0.0575	-3.76 (-7.45, -0.07)	**0.0460**
	Q3	2.50 (-1.52, 6.52)	0.2224	2.47 (-1.58, 6.51)	0.2306
	Q4	-0.08 (-4.40, 4.24)	0.9722	-0.40 (-4.74, 3.95)	0.8575
Fat Area (cm^2)					
Locomotion Muscle IMAT Area	Q2	0.17 (-0.05, 0.40)	0.1311	0.18 (-0.04, 0.41)	0.1069
	Q3	-0.04 (-0.29, 0.20)	0.7379	-0.04 (-0.28, 0.21)	0.7606
	Q4	-0.03 (-0.30, 0.23)	0.8147	-0.01 (-0.27, 0.26)	0.9551
Stabilization Muscle IMAT Area	Q2	0.13 (-0.03, 0.28)	0.1067	0.04 (-0.03, 0.11)	0.2372
	Q3	0.03 (-0.14, 0.20)	0.7157	0.04 (-0.04, 0.11)	0.3102
	Q4	0.01 (-0.17, 0.19)	0.9193	-0.01 (-0.09, 0.07)	0.8567
Total Abd IMAT Area	Q2	0.13 (-0.02, 0.28)	0.0932	0.14 (-0.01, 0.29)	0.0595
	Q3	0.03 (-0.14, 0.19)	0.7382	0.03 (-0.13, 0.19)	0.7169
	Q4	0.01 (-0.17, 0.18)	0.9303	0.02 (-0.15, 0.20)	0.7831

		Model 1 (Basic Model)		Model 2 (Advanced Model)	
		Beta (95% CI)	**p-value**	**Beta (95% CI)**	**p-value**
Visceral Fat Area	Q2	0.15 (-0.02, 0.31)	0.0762	0.16 (0.00, 0.32)	**0.0489**
	Q3	0.11 (-0.07, 0.29)	0.2277	0.11 (-0.06, 0.29)	0.2127
	Q4	0.02 (-0.17, 0.21)	0.8667	0.03 (-0.16, 0.22)	0.7201
Subcutaneous Fat Area	Q2	0.17 (0.01, 0.32)	**0.0355**	0.17 (0.01, 0.32)	**0.0369**
	Q3	0.12 (-0.05, 0.29)	0.1585	0.13 (-0.04, 0.29)	0.1450
	Q4	0.01 (-0.17, 0.19)	0.8975	0.02 (-0.17, 0.20)	0.8508
Anthropometrics					
BMI (kg/cm^2)	Q2	0.08 (0.02, 0.14)	**0.0125**	0.08 (0.02, 0.15)	**0.0092**
	Q3	0.08 (0.01, 0.15)	**0.0278**	0.08 (0.01, 0.15)	**0.0251**
	Q4	0.03 (-0.04, 0.11)	0.3916	0.04 (-0.04, 0.11)	0.3239
Waist Circumference (cm)	Q2	0.07 (0.02, 0.11)	**0.0087**	0.07 (0.02, 0.12)	**0.0068**
	Q3	0.07 (0.01, 0.12)	**0.0129**	0.07 (0.02, 0.12)	**0.0106**
	Q4	0.03 (-0.02, 0.09)	0.2470	0.04 (-0.02, 0.10)	0.1881

Note: *model 1 was adjusted for age, sex, race, region, urinary creatinine and eGFR. Model 2 further adjusted for smoking[1] and exercise status. eGFR: estimated glomerular filtration rate; iAs: inorganic arsenic; MMA: monomethylarsonic acid; DMA: dimethylarsinic acid.*

Table 4 Correlation of Body Composition with iAs%

		Model 1 (Basic Model)		Model 2 (Advanced Model)	
		Beta (95% CI)	**p-value**	**Beta (95% CI)**	**p-value**
Conventional Model: iAs% as independent variable alone	**Muscle Area (cm^2)**				
	Locomotion Area	0.02 (-0.04, 0.08)	0.5833	0.01 (-0.05, 0.07)	0.6399
	Stabilization Area	-0.04 (-0.12, 0.03)	0.2532	-0.03 (-0.11, 0.04)	0.3641
	Total Abd Muscle Area	-0.03 (-0.10, 0.03)	0.3492	-0.02 (-0.09, 0.04)	0.4609
	Muscle Density (HU)				
	Locomotion Density	158.11 (-99.63, 415.85)	0.2281	132.80 (-126.35, 391.95)	0.3138
	Stabilization Density	2.10 (-2.58, 6.78)	0.3769	1.70 (-3.01, 6.42)	0.4773
	Total Abd Muscle Density	2.29 (-1.80, 6.39)	0.2713	1.92 (-2.21, 6.05)	0.3598
	Fat Area (cm^2)				
	Locomotion Muscle IMAT Area	-0.12 (-0.37, 0.13)	0.3488	-0.09 (-0.34, 0.16)	0.4784
	Stabilization Muscle IMAT Area	-0.07 (-0.24, 0.10)	0.3964	-0.06 (-0.23, 0.11)	0.5091
	Total Abd IMAT Area	-0.07 (-0.24, 0.09)	0.3798	-0.06 (-0.23, 0.11)	0.4975
	Visceral Fat Area	-0.17 (-0.34, 0.01)	0.0644	-0.15 (-0.33, 0.03)	0.0925
	Subcutaneous Fat Area	-0.09 (-0.26, 0.08)	0.3186	-0.09 (-0.26, 0.08)	0.3100
	Anthropometrics				
	BMI (kg/cm^2)	-0.08 (-0.14, -0.01)	**0.0280**	-0.07 (-0.14, -0.01)	**0.0338**
	Waist Circumference (cm)	-0.06 (-0.11, 0.00)	**0.0322**	-0.05 (-0.11, 0.00)	**0.0439**
Leave-One-Out Model 1: iAs% adjusted for MMA% (DMA% ↓10%)	**Muscle Area (cm^2)**				
	Locomotion Area	0.04 (-0.02, 0.10)	0.1938	0.04 (-0.02, 0.10)	0.1966
	Stabilization Area	-0.02 (-0.10, 0.06)	0.6178	-0.01 (-0.08, 0.07)	0.8561
	Total Abd Muscle Area	-0.01 (-0.07, 0.06)	0.8313	0.00 (-0.06, 0.07)	0.9369
	Muscle Density (HU)				
	Locomotion Density	159.24 (-108.15, 426.63)	0.2420	130.61 (-138.28, 399.50)	0.3396
	Stabilization Density	1.72 (-3.13, 6.57)	0.4857	1.27 (-3.62, 6.16)	0.6092
	Total Abd Muscle Density	1.94 (-2.31, 6.18)	0.3698	1.53 (-2.75, 5.81)	0.4829
	Fat Area (cm^2)				
	Locomotion Muscle IMAT Area	-0.07 (-0.33, 0.18)	0.5782	-0.04 (-0.30, 0.21)	0.7461
	Stabilization Muscle IMAT Area	-0.04 (-0.22, 0.13)	0.6447	-0.02 (-0.20, 0.16)	0.8144
	Total Abd IMAT Area	-0.04 (-0.21, 0.13)	0.6443	-0.02 (-0.19, 0.15)	0.8215
	Visceral Fat Area	-0.11 (-0.29, 0.07)	0.2498	-0.09 (-0.27, 0.09)	0.3425
	Subcutaneous Fat Area	-0.03 (-0.21, 0.14)	0.7067	-0.03 (-0.21, 0.14)	0.7098
	Anthropometrics				
	BMI (kg/cm^2)	-0.04 (-0.11, 0.03)	0.2163	-0.04 (-0.11, 0.03)	0.2584
	Waist Circumference (cm)	-0.03 (-0.08, 0.02)	0.2679	-0.03 (-0.08, 0.03)	0.3416

		Model 1 (Basic Model)		Model 2 (Advanced Model)	
		Beta (95% CI)	**p-value**	**Beta (95% CI)**	**p-value**
Leave-One-Out Model 2: iAs% adjusted for DMA% (MMA% ↓10%)	**Muscle Area (cm^2)**				
	Locomotion Area	0.11 (0.03, 0.20)	**0.0116**	0.12 (0.03, 0.20)	**0.0077**
	Stabilization Area	0.05 (-0.06, 0.16)	0.3272	0.08 (-0.03, 0.18)	0.1642
	Total Abd Muscle Area	0.07 (-0.03, 0.16)	0.1713	0.08 (-0.01, 0.18)	0.0752
	Muscle Density (HU)				
	Locomotion Density	162.65 (-217.69, 543.00)	0.4004	123.94 (-259.28, 507.17)	0.5247
	Stabilization Density	0.56 (-6.34, 7.46)	0.8737	-0.05 (-7.02, 6.92)	0.9893
	Total Abd Muscle Density	0.86 (-5.18, 6.90)	0.7798	0.32 (-5.78, 6.42)	0.9173
	Fat Area (cm^2)				
	Locomotion Muscle IMAT Area	0.07 (-0.30, 0.43)	0.7211	0.10 (-0.27, 0.47)	0.5855
	Stabilization Muscle IMAT Area	0.06 (-0.19, 0.31)	0.6506	0.09 (-0.16, 0.34)	0.4807
	Total Abd IMAT Area	0.06 (-0.18, 0.31)	0.6060	0.10 (-0.15, 0.34)	0.4412
	Visceral Fat Area	0.08 (-0.18, 0.34)	0.5352	0.11 (-0.14, 0.37)	0.3914
	Subcutaneous Fat Area	0.16 (-0.09, 0.40)	0.2043	0.17 (-0.08, 0.41)	0.1858
	Anthropometrics				
	BMI (kg/cm^2)	0.06 (-0.04, 0.16)	0.2518	0.07 (-0.03, 0.16)	0.1938
	Waist Circumference (cm)	0.05 (-0.02, 0.13)	0.1580	0.06 (-0.01, 0.14)	0.1099

Note: Model 1 was adjusted for age, sex, race, region, urinary creatinine, eGFR and total urinary arsenicals. Model 2 further adjusted for smoking[1] and exercise status. Unit of change is 10%. All variables were log-transformed, except for muscle densities, which were square root transformed. eGFR: estimated glomerular filtration rate; iAs: inorganic arsenic; MMA: monomethylarsonic acid; DMA: dimethylarsinic acid.

[1] Smoking status are categorized as: Never smoke; Former smoker quit more than 1 year ago; Former smoker quit less than 1 year ago; Current smoke; Don't know.

Table 5 Correlation of Body Composition with MMA%

		Model 1 (Basic Model)		Model 2 (Advanced Model)	
		Beta (95% CI)	**p-value**	**Beta (95% CI)**	**p-value**
Conventional Model: MMA% as independent variable alone	**Muscle Area (cm^2)**				
	Locomotion Area	-0.06 (-0.11, -0.02)	**0.0074**	-0.07 (-0.12, -0.02)	**0.0032**
	Stabilization Area	-0.08 (-0.14, -0.02)	**0.0088**	-0.08 (-0.14, -0.03)	**0.0039**
	Total Abd Muscle Area	-0.08 (-0.13, -0.02)	**0.0038**	-0.08 (-0.13, -0.03)	**0.0014**
	Muscle Density (HU)				
	Locomotion Density	28.98 (-173.95, 231.91)	0.7788	33.39 (-171.37, 238.15)	0.7483
	Stabilization Density	1.51 (-2.16, 5.19)	0.4186	1.58 (-2.14, 5.30)	0.4040
	Total Abd Muscle Density	1.47 (-1.75, 4.69)	0.3683	1.52 (-1.74, 4.77)	0.3596
	Fat Area (cm^2)				
	Locomotion Muscle IMAT Area	-0.15 (-0.35, 0.04)	0.1210	-0.15 (-0.35, 0.04)	0.1255
	Stabilization Muscle IMAT Area	-0.11 (-0.24, 0.03)	0.1136	-0.11 (-0.25, 0.02)	0.0898
	Total Abd IMAT Area	-0.11 (-0.24, 0.02)	0.0890	-0.12 (-0.25, 0.01)	0.0713
	Visceral Fat Area	-0.21 (-0.34, -0.07)	**0.0032**	-0.22 (-0.35, -0.08)	**0.0022**
	Subcutaneous Fat Area	-0.20 (-0.33, -0.06)	**0.0041**	-0.20 (-0.34, -0.07)	**0.0031**
	Anthropometrics				
	BMI (kg/cm^2)	-0.11 (-0.16, -0.06)	**<.0001**	-0.11 (-0.17, -0.06)	**<.0001**
	Waist Circumference (cm)	-0.09 (-0.13, -0.05)	**<.0001**	-0.09 (-0.13, -0.05)	**<.0001**
Leave-One-Out Model 1: MMA% adjusted for iAs% (DMA% ↓10%)	**Muscle Area (cm^2)**				
	Locomotion Area	-0.07 (-0.12, -0.02)	**0.0035**	-0.08 (-0.13, -0.03)	**0.0015**
	Stabilization Area	-0.07 (-0.13, -0.01)	**0.0161**	-0.08 (-0.14, -0.02)	**0.0061**
	Total Abd Muscle Area	-0.07 (-0.13, -0.02)	**0.0061**	-0.08 (-0.13, -0.03)	**0.0019**
	Muscle Density (HU)				
	Locomotion Density	-3.42 (-213.37, 206.53)	0.9745	6.66 (-205.40, 218.72)	0.9507
	Stabilization Density	1.16 (-2.65, 4.97)	0.5484	1.32 (-2.54, 5.18)	0.5014
	Total Abd Muscle Density	1.08 (-2.26, 4.41)	0.5245	1.20 (-2.17, 4.58)	0.4827
	Fat Area (cm^2)				
	Locomotion Muscle IMAT Area	-0.14 (-0.34, 0.06)	0.1762	-0.14 (-0.35, 0.06)	0.1634
	Stabilization Muscle IMAT Area	-0.10 (-0.24, 0.04)	0.1583	-0.11 (-0.25, 0.03)	0.1147
	Total Abd IMAT Area	-0.10 (-0.24, 0.03)	0.1273	-0.12 (-0.25, 0.02)	0.0924
	Visceral Fat Area	-0.19 (-0.33, -0.04)	**0.0103**	-0.20 (-0.34, -0.06)	**0.0064**
	Subcutaneous Fat Area	-0.19 (-0.33, -0.05)	**0.0067**	-0.20 (-0.34, -0.06)	**0.0051**
	Anthropometrics				
	BMI (kg/cm^2)	-0.10 (-0.15, -0.05)	**0.0003**	-0.11 (-0.16, -0.05)	**0.0002**
	Waist Circumference (cm)	-0.08 (-0.13, -0.04)	**<.0001**	-0.09 (-0.13, -0.05)	**<.0001**

		Model 1 (Basic Model)		Model 2 (Advanced Model)	
		Beta (95% CI)	**p-value**	**Beta (95% CI)**	**p-value**
Leave-One-Out Model 2: MMA% adjusted for DMA% (iAs% ↓10%)	**Muscle Area (cm^2)**				
	Locomotion Area	-0.11 (-0.20, -0.03)	**0.0116**	-0.12 (-0.20, -0.03)	**0.0077**
	Stabilization Area	-0.05 (-0.16, 0.06)	0.3272	-0.08 (-0.18, 0.03)	0.1642
	Total Abd Muscle Area	-0.07 (-0.16, 0.03)	0.1713	-0.08 (-0.18, 0.01)	0.0752
	Muscle Density (HU)				
	Locomotion Density	-162.65 (-543.00, 217.69)	0.4004	-123.94 (-507.17, 259.28)	0.5247
	Stabilization Density	-0.56 (-7.46, 6.34)	0.8737	0.05 (-6.92, 7.02)	0.9893
	Total Abd Muscle Density	-0.86 (-6.90, 5.18)	0.7798	-0.32 (-6.42, 5.78)	0.9173
	Fat Area (cm^2)				
	Locomotion Muscle IMAT Area	-0.07 (-0.43, 0.30)	0.7211	-0.10 (-0.47, 0.27)	0.5855
	Stabilization Muscle IMAT Area	-0.06 (-0.31, 0.19)	0.6506	-0.09 (-0.34, 0.16)	0.4807
	Total Abd IMAT Area	-0.06 (-0.31, 0.18)	0.6060	-0.10 (-0.34, 0.15)	0.4412
	Visceral Fat Area	-0.08 (-0.34, 0.18)	0.5352	-0.11 (-0.37, 0.14)	0.3914
	Subcutaneous Fat Area	-0.16 (-0.40, 0.09)	0.2043	-0.17 (-0.41, 0.08)	0.1858
	Anthropometrics				
	BMI (kg/cm^2)	-0.06 (-0.16, 0.04)	0.2518	-0.07 (-0.16, 0.03)	0.1938
	Waist Circumference (cm)	-0.05 (-0.13, 0.02)	0.1580	-0.06 (-0.14, 0.01)	0.1099

Note: Model 1 was adjusted for age, sex, race, region, urinary creatinine, eGFR and total urinary arsenicals. Model 2 further adjusted for smoking[1] and exercise status. Unit of change is 10%. All variables were log-transformed, except for muscle densities, which were square root transformed. eGFR: estimated glomerular filtration rate; iAs: inorganic arsenic; MMA: monomethylarsonic acid; DMA: dimethylarsinic acid.

[1] Smoking status are categorized as: Never smoke; Former smoker quit more than 1 year ago; Former smoker quit less than 1 year ago; Current smoke; Don't know.

Table 6 Correlation of Body Composition with DMA%

		Model 1 (Basic Model)		Model 2 (Advanced Model)	
		Beta (95% CI)	**p-value**	**Beta (95% CI)**	**p-value**
Conventional Model: DMA% as independent variable alone	**Muscle Area (cm^2)**				
	Locomotion Area	0.03 (-0.01, 0.06)	0.1163	0.03 (0.00, 0.06)	0.0725
	Stabilization Area	0.05 (0.01, 0.09)	**0.0131**	0.05 (0.01, 0.09)	**0.0113**
	Total Abd Muscle Area	0.05 (0.01, 0.08)	**0.0106**	0.05 (0.01, 0.08)	**0.0079**
	Muscle Density (HU)				
	Locomotion Density	-62.50 (-204.97, 79.98)	0.3885	-57.10 (-200.62, 86.42)	0.4340
	Stabilization Density	-1.39 (-3.97, 1.19)	0.2906	-1.30 (-3.91, 1.31)	0.3276
	Total Abd Muscle Density	-1.43 (-3.69, 0.83)	0.2148	-1.34 (-3.62, 0.95)	0.2501
	Fat Area (cm^2)				
	Locomotion Muscle IMAT Area	0.11 (-0.02, 0.25)	0.1078	0.10 (-0.03, 0.24)	0.1422
	Stabilization Muscle IMAT Area	0.08 (-0.02, 0.17)	0.1130	0.07 (-0.02, 0.17)	0.1187
	Total Abd IMAT Area	0.08 (-0.01, 0.17)	0.0920	0.08 (-0.01, 0.17)	0.0998
	Visceral Fat Area	0.15 (0.06, 0.25)	**0.0019**	0.15 (0.06, 0.25)	**0.0020**
	Subcutaneous Fat Area	0.13 (0.03, 0.22)	**0.0093**	0.13 (0.04, 0.23)	**0.0075**
	Anthropometrics				
	BMI (kg/cm^2)	0.08 (0.04, 0.11)	**<.0001**	0.08 (0.04, 0.12)	**<.0001**
	Waist Circumference (cm)	0.06 (0.03, 0.09)	**<.0001**	0.06 (0.03, 0.09)	**<.0001**
Leave-One-Out Model 1: DMA% adjusted for iAs% (MMA% ↓10%)	**Muscle Area (cm^2)**				
	Locomotion Area	0.07 (0.02, 0.12)	**0.0035**	0.08 (0.03, 0.13)	**0.0015**
	Stabilization Area	0.07 (0.01, 0.13)	**0.0161**	0.08 (0.02, 0.14)	**0.0061**
	Total Abd Muscle Area	0.07 (0.02, 0.13)	**0.0061**	0.08 (0.03, 0.13)	**0.0019**
	Muscle Density (HU)				
	Locomotion Density	3.42 (-206.53, 213.37)	0.9745	-6.66 (-218.72, 205.40)	0.9507
	Stabilization Density	-1.16 (-4.97, 2.65)	0.5484	-1.32 (-5.18, 2.54)	0.5014
	Total Abd Muscle Density	-1.08 (-4.41, 2.26)	0.5245	-1.20 (-4.58, 2.17)	0.4827
	Fat Area (cm^2)				
	Locomotion Muscle IMAT Area	0.14 (-0.06, 0.34)	0.1762	0.14 (-0.06, 0.35)	0.1634
	Stabilization Muscle IMAT Area	0.10 (-0.04, 0.24)	0.1583	0.11 (-0.03, 0.25)	0.1147
	Total Abd IMAT Area	0.10 (-0.03, 0.24)	0.1273	0.12 (-0.02, 0.25)	0.0924
	Visceral Fat Area	0.19 (0.04, 0.33)	**0.0103**	0.20 (0.06, 0.34)	**0.0064**
	Subcutaneous Fat Area	0.19 (0.05, 0.33)	**0.0067**	0.20 (0.06, 0.34)	**0.0051**
	Anthropometrics				
	BMI (kg/cm^2)	0.10 (0.05, 0.15)	**0.0003**	0.11 (0.05, 0.16)	**0.0002**
	Waist Circumference (cm)	0.08 (0.04, 0.13)	**<.0001**	0.09 (0.05, 0.13)	**<.0001**

		Model 1 (Basic Model)		Model 2 (Advanced Model)	
		Beta (95% CI)	**p-value**	**Beta (95% CI)**	**p-value**
Leave-One-Out Model 2: DMA% adjusted for MMA% (iAs% ↓10%)	**Muscle Area (cm^2)**				
	Locomotion Area	-0.04 (-0.10, 0.02)	0.1938	-0.04 (-0.10, 0.02)	0.1966
	Stabilization Area	0.02 (-0.06, 0.10)	0.6178	0.01 (-0.07, 0.08)	0.8561
	Total Abd Muscle Area	0.01 (-0.06, 0.07)	0.8313	0.00 (-0.07, 0.06)	0.9369
	Muscle Density (HU)				
	Locomotion Density	-159.24 (-426.63, 108.15)	0.2420	-130.61 (-399.50, 138.28)	0.3396
	Stabilization Density	-1.72 (-6.57, 3.13)	0.4857	-1.27 (-6.16, 3.62)	0.6092
	Total Abd Muscle Density	-1.94 (-6.18, 2.31)	0.3698	-1.53 (-5.81, 2.75)	0.4829
	Fat Area (cm^2)				
	Locomotion Muscle IMAT Area	0.07 (-0.18, 0.33)	0.5782	0.04 (-0.21, 0.30)	0.7461
	Stabilization Muscle IMAT Area	0.04 (-0.13, 0.22)	0.6447	0.02 (-0.16, 0.20)	0.8144
	Total Abd IMAT Area	0.04 (-0.13, 0.21)	0.6443	0.02 (-0.15, 0.19)	0.8215
	Visceral Fat Area	0.11 (-0.07, 0.29)	0.2498	0.09 (-0.09, 0.27)	0.3425
	Subcutaneous Fat Area	0.03 (-0.14, 0.21)	0.7067	0.03 (-0.14, 0.21)	0.7098
	Anthropometrics				
	BMI (kg/cm^2)	0.04 (-0.03, 0.11)	0.2163	0.04 (-0.03, 0.11)	0.2584
	Waist Circumference (cm)	0.03 (-0.02, 0.08)	0.2679	0.03 (-0.03, 0.08)	0.3416

Note: Model 1 was adjusted for age, sex, race, region, urinary creatinine, eGFR and total urinary arsenicals. Model 2 further adjusted for smoking[1] and exercise status. Unit of change is 10%. All variables were log-transformed, except for muscle densities, which were square root transformed. eGFR: estimated glomerular filtration rate; iAs: inorganic arsenic; MMA: monomethylarsonic acid; DMA: dimethylarsinic acid.

[1] Smoking status are categorized as: Never smoke; Former smoker quit more than 1 year ago; Former smoker quit less than 1 year ago; Current smoke; Don't know.

Table 7 Correlation of Body Composition with Categorical Urinary Cd

		Model 1 (Basic Model)		Model 2 (Advanced Model)	
		Beta (95% CI)	**p-value**	**Beta (95% CI)**	**p-value**
Muscle Area (cm^2)					
Locomotion Area	Q2	-0.01 (-0.07, 0.04)	0.5923	-0.02 (-0.08, 0.03)	0.4159
	Q3	-0.01 (-0.07, 0.04)	0.6238	-0.02 (-0.07, 0.04)	0.5136
	Q4	0.02 (-0.04, 0.08)	0.5423	0.01 (-0.06, 0.07)	0.8605
Stabilization Area	Q2	0.02 (-0.05, 0.09)	0.5630	0.01 (-0.06, 0.08)	0.7634
	Q3	0.02 (-0.05, 0.09)	0.6195	0.00 (-0.07, 0.06)	0.9233
	Q4	0.03 (-0.04, 0.11)	0.4082	-0.01 (-0.08, 0.07)	0.8491
Total Abd Muscle Area	Q2	0.01 (-0.05, 0.07)	0.6641	0.00 (-0.06, 0.06)	0.8983
	Q3	0.01 (-0.05, 0.07)	0.7031	-0.01 (-0.06, 0.05)	0.8525
	Q4	0.03 (-0.03, 0.10)	0.3431	0.00 (-0.07, 0.06)	0.9591
Muscle Density (HU)					
Locomotion Density	Q2	14.41 (-219.8, 248.62)	0.9037	4.15 (-231.1, 239.4)	0.9723
	Q3	122.94 (-110.24, 356.13)	0.3001	136.11 (-99.7, 371.91)	0.2567
	Q4	97.29 (-161.31, 355.88)	0.4595	121.14 (-144.95, 387.23)	0.3708
Stabilization Density	Q2	-4.88 (-9.10, -0.65)	**0.0240**	-4.98 (-9.24, -0.72)	**0.0222**
	Q3	-1.07 (-5.28, 3.14)	0.6184	-0.76 (-5.04, 3.51)	0.7251
	Q4	-2.96 (-7.63, 1.71)	0.2127	-2.48 (-7.3, 2.34)	0.3127
Total Abd Muscle Density	Q2	-3.52 (-7.23, 0.19)	0.0630	-3.62 (-7.36, 0.12)	0.0576
	Q3	-0.53 (-4.22, 3.17)	0.7795	-0.24 (-3.98, 3.51)	0.9009
	Q4	-1.93 (-6.02, 2.17)	0.3558	-1.47 (-5.70, 2.76)	0.4943
Fat Area (cm^2)					
Locomotion Muscle IMAT Area	Q2	-0.04 (-0.27, 0.18)	0.7069	-0.04 (-0.26, 0.19)	0.7493
	Q3	-0.11 (-0.34, 0.11)	0.3175	-0.14 (-0.37, 0.09)	0.2326
	Q4	-0.02 (-0.27, 0.23)	0.8535	-0.06 (-0.32, 0.2)	0.6375
Stabilization Muscle IMAT Area	Q2	0.19 (0.04, 0.34)	**0.0156**	0.18 (0.03, 0.33)	**0.0205**
	Q3	0.06 (-0.09, 0.21)	0.4152	0.04 (-0.11, 0.19)	0.6321
	Q4	0.14 (-0.03, 0.31)	0.0980	0.10 (-0.08, 0.27)	0.2774
Total Abd IMAT Area	Q2	0.17 (0.02, 0.32)	**0.0230**	0.17 (0.02, 0.32)	**0.0288**
	Q3	0.05 (-0.10, 0.20)	0.5216	0.02 (-0.13, 0.17)	0.7623
	Q4	0.13 (-0.03, 0.30)	0.1118	0.09 (-0.08, 0.26)	0.3047
Visceral Fat Area	Q2	-0.01 (-0.17, 0.15)	0.9013	-0.02 (-0.19, 0.14)	0.7814
	Q3	0.02 (-0.14, 0.18)	0.8303	-0.01 (-0.17, 0.15)	0.9012
	Q4	0.13 (-0.05, 0.31)	0.1416	0.08 (-0.10, 0.27)	0.3779
Subcutaneous Fat Area	Q2	0.11 (-0.05, 0.27)	0.1956	0.10 (-0.06, 0.26)	0.2122
	Q3	0.07 (-0.09, 0.22)	0.4013	0.07 (-0.09, 0.22)	0.4079
	Q4	0.06 (-0.11, 0.23)	0.4939	0.05 (-0.13, 0.23)	0.6015
Anthropometrics					
BMI (kg/cm^2)	Q2	0.03 (-0.03, 0.09)	0.3598	0.02 (-0.04, 0.09)	0.4512
	Q3	0.01 (-0.05, 0.07)	0.7589	0.00 (-0.06, 0.07)	0.9564
	Q4	0.03 (-0.04, 0.10)	0.4330	0.01 (-0.06, 0.08)	0.7603
Waist Circumference (cm)	Q2	0.04 (-0.01, 0.09)	0.1195	0.04 (-0.01, 0.09)	0.1403
	Q3	0.02 (-0.03, 0.07)	0.4000	0.02 (-0.03, 0.07)	0.4971
	Q4	0.06 (0.00, 0.11)	**0.0447**	0.05 (-0.01, 0.10)	0.1025

Note: *model 1 was adjusted for age, sex, race, region, urinary creatinine and eGFR. Model 2 further adjusted for smoking[1] and exercise status. eGFR: estimated glomerular filtration rate.*

[1] Smoking status are categorized as: Never smoke; Former smoker quit more than 1 year ago; Former smoker quit less than 1 year ago; Current

Table 8 Correlation of Body Composition with Continuous Urinary Cd

	Model 1 (Basic Model)		Model 2 (Advanced Model)	
	Beta (95% CI)	**p-value**	**Beta (95% CI)**	**p-value**
Muscle Area (cm^2)				
Locomotion Area	0.01 (-0.02, 0.03)	0.5608	0.00 (-0.02, 0.03)	0.9039
Stabilization Area	0.02 (-0.01, 0.05)	0.2636	0.00 (-0.03, 0.03)	0.9967
Total Abd Muscle Area	0.02 (-0.01, 0.04)	0.2335	0.00 (-0.03, 0.03)	0.9296
Muscle Density (HU)				
Locomotion Density	21.77 (-83.82, 127.36)	0.6851	34.30 (-75.48, 144.07)	0.5389
Stabilization Density	-0.31 (-2.23, 1.61)	0.7494	-0.03 (-2.03, 1.98)	0.9794
Total Abd Muscle Density	-0.11 (-1.80, 1.57)	0.8950	0.16 (-1.60, 1.91)	0.8616
Fat Area (cm^2)				
Locomotion Muscle IMAT Area	-0.02 (-0.12, 0.08)	0.7108	-0.04 (-0.15, 0.06)	0.4375
Stabilization Muscle IMAT Area	0.03 (-0.04, 0.10)	0.3807	0.01 (-0.06, 0.08)	0.8019
Total Abd IMAT Area	0.03 (-0.04, 0.10)	0.4211	0.01 (-0.06, 0.08)	0.8600
Visceral Fat Area	0.05 (-0.02, 0.12)	0.1779	0.03 (-0.05, 0.10)	0.5036
Subcutaneous Fat Area	0.01 (-0.06, 0.09)	0.6831	0.01 (-0.07, 0.08)	0.8309
Anthropometrics				
BMI (kg/cm^2)	0.01 (-0.02, 0.04)	0.6715	0.00 (-0.03, 0.03)	0.8966
Waist Circumference (cm)	0.02 (-0.01, 0.04)	0.1500	0.01 (-0.01, 0.03)	0.3321

Note: *model 1 was adjusted for age, sex, race, region, urinary creatinine and eGFR. Model 2 further adjusted for smoking[1] and exercise status. eGFR: estimated glomerular filtration rate.*

[1] Smoking status are categorized as: Never smoke; Former smoker quit more than 1 year ago; Former smoker quit less than 1 year ago; Current

Appendix B Figures

Figure 4. Correlation of Body Composition with Categorical ΣAs (by Sex)

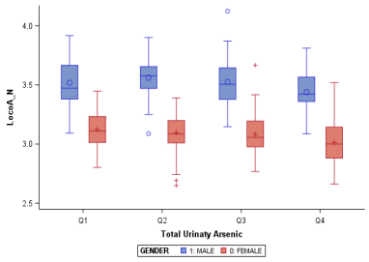
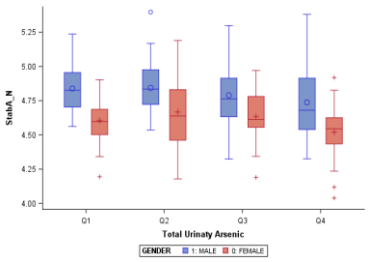
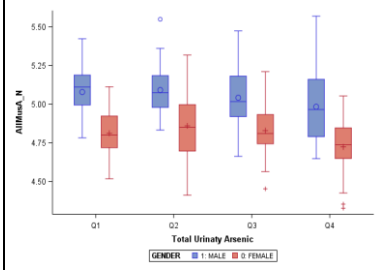
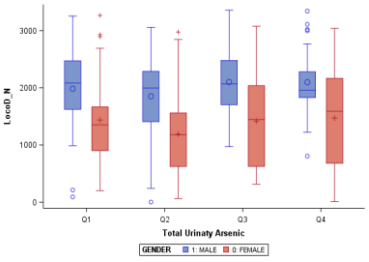
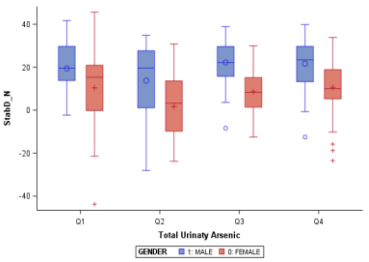
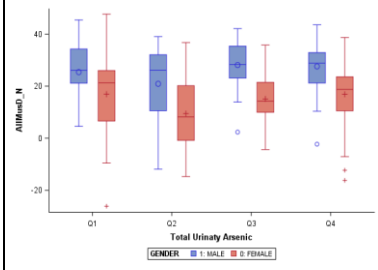
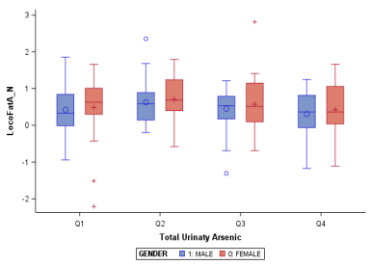
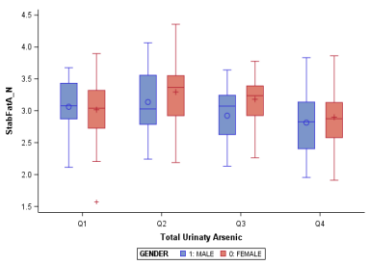
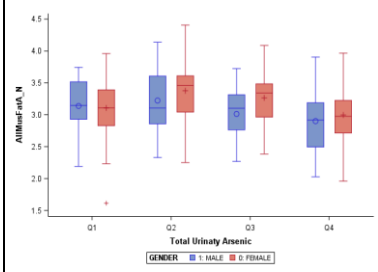
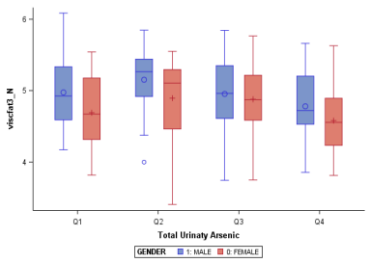
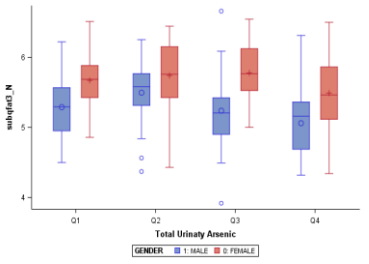
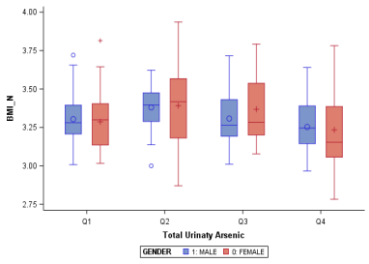
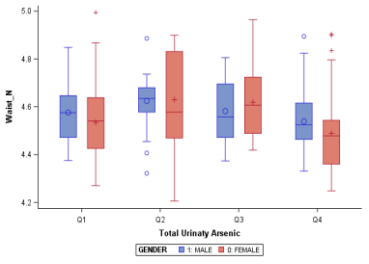
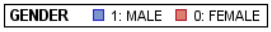
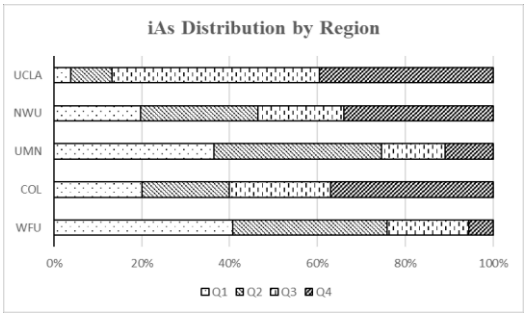
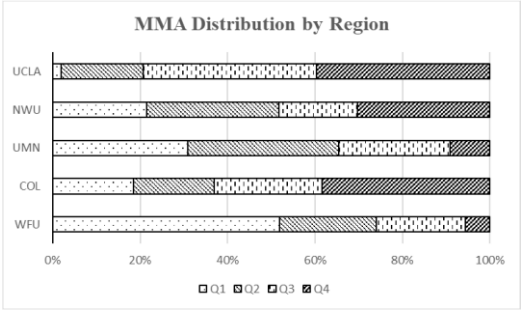
Locomotion Muscle Area	Stabilization Muscle Area	Total Abd Muscle Area
		
Locomotion Muscle Density	**Stabilization Muscle Density**	**Total Abd Muscle Density**
		
Locomotion Muscle IMAT Area	**Stabilization Muscle IMAT Area**	**Total Abd Muscle IMAT Area**
		
Visceral Fat Area	**Subcutaneous Fat Area**	
		
BMI	**Waist Circumference**	
		

Figure 5. Distribution of Each Quartile of Exposure (by Region)

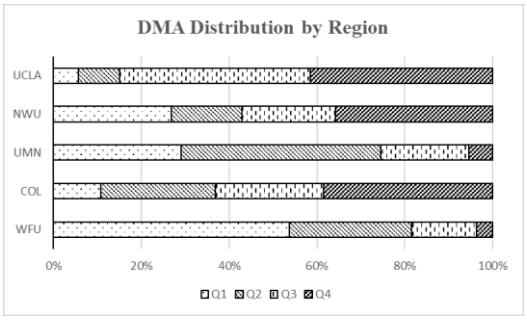
iAs



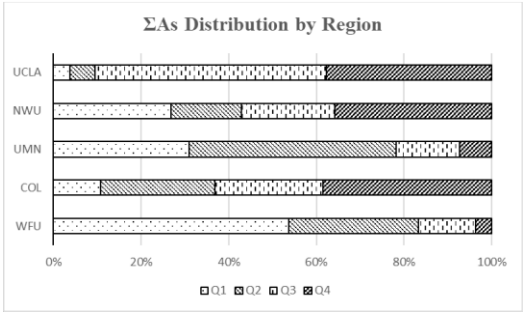
MMA



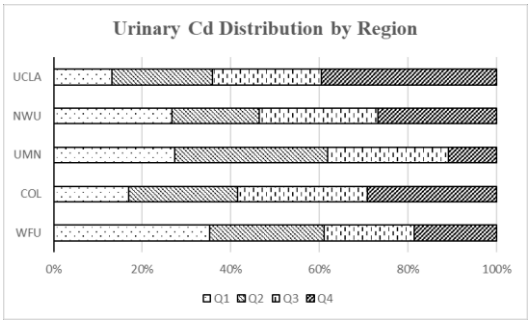
DMA



ΣAs

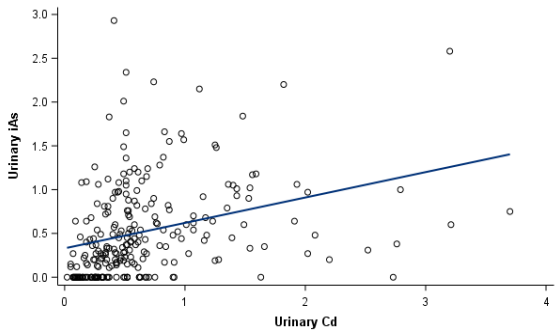
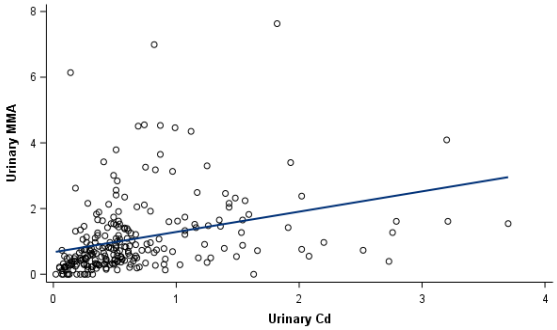
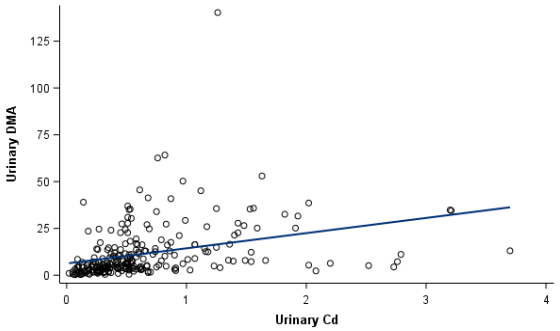
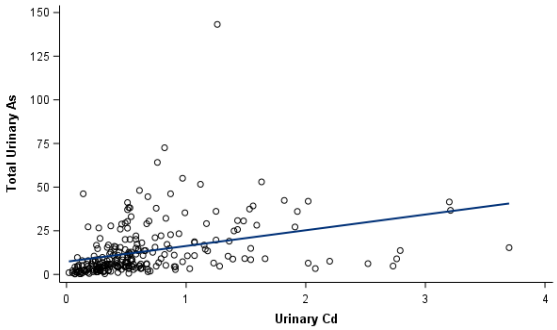


Cd



Note: UCLA: University of California Los Angeles, Los Angeles; NWU: Northwestern University, Chicago; UMN: University of Minnesota, Twin Cities; COL: Columbia University, New York; WFU: Wake Forest University, Winston Salem.

Figure 6. Correlation Between Urinary As and Cd

Urinary Cd vs iAs	Urinary Cd vs MMA
	
r=0.47, p<.0001	r=0.50, p<.0001
Urinary Cd vs DMA	**Urinary Cd vs ΣAs**
	
r=0.55, p<.0001	r=0.55, p<.0001

Appendix C Supplementary Tables

Supp Table S1 Correlation of Body Composition with Continuous ΣAs

		Model 1 (Basic Model)		Model 2 (Advanced Model)	
		Beta (95% CI)	**p-value**	**Beta (95% CI)**	**p-value**
All Participants	**Muscle Area (cm^2)**				
	Locomotion Area	0.00 (-0.02, 0.02)	0.9439	0.00 (-0.02, 0.02)	0.8905
	Stabilization Area	0.00 (-0.03, 0.02)	0.8807	0.00 (-0.02, 0.03)	0.8297
	Total Abd Muscle Area	0.00 (-0.02, 0.02)	0.9055	0.00 (-0.02, 0.03)	0.8197
	Muscle Density (HU)				
	Locomotion Density	14.61 (-77.53, 106.76)	0.7551	2.07 (-90.85, 94.99)	0.9650
	Stabilization Density	-0.39 (-2.06, 1.29)	0.6496	-0.58 (-2.27, 1.12)	0.5041
	Total Abd Muscle Density	-0.27 (-1.74, 1.20)	0.7198	-0.44 (-1.92, 1.04)	0.5597
	Fat Area (cm^2)				
	Locomotion Muscle IMAT Area	-0.02 (-0.10, 0.07)	0.7228	0.00 (-0.09, 0.09)	0.9370
	Stabilization Muscle IMAT Area	0.01 (-0.05, 0.07)	0.6422	0.02 (-0.04, 0.08)	0.4788
	Total Abd IMAT Area	0.01 (-0.05, 0.07)	0.6862	0.02 (-0.04, 0.08)	0.5149
	Visceral Fat Area	0.02 (-0.05, 0.08)	0.5654	0.03 (-0.04, 0.09)	0.4036
	Subcutaneous Fat Area	0.02 (-0.04, 0.08)	0.4866	0.03 (-0.04, 0.09)	0.4158
	Anthropometrics				
	BMI (kg/cm^2)	0.02 (-0.01, 0.04)	0.2231	0.02 (-0.01, 0.04)	0.1585
	Waist Circumference (cm)	0.01 (0.00, 0.03)	0.1349	0.02 (0.00, 0.04)	0.0818
Females	**Muscle Area (cm^2)**				
	Locomotion Area	-0.01 (-0.04, 0.02)	0.6331	-0.01 (-0.04, 0.03)	0.7389
	Stabilization Area	0.01 (-0.03, 0.04)	0.7769	0.01 (-0.03, 0.05)	0.5638
	Total Abd Muscle Area	0.00 (-0.03, 0.04)	0.8615	0.01 (-0.02, 0.04)	0.6358
	Muscle Density (HU)				
	Locomotion Density	-8.39 (-146.84, 130.06)	0.9048	2.13 (-137.46, 141.72)	0.9759
	Stabilization Density	-1.01 (-3.36, 1.35)	0.3989	-0.99 (-3.38, 1.41)	0.4164
	Total Abd Muscle Density	-0.89 (-2.99, 1.21)	0.4041	-0.83 (-2.98, 1.31)	0.4426
	Fat Area (cm^2)				
	Locomotion Muscle IMAT Area	0.00 (-0.14, 0.13)	0.9697	-0.01 (-0.14, 0.13)	0.9347
	Stabilization Muscle IMAT Area	0.04 (-0.04, 0.12)	0.2918	0.05 (-0.03, 0.13)	0.2575
	Total Abd IMAT Area	0.04 (-0.04, 0.12)	0.3282	0.04 (-0.04, 0.12)	0.2994
	Visceral Fat Area	0.05 (-0.04, 0.15)	0.2428	0.06 (-0.03, 0.15)	0.1885
	Subcutaneous Fat Area	0.04 (-0.04, 0.13)	0.3229	0.04 (-0.04, 0.13)	0.3393
	Anthropometrics				
	BMI (kg/cm^2)	0.02 (-0.02, 0.07)	0.2415	0.03 (-0.02, 0.07)	0.2161
	Waist Circumference (cm)	0.02 (-0.01, 0.06)	0.1579	0.02 (-0.01, 0.06)	0.1642
Males	**Muscle Area (cm^2)**				
	Locomotion Area	0.01 (-0.02, 0.04)	0.4508	0.01 (-0.02, 0.04)	0.4174
	Stabilization Area	-0.01 (-0.05, 0.03)	0.5378	-0.01 (-0.05, 0.03)	0.5812
	Total Abd Muscle Area	-0.01 (-0.04, 0.03)	0.6480	-0.01 (-0.04, 0.03)	0.6927
	Muscle Density (HU)				
	Locomotion Density	42.40 (-83.93, 168.73)	0.5079	12.11 (-112.15, 136.38)	0.8473
	Stabilization Density	0.15 (-2.25, 2.54)	0.9034	-0.05 (-2.51, 2.40)	0.9664
	Total Abd Muscle Density	0.30 (-1.75, 2.36)	0.7715	0.06 (-2.03, 2.15)	0.9561
	Fat Area (cm^2)				
	Locomotion Muscle IMAT Area	-0.03 (-0.16, 0.09)	0.5767	-0.01 (-0.13, 0.11)	0.8650
	Stabilization Muscle IMAT Area	-0.02 (-0.11, 0.07)	0.6884	-0.02 (-0.11, 0.07)	0.7139
	Total Abd IMAT Area	-0.02 (-0.11, 0.07)	0.6743	-0.02 (-0.11, 0.07)	0.7180
	Visceral Fat Area	-0.02 (-0.11, 0.07)	0.7078	-0.02 (-0.11, 0.07)	0.6901
	Subcutaneous Fat Area	0.00 (-0.09, 0.09)	0.9369	0.01 (-0.09, 0.10)	0.8947
	Anthropometrics				
	BMI (kg/cm^2)	0.01 (-0.02, 0.04)	0.4163	0.02 (-0.02, 0.05)	0.3200
	Waist Circumference (cm)	0.01 (-0.01, 0.03)	0.4319	0.01 (-0.01, 0.04)	0.2659

Note: Model 1 was adjusted for age, sex, race, region, urinary creatinine and eGFR. Model 2 further adjusted for smoking[1] and exercise status. All variables were log-transformed, except for muscle densities, which were square root transformed. eGFR: estimated glomerular filtration rate.

[1] Smoking status are categorized as: Never smoke; Former smoker quit more than 1 year ago; Former smoker quit less than 1 year ago; Current smoke; Don't know.

Supp Table S2 Correlation of Body Composition with Categorical ΣAs (by Sex)

		Females				Males			
		Model 1 (Basic Model)		Model 2 (Advanced Model)		Model 1 (Basic Model)		Model 2 (Advanced Model)	
		Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value
Muscle Area (cm^2)									
Locomotion Area	Q2	0.01 (-0.07, 0.09)	0.8310	0.02 (-0.07, 0.10)	0.7188	0.06 (-0.01, 0.13)	0.0992	0.06 (-0.01, 0.14)	0.0896
	Q3	-0.03 (-0.11, 0.06)	0.5730	-0.02 (-0.11, 0.06)	0.5787	0.07 (-0.01, 0.15)	0.0781	0.08 (-0.01, 0.16)	0.0686
	Q4	-0.03 (-0.13, 0.07)	0.5921	-0.03 (-0.13, 0.07)	0.5712	0.01 (-0.07, 0.10)	0.7498	0.02 (-0.07, 0.10)	0.7170
Stabilization Area	Q2	0.06 (-0.03, 0.15)	0.1985	0.06 (-0.03, 0.15)	0.1819	0.01 (-0.09, 0.11)	0.8568	0.04 (-0.06, 0.15)	0.3962
	Q3	0.09 (0.00, 0.19)	0.0607	0.09 (-0.01, 0.18)	0.0749	0.03 (-0.09, 0.14)	0.6323	0.05 (-0.06, 0.16)	0.3882
	Q4	0.00 (-0.12, 0.11)	0.9813	0.00 (-0.12, 0.11)	0.9368	-0.03 (-0.15, 0.08)	0.5561	-0.02 (-0.14, 0.09)	0.7170
Total Abd Muscle Area	Q2	0.05 (-0.03, 0.13)	0.2193	0.05 (-0.03, 0.13)	0.1934	0.02 (-0.07, 0.11)	0.6870	0.05 (-0.04, 0.13)	0.3171
	Q3	0.07 (-0.02, 0.16)	0.1039	0.07 (-0.02, 0.15)	0.1235	0.04 (-0.06, 0.13)	0.4645	0.05 (-0.04, 0.15)	0.2804
	Q4	-0.01 (-0.11, 0.10)	0.9124	-0.01 (-0.11, 0.09)	0.8651	-0.03 (-0.13, 0.07)	0.6100	-0.02 (-0.11, 0.08)	0.7610
Muscle Density (HU)									
Locomotion Density	Q2	-60.85 (-419.05, 297.34)	0.7372	-72.38 (-434.76, 290.01)	0.6932	-84.41 (-399.51, 230.70)	0.5970	-128.73 (-440.57, 183.11)	0.4154
	Q3	-3.59 (-385.07, 377.90)	0.9852	-12.44 (-400.13, 375.25)	0.9494	202.37 (-143.03, 547.77)	0.2485	114.33 (-226.27, 454.93)	0.5076
	Q4	25.33 (-419.48, 470.14)	0.9104	8.35 (-439.57, 456.27)	0.9706	183.63 (-176.36, 543.62)	0.3147	113.36 (-238.61, 465.33)	0.5249
Stabilization Density	Q2	-4.78 (-10.82, 1.26)	0.1196	-4.65 (-10.83, 1.53)	0.1390	-5.29 (-11.01, 0.42)	0.0691	-6.26 (-12.12, -0.41)	**0.0362**
	Q3	-2.00 (-8.43, 4.43)	0.5398	-1.94 (-8.55, 4.67)	0.5623	6.34 (0.08, 12.60)	**0.0473**	5.83 (-0.57, 12.22)	0.0736
	Q4	-3.60 (-11.10, 3.90)	0.3441	-3.57 (-11.21, 4.07)	0.3566	2.00 (-4.53, 8.52)	0.5462	1.66 (-4.95, 8.27)	0.6199
Total Abd Muscle Density	Q2	-3.94 (-9.36, 1.48)	0.1524	-3.89 (-9.43, 1.65)	0.1668	-4.17 (-9.07, 0.74)	0.0956	-5.06 (-10.06, -0.05)	**0.0478**
	Q3	-1.87 (-7.64, 3.89)	0.5212	-1.86 (-7.78, 4.07)	0.5360	5.62 (0.24, 11.00)	**0.0407**	4.98 (-0.49, 10.45)	0.0739
	Q4	-2.76 (-9.48, 3.97)	0.4185	-2.81 (-9.66, 4.03)	0.4172	2.32 (-3.29, 7.93)	0.4144	1.86 (-3.79, 7.51)	0.5152
Fat Area (cm^2)									
Locomotion Muscle IMAT Area	Q2	0.16 (-0.19, 0.50)	0.3790	0.16 (-0.20, 0.51)	0.3791	0.23 (-0.06, 0.53)	0.1231	0.29 (-0.01, 0.59)	0.0614
	Q3	0.07 (-0.30, 0.44)	0.7199	0.06 (-0.32, 0.44)	0.7604	-0.12 (-0.45, 0.21)	0.4686	-0.06 (-0.39, 0.27)	0.7078
	Q4	-0.03 (-0.46, 0.40)	0.8858	-0.02 (-0.46, 0.42)	0.9134	-0.06 (-0.41, 0.28)	0.7127	-0.02 (-0.35, 0.32)	0.9263
Stabilization Muscle IMAT Area	Q2	0.18 (-0.03, 0.39)	0.0851	0.18 (-0.03, 0.39)	0.0934	0.10 (-0.13, 0.32)	0.4036	0.16 (-0.07, 0.39)	0.1793
	Q3	0.24 (0.02, 0.46)	**0.0339**	0.24 (0.01, 0.46)	**0.0381**	-0.12 (-0.37, 0.12)	0.3248	-0.10 (-0.35, 0.15)	0.4415
	Q4	0.10 (-0.16, 0.35)	0.4442	0.09 (-0.17, 0.35)	0.4921	-0.09 (-0.35, 0.16)	0.4673	-0.08 (-0.33, 0.18)	0.5469
Total Abd IMAT Area	Q2	0.18 (-0.03, 0.38)	0.0887	0.18 (-0.03, 0.38)	0.0968	0.11 (-0.11, 0.33)	0.3452	0.17 (-0.06, 0.39)	0.1415
	Q3	0.23 (0.01, 0.44)	**0.0403**	0.23 (0.00, 0.45)	**0.0462**	-0.12 (-0.36, 0.12)	0.3212	-0.09 (-0.34, 0.15)	0.4485
	Q4	0.09 (-0.16, 0.34)	0.4821	0.08 (-0.17, 0.34)	0.5237	-0.09 (-0.34, 0.16)	0.4830	-0.07 (-0.32, 0.18)	0.5762
Visceral Fat Area	Q2	0.17 (-0.06, 0.41)	0.1519	0.19 (-0.05, 0.43)	0.1129	0.20 (-0.02, 0.42)	0.0793	0.25 (0.03, 0.48)	**0.0293**
	Q3	0.26 (0.01, 0.51)	**0.0444**	0.24 (-0.01, 0.49)	0.0616	0.03 (-0.22, 0.27)	0.8375	0.04 (-0.21, 0.29)	0.7378
	Q4	0.19 (-0.10, 0.49)	0.1892	0.21 (-0.08, 0.50)	0.1626	-0.08 (-0.34, 0.17)	0.5266	-0.07 (-0.33, 0.18)	0.5637

		Females				Males			
		Model 1 (Basic Model)		Model 2 (Advanced Model)		Model 1 (Basic Model)		Model 2 (Advanced Model)	
		Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value
Subcutaneous Fat Area	Q2	0.17 (-0.05, 0.39)	0.1370	0.18 (-0.05, 0.40)	0.1285	0.23 (0.00, 0.46)	**0.0457**	0.24 (0.00, 0.48)	0.0500
	Q3	0.22 (-0.01, 0.45)	0.0653	0.22 (-0.02, 0.45)	0.0697	0.05 (-0.20, 0.30)	0.6899	0.07 (-0.18, 0.33)	0.5756
	Q4	0.09 (-0.18, 0.36)	0.4895	0.09 (-0.19, 0.36)	0.5250	0.01 (-0.25, 0.27)	0.9584	0.03 (-0.24, 0.29)	0.8489
Anthropometrics									
BMI (kg/cm^2)	Q2	0.13 (0.03, 0.23)	**0.0123**	0.14 (0.03, 0.24)	**0.0109**	0.08 (0.00, 0.15)	**0.0500**	0.09 (0.01, 0.17)	**0.0239**
	Q3	0.14 (0.03, 0.24)	**0.0155**	0.14 (0.02, 0.25)	**0.0176**	0.06 (-0.02, 0.14)	0.1520	0.07 (-0.01, 0.15)	0.0993
	Q4	0.08 (-0.05, 0.20)	0.2417	0.07 (-0.05, 0.20)	0.2570	0.04 (-0.04, 0.13)	0.3380	0.05 (-0.04, 0.14)	0.2676
Waist Circumference (cm)	Q2	0.12 (0.04, 0.20)	**0.0036**	0.13 (0.04, 0.21)	**0.0030**	0.05 (0.00, 0.11)	0.0527	0.06 (0.01, 0.12)	**0.0273**
	Q3	0.11 (0.03, 0.20)	**0.0103**	0.11 (0.03, 0.20)	**0.0111**	0.04 (-0.02, 0.10)	0.2180	0.05 (-0.01, 0.11)	0.1114
	Q4	0.07 (-0.03, 0.17)	0.1725	0.07 (-0.03, 0.17)	0.1791	0.04 (-0.02, 0.10)	0.2255	0.05 (-0.02, 0.11)	0.1390

Note: *model 1 was adjusted for age, sex, race, region, urinary creatinine and eGFR. Model 2 further adjusted for smoking[1] and exercise status. eGFR: estimated glomerular filtration rate.*

[1] *Smoking status are categorized as: Never smoke; Former smoker quit more than 1 year ago; Former smoker quit less than 1 year ago; Current smoke; Don't know.*

Supp Table S3 Correlation of Body Composition with iAs% (by Sex)

Females	**Conventional Model iAs% as independent variable alone**				**Leave-One-Out Model 1 iAs% adjusted for MMA% (DMA% ↓10%)**				**Leave-One-Out Model 2 iAs% adjusted for DMA% (MMA% ↓10%)**			
	Model 1 (Basic Model)		Model 2 (Advanced Model)		Model 1 (Basic Model)		Model 2 (Advanced Model)		Model 1 (Basic Model)		Model 2 (Advanced Model)	
	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value
Muscle Area (cm^2)												
Locomotion Area	-0.06 (-0.16, 0.05)	0.2827	-0.05 (-0.15, 0.05)	0.3081	-0.03 (-0.14, 0.07)	0.5230	-0.03 (-0.13, 0.08)	0.6254	0.05 (-0.10, 0.19)	0.5273	0.07 (-0.08, 0.21)	0.3665
Stabilization Area	-0.09 (-0.21, 0.02)	0.1193	-0.09 (-0.20, 0.03)	0.1351	-0.07 (-0.19, 0.05)	0.2554	-0.06 (-0.17, 0.06)	0.3371	0.02 (-0.15, 0.19)	0.8230	0.05 (-0.12, 0.21)	0.5651
Total Abd Muscle Area	-0.08 (-0.19, 0.02)	0.1157	-0.08 (-0.18, 0.02)	0.1309	-0.06 (-0.17, 0.05)	0.2648	-0.05 (-0.15, 0.05)	0.3540	0.03 (-0.12, 0.18)	0.7276	0.05 (-0.09, 0.20)	0.4622
Muscle Density (HU)												
Locomotion Density	298.25 (-144.82, 741.32)	0.1850	307.39 (-138.43, 753.21)	0.1746	267.51 (-188.13, 723.14)	0.2472	280.58 (-179.90, 741.06)	0.2298	156.17 (-487.53, 799.87)	0.6317	189.22 (-467.04, 845.49)	0.5689
Stabilization Density	3.68 (-3.86, 11.21)	0.3356	3.67 (-4.02, 11.37)	0.3463	2.96 (-4.77, 10.70)	0.4495	2.92 (-5.01, 10.85)	0.4670	0.38 (-10.56, 11.31)	0.9457	0.36 (-10.94, 11.67)	0.9494
Total Abd Muscle Density	4.09 (-2.64, 10.82)	0.2315	4.11 (-2.76, 10.97)	0.2387	3.34 (-3.57, 10.24)	0.3407	3.33 (-3.75, 10.40)	0.3531	0.61 (-9.15, 10.36)	0.9023	0.68 (-9.40, 10.76)	0.8940
Fat Area (cm^2)												
Locomotion IMAT Area	-0.29 (-0.72, 0.14)	0.1791	-0.29 (-0.72, 0.15)	0.1952	-0.22 (-0.66, 0.22)	0.3207	-0.21 (-0.65, 0.24)	0.3593	0.04 (-0.58, 0.66)	0.8928	0.06 (-0.57, 0.70)	0.8434
Stabilization IMAT Area	-0.11 (-0.37, 0.15)	0.3982	-0.10 (-0.37, 0.16)	0.4374	-0.06 (-0.32, 0.21)	0.6626	-0.04 (-0.31, 0.23)	0.7583	0.13 (-0.24, 0.51)	0.4793	0.17 (-0.21, 0.55)	0.3811
Total Abd IMAT Area	-0.12 (-0.38, 0.14)	0.3605	-0.11 (-0.37, 0.15)	0.3998	-0.06 (-0.32, 0.20)	0.6315	-0.05 (-0.31, 0.22)	0.7285	0.14 (-0.23, 0.51)	0.4556	0.17 (-0.20, 0.55)	0.3618
Visceral Fat Area	-0.17 (-0.46, 0.12)	0.2482	-0.16 (-0.45, 0.13)	0.2714	-0.08 (-0.37, 0.21)	0.5861	-0.05 (-0.34, 0.23)	0.7139	0.27 (-0.14, 0.68)	0.2022	0.34 (-0.07, 0.75)	0.1035
Subcutaneous Fat Area	-0.05 (-0.32, 0.22)	0.7087	-0.04 (-0.32, 0.24)	0.7646	-0.01 (-0.29, 0.27)	0.9431	0.01 (-0.27, 0.29)	0.9553	0.16 (-0.23, 0.55)	0.4214	0.20 (-0.20, 0.61)	0.3213
Anthropometrics												
BMI (kg/cm^2)	-0.10 (-0.23, 0.03)	0.1254	-0.10 (-0.23, 0.03)	0.1393	-0.06 (-0.19, 0.07)	0.3579	-0.05 (-0.18, 0.08)	0.4256	0.09 (-0.09, 0.27)	0.3402	0.10 (-0.08, 0.29)	0.2712
Waist circumference (cm)	-0.07 (-0.17, 0.04)	0.1987	-0.06 (-0.17, 0.04)	0.2242	-0.03 (-0.13, 0.07)	0.6025	-0.02 (-0.12, 0.08)	0.7092	0.12 (-0.02, 0.26)	0.0932	0.14 (-0.01, 0.28)	0.0677

Males	**Conventional Model iAs% as independent variable alone**				**Leave-One-Out Model 1 iAs% adjusted for MMA% (DMA% ↓10%)**				**Leave-One-Out Model 2 iAs% adjusted for DMA% (MMA% ↓10%)**			
	Model 1 (Basic Model)		Model 2 (Advanced Model)		Model 1 (Basic Model)		Model 2 (Advanced Model)		Model 1 (Basic Model)		Model 2 (Advanced Model)	
	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value
Muscle Area (cm^2)												
Locomotion Area	0.07 (-0.01, 0.14)	0.0738	0.06 (-0.01, 0.13)	0.1169	0.09 (0.02, 0.17)	**0.0148**	0.09 (0.01, 0.16)	**0.0265**	0.16 (0.05, 0.27)	**0.0035**	0.16 (0.05, 0.27)	**0.0057**
Stabilization Area	0.00 (-0.10, 0.11)	0.9660	0.01 (-0.09, 0.12)	0.8331	0.04 (-0.07, 0.15)	0.4534	0.05 (-0.06, 0.16)	0.3578	0.14 (-0.01, 0.29)	0.0754	0.15 (0.00, 0.30)	0.0524
Total Abd Muscle Area	0.01 (-0.07, 0.10)	0.7526	0.02 (-0.07, 0.11)	0.6839	0.05 (-0.04, 0.14)	0.2798	0.05 (-0.04, 0.15)	0.2402	0.14 (0.01, 0.27)	**0.0340**	0.15 (0.02, 0.28)	**0.0260**
Muscle Density (HU)												
Locomotion Density	79.68 (-239.21, 398.58)	0.6218	7.29 (-304.60, 319.18)	0.9632	106.34 (-229.90, 442.57)	0.5324	24.17 (-304.82, 353.17)	0.8846	173.84 (-312.13, 659.82)	0.4802	67.70 (-410.48, 545.87)	0.7797
Stabilization Density	0.00 (-6.06, 6.06)	1.0000	-0.65 (-6.83, 5.53)	0.8352	-0.52 (-6.91, 5.87)	0.8720	-1.25 (-7.76, 5.26)	0.7043	-1.84 (-11.07, 7.39)	0.6940	-2.80 (-12.26, 6.67)	0.5594
Total Abd Muscle Density	0.37 (-4.83, 5.56)	0.8895	-0.33 (-5.59, 4.94)	0.9024	-0.02 (-5.50, 5.45)	0.9938	-0.79 (-6.34, 4.76)	0.7789	-1.00 (-8.91, 6.91)	0.8027	-1.98 (-10.05, 6.09)	0.6280
Fat Area (cm^2)												
Locomotion IMAT Area	-0.02 (-0.33, 0.29)	0.8927	0.04 (-0.27, 0.35)	0.7947	0.02 (-0.30, 0.34)	0.9073	0.08 (-0.24, 0.40)	0.6272	0.12 (-0.35, 0.59)	0.6109	0.18 (-0.29, 0.65)	0.4493
Stabilization IMAT Area	-0.01 (-0.24, 0.23)	0.9601	0.02 (-0.21, 0.26)	0.8464	0.03 (-0.21, 0.27)	0.8094	0.06 (-0.19, 0.31)	0.6324	0.12 (-0.23, 0.47)	0.4944	0.16 (-0.20, 0.51)	0.3837
Total Abd IMAT Area	-0.01 (-0.24, 0.22)	0.9366	0.02 (-0.21, 0.25)	0.8425	0.03 (-0.21, 0.27)	0.8198	0.06 (-0.18, 0.30)	0.6187	0.12 (-0.22, 0.46)	0.4835	0.16 (-0.19, 0.51)	0.3624
Visceral Fat Area	-0.12 (-0.34, 0.11)	0.3065	-0.10 (-0.33, 0.13)	0.3950	-0.05 (-0.29, 0.18)	0.6596	-0.03 (-0.27, 0.21)	0.7952	0.11 (-0.23, 0.45)	0.5187	0.14 (-0.20, 0.49)	0.4172
Subcutaneous Fat Area	-0.08 (-0.31, 0.16)	0.5160	-0.09 (-0.33, 0.15)	0.4619	0.00 (-0.23, 0.24)	0.9713	0.00 (-0.24, 0.24)	0.9977	0.24 (-0.09, 0.58)	0.1478	0.27 (-0.07, 0.61)	0.1216
Anthropometrics												
BMI (kg/cm^2)	-0.04 (-0.12, 0.03)	0.2640	-0.04 (-0.12, 0.03)	0.2727	0.00 (-0.08, 0.07)	0.9626	0.00 (-0.08, 0.07)	0.9561	0.10 (-0.01, 0.21)	0.0686	0.10 (-0.01, 0.21)	0.0739
Waist circumference (cm)	-0.03 (-0.09, 0.02)	0.2114	-0.03 (-0.09, 0.02)	0.2688	-0.01 (-0.06, 0.05)	0.7248	-0.01 (-0.06, 0.05)	0.8461	0.05 (-0.03, 0.13)	0.1991	0.06 (-0.02, 0.14)	0.1485

Note: Model 1 was adjusted for age, sex, race, region, urinary creatinine and eGFR and total urinary arsenicals. Model 2 further adjusted for smoking and exercise status. Unit of change is 10%. All variables were log-transformed, except for muscle densities, which were square root transformed. eGFR: estimated glomerular filtration rate; iAs: inorganic arsenic; MMA: monomethylarsonic acid; DMA: dimethylarsinic acid.

[1] *Smoking status are categorized as: Never smoke; Former smoker quit more than 1 year ago; Former smoker quit less than 1 year ago; Current smoke; Don't know.*

Supp Table S4 Correlation of Body Composition with MMA% (by Sex)

Females	Conventional Model MMA% as independent variable alone				Leave-One-Out Model 1 MMA% adjusted for iAs% (DMA% ↓10%)				Leave-One-Out Model 2 MMA% adjusted for DMA% (iAs% ↓10%)			
	Model 1 (Basic Model)		Model 2 (Advanced Model)		Model 1 (Basic Model)		Model 2 (Advanced Model)		Model 1 (Basic Model)		Model 2 (Advanced Model)	
	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value
Muscle Area (cm^2)												
Locomotion Area	-0.09 (-0.17, -0.01)	**0.0364**	-0.10 (-0.18, -0.02)	**0.0180**	-0.08 (-0.16, 0.00)	0.0576	-0.09 (-0.18, -0.01)	**0.0292**	-0.05 (-0.19, 0.10)	0.5273	-0.07 (-0.21, 0.08)	0.3665
Stabilization Area	-0.10 (-0.19, -0.01)	**0.0357**	-0.12 (-0.21, -0.02)	**0.0133**	-0.09 (-0.18, 0.01)	0.0710	-0.10 (-0.20, -0.01)	**0.0288**	-0.02 (-0.19, 0.15)	0.8230	-0.05 (-0.21, 0.12)	0.5651
Total Abd Muscle Area	-0.10 (-0.18, -0.01)	**0.0222**	-0.11 (-0.19, -0.03)	**0.0068**	-0.09 (-0.17, 0.00)	**0.0463**	-0.10 (-0.19, -0.02)	**0.0155**	-0.03 (-0.18, 0.12)	0.7276	-0.05 (-0.20, 0.09)	0.4622
Muscle Density (HU)												
Locomotion Density	158.73 (-197.71, 515.16)	0.3795	144.85 (-216.53, 506.24)	0.4287	111.34 (-253.62, 476.30)	0.5468	91.36 (-279.84, 462.56)	0.6267	-156.17 (-799.87, 487.53)	0.6317	-189.22 (-845.49, 467.04)	0.5689
Stabilization Density	3.11 (-2.92, 9.15)	0.3089	3.12 (-3.08, 9.32)	0.3214	2.59 (-3.61, 8.79)	0.4099	2.56 (-3.84, 8.95)	0.4294	-0.38 (-11.31, 10.56)	0.9457	-0.36 (-11.67, 10.94)	0.9494
Total Abd Muscle Density	3.32 (-2.07, 8.71)	0.2251	3.28 (-2.25, 8.82)	0.2424	2.73 (-2.80, 8.26)	0.3304	2.65 (-3.05, 8.35)	0.3592	-0.61 (-10.36, 9.15)	0.9023	-0.68 (-10.76, 9.40)	0.8940
Fat Area (cm^2)												
Locomotion IMAT Area	-0.30 (-0.64, 0.04)	0.0833	-0.31 (-0.66, 0.04)	0.0810	-0.26 (-0.61, 0.09)	0.1407	-0.27 (-0.63, 0.09)	0.1386	-0.04 (-0.66, 0.58)	0.8928	-0.06 (-0.70, 0.57)	0.8434
Stabilization IMAT Area	-0.20 (-0.41, 0.00)	0.0536	-0.22 (-0.43, -0.01)	**0.0401**	-0.19 (-0.40, 0.02)	0.0748	-0.21 (-0.43, 0.00)	0.0553	-0.13 (-0.51, 0.24)	0.4793	-0.17 (-0.55, 0.21)	0.3811
Total Abd IMAT Area	-0.21 (-0.42, -0.01)	**0.0392**	-0.23 (-0.44, -0.02)	**0.0296**	-0.20 (-0.41, 0.01)	0.0572	-0.22 (-0.44, -0.01)	**0.0427**	-0.14 (-0.51, 0.23)	0.4556	-0.17 (-0.55, 0.20)	0.3618
Visceral Fat Area	-0.36 (-0.59, -0.13)	**0.0023**	-0.40 (-0.63, -0.18)	**0.0007**	-0.35 (-0.58, -0.11)	**0.0043**	-0.39 (-0.63, -0.16)	**0.0013**	-0.27 (-0.68, 0.14)	0.2022	-0.34 (-0.75, 0.07)	0.1035
Subcutaneous Fat Area	-0.17 (-0.39, 0.05)	0.1284	-0.19 (-0.42, 0.04)	0.0964	-0.17 (-0.40, 0.06)	0.1419	-0.20 (-0.43, 0.04)	0.1034	-0.16 (-0.55, 0.23)	0.4214	-0.20 (-0.61, 0.20)	0.3213
Anthropometrics												
BMI (kg/cm^2)	-0.16 (-0.26, -0.06)	**0.0023**	-0.17 (-0.27, -0.06)	**0.0016**	-0.15 (-0.25, -0.04)	**0.0053**	-0.16 (-0.26, -0.05)	**0.0039**	-0.09 (-0.27, 0.09)	0.3402	-0.10 (-0.29, 0.08)	0.2712
Waist circumference (cm)	-0.15 (-0.23, -0.07)	**0.0002**	-0.16 (-0.24, -0.08)	**0.0001**	-0.15 (-0.23, -0.07)	**0.0004**	-0.16 (-0.24, -0.07)	**0.0003**	-0.12 (-0.26, 0.02)	0.0932	-0.14 (-0.28, 0.01)	0.0677

Males	Conventional Model MMA% as independent variable alone				Leave-One-Out Model 1 MMA% adjusted for iAs% (DMA% ↓10%)				Leave-One-Out Model 2 MMA% adjusted for DMA% (iAs% ↓10%)			
	Model 1 (Basic Model)		Model 2 (Advanced Model)		Model 1 (Basic Model)		Model 2 (Advanced Model)		Model 1 (Basic Model)		Model 2 (Advanced Model)	
	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value
Muscle Area (cm^2)												
Locomotion Area	-0.05 (-0.10, 0.01)	0.1034	-0.05 (-0.11, 0.01)	0.0925	-0.07 (-0.13, -0.01)	**0.0201**	-0.07 (-0.13, -0.01)	**0.0214**	-0.16 (-0.27, -0.05)	**0.0035**	-0.16 (-0.27, -0.05)	**0.0057**
Stabilization Area	-0.09 (-0.17, -0.01)	**0.0265**	-0.09 (-0.17, -0.01)	**0.0251**	-0.10 (-0.18, -0.02)	**0.0196**	-0.10 (-0.18, -0.02)	**0.0163**	-0.14 (-0.29, 0.01)	0.0754	-0.15 (-0.30, 0.00)	0.0524
Total Abd Muscle Area	-0.08 (-0.15, -0.01)	**0.0195**	-0.08 (-0.15, -0.01)	**0.0175**	-0.09 (-0.16, -0.02)	**0.0109**	-0.10 (-0.17, -0.02)	**0.0091**	-0.14 (-0.27, -0.01)	**0.0340**	-0.15 (-0.28, -0.02)	**0.0260**
Muscle Density (HU)												
Locomotion Density	-41.95 (-290.84, 206.93)	0.7392	-37.64 (-284.40, 209.11)	0.7631	-67.50 (-329.78, 194.77)	0.6113	-43.52 (-303.91, 216.86)	0.7412	-173.84 (-659.82, 312.13)	0.4802	-67.70 (-545.87, 410.48)	0.7797
Stabilization Density	1.19 (-3.53, 5.91)	0.6177	1.24 (-3.64, 6.13)	0.6155	1.32 (-3.66, 6.30)	0.6013	1.55 (-3.61, 6.70)	0.5534	1.84 (-7.39, 11.07)	0.6940	2.80 (-6.67, 12.26)	0.5594
Total Abd Muscle Density	0.97 (-3.07, 5.02)	0.6345	1.00 (-3.17, 5.16)	0.6358	0.98 (-3.29, 5.25)	0.6506	1.19 (-3.20, 5.58)	0.5926	1.00 (-6.91, 8.91)	0.8027	1.98 (-6.09, 10.05)	0.6280
Fat Area (cm^2)												
Locomotion IMAT Area	-0.10 (-0.33, 0.14)	0.4242	-0.08 (-0.32, 0.16)	0.5084	-0.10 (-0.35, 0.15)	0.4278	-0.10 (-0.35, 0.15)	0.4377	-0.12 (-0.59, 0.35)	0.6109	-0.18 (-0.65, 0.29)	0.4493
Stabilization IMAT Area	-0.08 (-0.26, 0.09)	0.3503	-0.08 (-0.26, 0.10)	0.3688	-0.09 (-0.28, 0.10)	0.3373	-0.10 (-0.29, 0.09)	0.3192	-0.12 (-0.47, 0.23)	0.4944	-0.16 (-0.51, 0.20)	0.3837
Total Abd IMAT Area	-0.09 (-0.26, 0.09)	0.3222	-0.09 (-0.26, 0.09)	0.3453	-0.09 (-0.28, 0.09)	0.3132	-0.10 (-0.29, 0.09)	0.2962	-0.12 (-0.46, 0.22)	0.4835	-0.16 (-0.51, 0.19)	0.3624
Visceral Fat Area	-0.18 (-0.35, 0.00)	**0.0471**	-0.18 (-0.36, 0.00)	**0.0469**	-0.16 (-0.35, 0.02)	0.0800	-0.17 (-0.36, 0.01)	0.0707	-0.11 (-0.45, 0.23)	0.5187	-0.14 (-0.49, 0.20)	0.4172
Subcutaneous Fat Area	-0.24 (-0.41, -0.06)	**0.0078**	-0.27 (-0.45, -0.09)	**0.0038**	-0.24 (-0.42, -0.06)	**0.0102**	-0.27 (-0.46, -0.08)	**0.0054**	-0.24 (-0.58, 0.09)	0.1478	-0.27 (-0.61, 0.07)	0.1216
Anthropometrics												
BMI (kg/cm^2)	-0.10 (-0.16, -0.05)	**0.0004**	-0.10 (-0.16, -0.05)	**0.0005**	-0.10 (-0.16, -0.04)	**0.0007**	-0.10 (-0.16, -0.04)	**0.0010**	-0.10 (-0.21, 0.01)	0.0686	-0.10 (-0.21, 0.01)	0.0739
Waist circumference (cm)	-0.06 (-0.10, -0.02)	**0.0023**	-0.07 (-0.11, -0.02)	**0.0021**	-0.06 (-0.10, -0.02)	**0.0052**	-0.07 (-0.11, -0.02)	**0.0042**	-0.05 (-0.13, 0.03)	0.1991	-0.06 (-0.14, 0.02)	0.1485

Note: Model 1 was adjusted for age, sex, race, region, urinary creatinine and eGFR and total urinary arsenicals. Model 2 further adjusted for smoking and exercise status. Unit of change is 10%. All variables were log-transformed, except for muscle densities, which were square root transformed. eGFR: estimated glomerular filtration rate; iAs: inorganic arsenic; MMA: monomethylarsonic acid; DMA: dimethylarsinic acid.

[1] *Smoking status are categorized as: Never smoke; Former smoker quit more than 1 year ago; Former smoker quit less than 1 year ago; Current smoke; Don't know.*

Supp Table S5 Correlation of Body Composition with DMA% (by Sex)

Females	Conventional Model DMA% as independent variable alone				Leave-One-Out Model 1 DMA% adjusted for iAs% (MMA% ↓10%)				Leave-One-Out Model 2 DMA% adjusted for MMA% (iAs% ↓10%)			
	Model 1 (Basic Model)		Model 2 (Advanced Model)		Model 1 (Basic Model)		Model 2 (Advanced Model)		Model 1 (Basic Model)		Model 2 (Advanced Model)	
	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value
Muscle Area (cm^2)												
Locomotion Area	0.06 (0.00, 0.12)	**0.0362**	0.07 (0.01, 0.12)	**0.0251**	0.08 (0.00, 0.16)	0.0576	0.09 (0.01, 0.18)	**0.0292**	0.03 (-0.07, 0.14)	0.5230	0.03 (-0.08, 0.13)	0.6254
Stabilization Area	0.08 (0.01, 0.15)	**0.0173**	0.08 (0.02, 0.15)	**0.0095**	0.09 (-0.01, 0.18)	0.0710	0.10 (0.01, 0.20)	**0.0288**	0.07 (-0.05, 0.19)	0.2554	0.06 (-0.06, 0.17)	0.3371
Total Abd Muscle Area	0.08 (0.02, 0.13)	**0.0117**	0.08 (0.02, 0.14)	**0.0057**	0.09 (0.00, 0.17)	**0.0463**	0.10 (0.02, 0.19)	**0.0155**	0.06 (-0.05, 0.17)	0.2648	0.05 (-0.05, 0.15)	0.3540
Muscle Density (HU)												
Locomotion Density	-175.40 (-426.46, 75.66)	0.1691	-169.66 (-421.93, 82.61)	0.1853	-111.34 (-476.30, 253.62)	0.5468	-91.36 (-462.56, 279.84)	0.6267	-267.51 (-723.14, 188.13)	0.2472	-280.58 (-741.06, 179.90)	0.2298
Stabilization Density	-2.74 (-7.00, 1.52)	0.2048	-2.71 (-7.05, 1.63)	0.2187	-2.59 (-8.79, 3.61)	0.4099	-2.56 (-8.95, 3.84)	0.4294	-2.96 (-10.70, 4.77)	0.4495	-2.92 (-10.85, 5.01)	0.4670
Total Abd Muscle Density	-2.98 (-6.78, 0.82)	0.1235	-2.93 (-6.80, 0.94)	0.1363	-2.73 (-8.26, 2.80)	0.3304	-2.65 (-8.35, 3.05)	0.3592	-3.34 (-10.24, 3.57)	0.3407	-3.33 (-10.40, 3.75)	0.3531
Fat Area (cm^2)												
Locomotion Fat Area	0.25 (0.00, 0.49)	**0.0461**	0.25 (0.00, 0.49)	**0.0497**	0.26 (-0.09, 0.61)	0.1407	0.27 (-0.09, 0.63)	0.1386	0.22 (-0.22, 0.66)	0.3207	0.21 (-0.24, 0.65)	0.3593
Stabilization Fat Area	0.14 (-0.01, 0.28)	0.0648	0.14 (-0.01, 0.29)	0.0600	0.19 (-0.02, 0.40)	0.0748	0.21 (0.00, 0.43)	0.0553	0.06 (-0.21, 0.32)	0.6626	0.04 (-0.23, 0.31)	0.7583
Total Abd Muscle Fat Area	0.15 (0.00, 0.29)	**0.0477**	0.15 (0.00, 0.30)	**0.0451**	0.20 (-0.01, 0.41)	0.0572	0.22 (0.01, 0.44)	**0.0427**	0.06 (-0.20, 0.32)	0.6315	0.05 (-0.22, 0.31)	0.7285
Visceral Fat Area	0.24 (0.07, 0.40)	**0.0049**	0.25 (0.09, 0.41)	**0.0027**	0.35 (0.11, 0.58)	**0.0043**	0.39 (0.16, 0.63)	**0.0013**	0.08 (-0.21, 0.37)	0.5861	0.05 (-0.23, 0.34)	0.7139
Subcutaneous Fat Area	0.10 (-0.05, 0.26)	0.1969	0.11 (-0.05, 0.27)	0.1828	0.17 (-0.06, 0.40)	0.1419	0.20 (-0.04, 0.43)	0.1034	0.01 (-0.27, 0.29)	0.9431	-0.01 (-0.29, 0.27)	0.9553
Anthropometrics												
BMI (kg/cm^2)	0.11 (0.04, 0.18)	**0.0023**	0.11 (0.04, 0.19)	**0.0022**	0.15 (0.04, 0.25)	**0.0053**	0.16 (0.05, 0.26)	**0.0039**	0.06 (-0.07, 0.19)	0.3579	0.05 (-0.08, 0.18)	0.4256
Waist circumference (cm)	0.10 (0.04, 0.15)	**0.0007**	0.10 (0.04, 0.16)	**0.0008**	0.15 (0.07, 0.23)	**0.0004**	0.16 (0.07, 0.24)	**0.0003**	0.03 (-0.07, 0.13)	0.6025	0.02 (-0.08, 0.12)	0.7092

Males	Conventional Model DMA% as independent variable alone				Leave-One-Out Model 1 DMA% adjusted for iAs% (MMA% ↓10%)				Leave-One-Out Model 2 DMA% adjusted for MMA% (iAs% ↓10%)			
	Model 1 (Basic Model)		Model 2 (Advanced Model)		Model 1 (Basic Model)		Model 2 (Advanced Model)		Model 1 (Basic Model)		Model 2 (Advanced Model)	
	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value
Muscle Area (cm^2)												
Locomotion Area	0.00 (-0.04, 0.04)	0.8714	0.01 (-0.03, 0.05)	0.7632	0.07 (0.01, 0.13)	**0.0201**	0.07 (0.01, 0.13)	**0.0214**	-0.09 (-0.17, -0.02)	**0.0148**	-0.09 (-0.16, -0.01)	**0.0265**
Stabilization Area	0.04 (-0.01, 0.10)	0.1291	0.04 (-0.01, 0.10)	0.1499	0.10 (0.02, 0.18)	**0.0196**	0.10 (0.02, 0.18)	**0.0163**	-0.04 (-0.15, 0.07)	0.4534	-0.05 (-0.16, 0.06)	0.3578
Total Abd Muscle Area	0.03 (-0.01, 0.08)	0.1472	0.03 (-0.01, 0.08)	0.1541	0.09 (0.02, 0.16)	**0.0109**	0.10 (0.02, 0.17)	**0.0091**	-0.05 (-0.14, 0.04)	0.2798	-0.05 (-0.15, 0.04)	0.2402
Muscle Density (HU)												
Locomotion Density	-3.13 (-175.40, 169.15)	0.9714	15.66 (-154.16, 185.47)	0.8554	67.50 (-194.77, 329.78)	0.6113	43.52 (-216.86, 303.91)	0.7412	-106.34 (-442.57, 229.90)	0.5324	-24.17 (-353.17, 304.82)	0.8846
Stabilization Density	-0.57 (-3.84, 2.70)	0.7300	-0.40 (-3.76, 2.97)	0.8165	-1.32 (-6.30, 3.66)	0.6013	-1.55 (-6.70, 3.61)	0.5534	0.52 (-5.87, 6.91)	0.8720	1.25 (-5.26, 7.76)	0.7043
Total Abd Muscle Density	-0.57 (-3.37, 2.23)	0.6863	-0.38 (-3.24, 2.49)	0.7957	-0.98 (-5.25, 3.29)	0.6506	-1.19 (-5.58, 3.20)	0.5926	0.02 (-5.45, 5.50)	0.9938	0.79 (-4.76, 6.34)	0.7789
Fat Area (cm^2)												
Locomotion IMAT Area	0.05 (-0.11, 0.22)	0.5317	0.03 (-0.14, 0.19)	0.7543	0.10 (-0.15, 0.35)	0.4278	0.10 (-0.15, 0.35)	0.4377	-0.02 (-0.34, 0.30)	0.9073	-0.08 (-0.40, 0.24)	0.6272
Stabilization IMAT Area	0.04 (-0.08, 0.17)	0.4977	0.03 (-0.09, 0.16)	0.6014	0.09 (-0.10, 0.28)	0.3373	0.10 (-0.09, 0.29)	0.3192	-0.03 (-0.27, 0.21)	0.8094	-0.06 (-0.31, 0.19)	0.6324
Total Abd IMAT Area	0.05 (-0.08, 0.17)	0.4636	0.03 (-0.09, 0.16)	0.5816	0.09 (-0.09, 0.28)	0.3132	0.10 (-0.09, 0.29)	0.2962	-0.03 (-0.27, 0.21)	0.8198	-0.06 (-0.30, 0.18)	0.6187
Visceral Fat Area	0.12 (0.00, 0.24)	0.0539	0.12 (-0.01, 0.24)	0.0670	0.16 (-0.02, 0.35)	0.0800	0.17 (-0.01, 0.36)	0.0707	0.05 (-0.18, 0.29)	0.6596	0.03 (-0.21, 0.27)	0.7952
Subcutaneous Fat Area	0.14 (0.02, 0.27)	**0.0258**	0.16 (0.03, 0.29)	**0.0148**	0.24 (0.06, 0.42)	**0.0102**	0.27 (0.08, 0.46)	**0.0054**	0.00 (-0.24, 0.23)	0.9713	0.00 (-0.24, 0.24)	0.9977
Anthropometrics												
BMI (kg/cm^2)	0.06 (0.02, 0.10)	**0.0022**	0.06 (0.02, 0.10)	**0.0028**	0.10 (0.04, 0.16)	**0.0007**	0.10 (0.04, 0.16)	**0.0010**	0.00 (-0.07, 0.08)	0.9626	0.00 (-0.07, 0.08)	0.9561
Waist circumference (cm)	0.04 (0.01, 0.07)	**0.0053**	0.04 (0.01, 0.07)	**0.0066**	0.06 (0.02, 0.10)	**0.0052**	0.07 (0.02, 0.11)	**0.0042**	0.01 (-0.05, 0.06)	0.7248	0.01 (-0.05, 0.06)	0.8461

Note: Model 1 was adjusted for age, sex, race, region, urinary creatinine and eGFR and total urinary arsenicals. Model 2 further adjusted for smoking and exercise status. Unit of change is 10%. All variables were log-transformed, except for muscle densities, which were square root transformed. eGFR: estimated glomerular filtration rate; iAs: inorganic arsenic; MMA: monomethylarsonic acid; DMA: dimethylarsinic acid.

[1] *Smoking status are categorized as: Never smoke; Former smoker quit more than 1 year ago; Former smoker quit less than 1 year ago; Current smoke; Don't know.*

Supp Table S6 Correlation of Body Composition with Categorical Urinary Cd (by Sex)

		Females				Males			
		Model 1 (Basic Model)		Model 2 (Advanced Model)		Model 1 (Basic Model)		Model 2 (Advanced Model)	
		Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value
Muscle Area (cm^2)									
Locomotion Area	Q2	0.00 (-0.08, 0.08)	0.9943	0.00 (-0.09, 0.08)	0.9147	0.01 (-0.06, 0.09)	0.7580	0.00 (-0.07, 0.08)	0.9317
	Q3	-0.02 (-0.11, 0.06)	0.6069	-0.04 (-0.12, 0.05)	0.4150	-0.02 (-0.09, 0.06)	0.6424	-0.02 (-0.1, 0.05)	0.5500
	Q4	0.00 (-0.09, 0.09)	0.9248	-0.02 (-0.12, 0.07)	0.6696	0.02 (-0.06, 0.10)	0.6190	0.02 (-0.07, 0.10)	0.6963
Stabilization Area	Q2	0.07 (-0.03, 0.16)	0.1639	0.06 (-0.04, 0.15)	0.2429	-0.05 (-0.16, 0.05)	0.3306	-0.05 (-0.15, 0.06)	0.3952
	Q3	0.05 (-0.05, 0.15)	0.3027	0.03 (-0.07, 0.13)	0.5669	-0.05 (-0.15, 0.05)	0.3341	-0.07 (-0.17, 0.03)	0.1954
	Q4	0.06 (-0.04, 0.16)	0.2184	0.02 (-0.09, 0.12)	0.7637	0.00 (-0.12, 0.11)	0.9710	-0.03 (-0.15, 0.08)	0.5629
Total Abd Muscle Area	Q2	0.05 (-0.03, 0.14)	0.2070	0.04 (-0.04, 0.13)	0.3002	-0.04 (-0.13, 0.05)	0.3753	-0.04 (-0.13, 0.05)	0.4071
	Q3	0.04 (-0.05, 0.13)	0.3975	0.02 (-0.07, 0.10)	0.7121	-0.04 (-0.13, 0.04)	0.3224	-0.06 (-0.14, 0.03)	0.1914
	Q4	0.05 (-0.04, 0.15)	0.2408	0.01 (-0.08, 0.10)	0.8244	0.00 (-0.09, 0.10)	0.9441	-0.02 (-0.12, 0.08)	0.6613
Muscle Density (HU)									
Locomotion Density	Q2	71.85 (-292.51, 436.21)	0.6969	53.68 (-315.51, 422.88)	0.7739	-57.61 (-382.03, 266.80)	0.7258	-112.98 (-428.36, 202.41)	0.4796
	Q3	72.64 (-300.92, 446.2)	0.7009	46.51 (-335.78, 428.8)	0.8100	154.99 (-160.91, 470.88)	0.3335	130.22 (-177.03, 437.46)	0.4031
	Q4	200.80 (-186.12, 587.73)	0.3063	160.37 (-254.78, 575.52)	0.4458	26.54 (-326.93, 380.02)	0.8821	23.99 (-323.32, 371.30)	0.8915
Stabilization Density	Q2	-3.17 (-9.37, 3.04)	0.3146	-3.30 (-9.65, 3.04)	0.3050	-4.76 (-10.9, 1.37)	0.1267	-5.35 (-11.56, 0.86)	0.0907
	Q3	-1.21 (-7.57, 5.16)	0.7079	-1.54 (-8.11, 5.03)	0.6440	-2.48 (-8.45, 3.49)	0.4132	-2.48 (-8.53, 3.57)	0.4192
	Q4	-1.78 (-8.37, 4.81)	0.5946	-2.11 (-9.25, 5.02)	0.5590	-1.34 (-8.02, 5.34)	0.6921	-0.98 (-7.82, 5.86)	0.7772
Total Abd Muscle Density	Q2	-2.14 (-7.70, 3.43)	0.4490	-2.31 (-8.00, 3.37)	0.4222	-3.57 (-8.84, 1.70)	0.1824	-4.16 (-9.46, 1.14)	0.1228
	Q3	-1.01 (-6.72, 4.69)	0.7259	-1.36 (-7.25, 4.52)	0.6471	-1.44 (-6.57, 3.69)	0.5784	-1.49 (-6.66, 3.67)	0.5681
	Q4	-0.55 (-6.46, 5.36)	0.8532	-0.92 (-7.31, 5.48)	0.7769	-0.65 (-6.39, 5.09)	0.8220	-0.38 (-6.22, 5.46)	0.8981
Fat Area (cm^2)									
Locomotion Muscle IMAT Area	Q2	-0.09 (-0.44, 0.27)	0.6287	-0.08 (-0.45, 0.28)	0.6572	0.13 (-0.18, 0.44)	0.4223	0.18 (-0.13, 0.49)	0.2498
	Q3	-0.05 (-0.41, 0.32)	0.8051	-0.04 (-0.42, 0.34)	0.8323	-0.09 (-0.39, 0.22)	0.5744	-0.07 (-0.37, 0.23)	0.6416
	Q4	-0.07 (-0.45, 0.31)	0.7141	-0.09 (-0.50, 0.32)	0.6540	-0.04 (-0.38, 0.30)	0.8167	-0.03 (-0.36, 0.31)	0.8812
Stabilization Muscle IMAT Area	Q2	0.20 (-0.01, 0.41)	0.0679	0.20 (-0.02, 0.41)	0.0745	0.14 (-0.10, 0.37)	0.2555	0.17 (-0.07, 0.40)	0.1597
	Q3	0.13 (-0.08, 0.35)	0.2222	0.13 (-0.09, 0.35)	0.2475	0.06 (-0.16, 0.28)	0.5982	0.04 (-0.18, 0.26)	0.7150
	Q4	0.14 (-0.08, 0.37)	0.2048	0.11 (-0.13, 0.36)	0.3546	0.02 (-0.23, 0.27)	0.8953	-0.03 (-0.28, 0.22)	0.8234
Total Abd IMAT Area	Q2	0.17 (-0.04, 0.38)	0.1112	0.17 (-0.04, 0.38)	0.1189	0.14 (-0.09, 0.37)	0.2210	0.18 (-0.05, 0.41)	0.1284
	Q3	0.12 (-0.10, 0.34)	0.2717	0.12 (-0.10, 0.34)	0.2957	0.06 (-0.16, 0.28)	0.6115	0.04 (-0.18, 0.26)	0.7196
	Q4	0.12 (-0.10, 0.35)	0.2716	0.09 (-0.15, 0.33)	0.4398	0.02 (-0.23, 0.27)	0.8689	-0.02 (-0.27, 0.23)	0.8600

		Females				Males			
		Model 1 (Basic Model)		Model 2 (Advanced Model)		Model 1 (Basic Model)		Model 2 (Advanced Model)	
		Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value
Visceral Fat Area	Q2	0.13 (-0.11, 0.37)	0.2796	0.12 (-0.12, 0.37)	0.3265	-0.14 (-0.37, 0.10)	0.2512	-0.12 (-0.35, 0.12)	0.3173
	Q3	0.14 (-0.11, 0.39)	0.2650	0.10 (-0.15, 0.36)	0.4166	-0.17 (-0.4, 0.05)	0.1321	-0.19 (-0.42, 0.03)	0.0962
	Q4	0.23 (-0.03, 0.48)	0.0791	0.15 (-0.12, 0.43)	0.2718	-0.14 (-0.4, 0.11)	0.2624	-0.19 (-0.45, 0.07)	0.1544
Subcutaneous Fat Area	Q2	0.10 (-0.12, 0.32)	0.3843	0.11 (-0.12, 0.34)	0.3305	0.12 (-0.13, 0.36)	0.3497	0.11 (-0.14, 0.37)	0.3768
	Q3	0.02 (-0.21, 0.25)	0.8638	0.03 (-0.21, 0.27)	0.7840	0.18 (-0.05, 0.41)	0.1175	0.19 (-0.04, 0.43)	0.1036
	Q4	0.13 (-0.11, 0.37)	0.2720	0.11 (-0.14, 0.37)	0.3753	-0.01 (-0.27, 0.24)	0.9220	-0.01 (-0.27, 0.25)	0.9376
Anthropometrics									
BMI (kg/cm^2)	Q2	0.05 (-0.06, 0.16)	0.3410	0.05 (-0.06, 0.16)	0.3595	0.02 (-0.06, 0.10)	0.6008	0.02 (-0.06, 0.10)	0.5889
	Q3	0.05 (-0.06, 0.16)	0.3836	0.04 (-0.07, 0.16)	0.4537	0.02 (-0.06, 0.09)	0.6382	0.01 (-0.06, 0.09)	0.7621
	Q4	0.05 (-0.07, 0.16)	0.4296	0.02 (-0.10, 0.15)	0.7090	-0.04 (-0.12, 0.05)	0.3940	-0.04 (-0.13, 0.04)	0.3134
Waist Circumference (cm)	Q2	0.05 (-0.04, 0.13)	0.2881	0.05 (-0.04, 0.14)	0.2598	0.02 (-0.03, 0.08)	0.4119	0.03 (-0.03, 0.09)	0.3552
	Q3	0.05 (-0.04, 0.14)	0.2727	0.05 (-0.04, 0.14)	0.2587	0.02 (-0.04, 0.08)	0.4844	0.02 (-0.04, 0.08)	0.5031
	Q4	0.06 (-0.03, 0.15)	0.1942	0.05 (-0.04, 0.15)	0.2852	0.00 (-0.06, 0.06)	0.9946	0.00 (-0.07, 0.06)	0.9432

Note: model 1 was adjusted for age, sex, race, region, urinary creatinine and eGFR. Model 2 further adjusted for smoking[1] and exercise status. eGFR: estimated glomerular filtration rate.

[1] Smoking status are categorized as: Never smoke; Former smoker quit more than 1 year ago; Former smoker quit less than 1 year ago; Current smoke; Don't know.

Supp Table S7 Correlation of Body Composition with Continuous Urinary Cd (by Sex)

	Females				Males			
	Model 1 (Basic Model)		Model 2 (Advanced Model)		Model 1 (Basic Model)		Model 2 (Advanced Model)	
	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value
Muscle Area (cm^2)								
Locomotion Area	0.01 (-0.03, 0.04)	0.6000	0.00 (-0.04, 0.04)	0.9775	0.01 (-0.03, 0.04)	0.7353	0.00 (-0.03, 0.04)	0.8421
Stabilization Area	0.02 (-0.02, 0.06)	0.2945	0.00 (-0.04, 0.05)	0.8549	0.00 (-0.05, 0.05)	0.9822	-0.02 (-0.07, 0.03)	0.3906
Total Abd Muscle Area	0.02 (-0.02, 0.06)	0.2780	0.00 (-0.03, 0.04)	0.8450	0.00 (-0.04, 0.05)	0.9154	-0.02 (-0.06, 0.03)	0.4774
Muscle Density (HU)								
Locomotion Density	84.71 (-65.85, 235.27)	0.2676	68.87 (-92.84, 230.59)	0.4007	-20.46 (-176.31, 135.40)	0.7955	-20.19 (-176.82, 136.43)	0.7990
Stabilization Density	0.53 (-2.05, 3.10)	0.6862	0.52 (-2.27, 3.31)	0.7143	-0.50 (-3.46, 2.45)	0.7357	-0.29 (-3.38, 2.81)	0.8549
Total Abd Muscle Density	0.67 (-1.64, 2.97)	0.5669	0.60 (-1.89, 3.10)	0.6323	-0.34 (-2.87, 2.19)	0.7920	-0.16 (-2.79, 2.48)	0.9074
Fat Area (cm^2)								
Locomotion Muscle IMAT Area	-0.03 (-0.18, 0.12)	0.6846	-0.04 (-0.20, 0.12)	0.6026	-0.03 (-0.18, 0.12)	0.6617	-0.03 (-0.18, 0.12)	0.6815
Stabilization Muscle IMAT Area	0.02 (-0.07, 0.11)	0.6662	0.01 (-0.09, 0.10)	0.9129	0.02 (-0.09, 0.14)	0.6734	0.00 (-0.12, 0.11)	0.9396
Total Abd IMAT Area	0.02 (-0.07, 0.10)	0.7295	0.00 (-0.09, 0.10)	0.9724	0.02 (-0.09, 0.13)	0.6752	0.00 (-0.12, 0.11)	0.9498
Visceral Fat Area	0.09 (-0.01, 0.19)	0.0788	0.06 (-0.05, 0.17)	0.2616	-0.05 (-0.16, 0.06)	0.4015	-0.08 (-0.19, 0.04)	0.1909
Subcutaneous Fat Area	0.04 (-0.06, 0.13)	0.4283	0.03 (-0.07, 0.13)	0.6034	0.00 (-0.11, 0.12)	0.9775	0.01 (-0.11, 0.13)	0.9204
Anthropometrics								
BMI (kg/cm^2)	0.02 (-0.02, 0.06)	0.3711	0.01 (-0.04, 0.06)	0.6068	-0.01 (-0.05, 0.03)	0.5752	-0.02 (-0.06, 0.02)	0.4031
Waist Circumference (cm)	0.02 (-0.01, 0.06)	0.2201	0.02 (-0.02, 0.06)	0.3203	0.00 (-0.02, 0.03)	0.8531	0.00 (-0.03, 0.03)	0.9678

Note: model 1 was adjusted for age, sex, race, region, urinary creatinine and eGFR. Model 2 further adjusted for smoking[1] and exercise status. eGFR: estimated glomerular filtration rate.

[1] Smoking status are categorized as: Never smoke; Former smoker quit more than 1 year ago; Former smoker quit less than 1 year ago; Current smoke; Don't know.

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