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Plasma Proteomic Markers of Iron and Risk of Diabetes in a Cohort of African American and White American Current and Former Smokers

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Background: Little information is available on iron with diabetes risk among African Americans, a population where both anemia and elevated ferritin are common. We tested whether plasma proteomic measurements of ferritin and transferrin were associated with increased diabetes risk in a cohort of current and former African American (NHB) and Non-Hispanic White (NHW) smokers.

Methods: NHB and NHW participants from the COPDGene study who were free of diabetes (n = 4693) at baseline were followed for incident diabetes. The SomaScan was used to determine the relative amounts of natural log-transformed ferritin, transferrin, and hepcidin.

Findings: During an average of 5.6 years of follow-up, diabetes incidence was 7.9%. Ferritin at follow-up was higher in NHB than NHW participants (p = <0.0001). Ferritin at follow-up was associated with increased diabetes risk (OR = 1.36, 95% CI = 1.08–1.70), while transferrin was associated with decreased risk (OR = 0.25, 95% CI = 0.08–0.77) controlling for age, sex, BMI, smoking pack-years, hepcidin, CRP, and Il-6. Race-specifically, increased risk associated with higher ferritin levels among NHB (OR = 1.56, 95% CI = 1.13–2.16) but not NHW (OR = 1.22, 95% CI = 0.89–1.68) participants. Sex-specifically, ferritin's relationship was similar among NHB men and women and NHW women (ORs ranging from 1.41–1.59); but not NHW men (OR = 0.98, 95% CI = 0.64–1.49). Similarly, transferrin ORs non-significantly ranged from 0.19–0.30 for NHB men and women and NHW women, but was significant for NHW men (OR = 0.07, 95% CI = 0.01–0.63).

Interpretation: Higher body iron stores is associated with increased diabetes risk among both NHB and NHW people. Unsuspected elevated iron stores may increase diabetes risk in NHB patients and should be monitored.

Keywords: diabetes, iron, ferritin, transferrin, African Americans

Diabetes disproportionately affects African Americans, with rates 50 to 100% higher than non-Hispanic Whites,[1,2] for reasons only partially accounted for by obesity, physical activity, and socioeconomic status.[2] Socioeconomic status is often put forward as the reason for Black-White differences in chronic diseases, including diabetes, but unsuspected increased iron stores may be playing a role. Higher levels of iron have been linked to increased diabetes risk among European and Non-Hispanic White (NHW) American populations;[3–6] however, limited data is available on the relationship between iron and diabetes among African Americans, despite their on average higher levels of ferritin, the strongest marker of body iron stores.

Ferritin is an iron storage protein linked to diabetes risk[4,5,7,8] and is the most reliable marker of body iron stores; transferrin transports catalytic iron, reducing its oxidative damage, and has also been linked to diabetes.[4] Both the Nurses' Health Study[6] and the EPIC-Norfolk study[4,5] observed an increased likelihood of diabetes associated with higher

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ferritin levels, while a large study by Ellervik et al examining three European populations observed increased likelihood of diabetes with transferrin saturation (TSAT) levels greater than 50%.[3] However, these were all almost exclusively White European ancestry populations. In the Hemochromatosis and Iron Overload Screening Study (HEIRS) study, higher ferritin levels were associated with increased odds of diabetes in all ethnic groups investigated, including African Americans.[9] However, in contrast to the Ellervik et al study in Europeans, the HEIRS study found that higher TSAT levels were associated with lower odds of diabetes.

The distribution of iron varies by race,[9,10] with classic hereditary iron overload, or hemochromatosis being more common among those of European ancestry.[11] While less likely to have the rare condition of iron overload typified by classic hemochromatosis, ferritin levels are generally at the higher end of the normal range in African Americans compared to NHW Americans.[12,13] This paradox is further heightened because although some of the racial differences in body iron stores may be due to differences in protein and in particular iron consumption, the strongest determinant of body iron stores, African Americans are known to have lower protein and iron consumption than other races.[14,15] The iron hypothesis posits that variations in iron stores contribute to the disparities in chronic diseases. We investigated whether plasma proteomic measurements of ferritin and transferrin were associated with an increased risk of diabetes in a biracial cohort of current and former smokers.

Research Design and Methods

COPDGene (ClinicalTrial.gov identifier: NCT000608764) is a longitudinal observational study of 10,198 self-identified NHW and African American current and former smokers from 21 clinical centers throughout the United States. Institutional review board approval (November 8, 2004; IRB # HS-1883) was obtained from National Jewish Health, and all subjects provided written informed consent. Our study complies with the Declaration of Helsinki. At baseline (Phase 1, 2008–2011), participants were aged 45–80 years, with 10 or more pack-years of cigarette smoking history; exclusion criteria included a history of significant lung disease other than chronic obstructive pulmonary disease (COPD) or asthma and history of lung volume reduction surgery or lung transplantation. Phase 1 participants were invited to return for a 5-year follow-up study visit (Phase 2, 2012–2016). The study protocol and related documents are available at www.copdgene.org.

Diabetes was based on self-reported physician diagnosis of diabetes. Specifically, at the study baseline and in repeated surveys occurring every six months during follow-up, participants were asked, "Have you been diagnosed with diabetes by a doctor?". Data on height, weight, smoking history, and other clinical data, such as complete blood count, were also collected. Participants reporting at study baseline not having a physician diagnosis of diabetes but reporting during follow-up as having been diagnosed with diabetes were considered incident diabetes cases. Race was based on self-report. Sex as a biological variable was also based on self-report and verified by both genotyping and follow-up with the participants about sex assigned at birth. As per SAGER guidelines,[16] in this study sex is used as a biological variable. Certain measurements such as hemoglobin and proteomics plasma measurements were not conducted for the majority of the study population at baseline and thus for these specific measurements only phase 2 data will be used.

The proteomic measurements were performed on plasma samples collected during the 5-year follow-up visit. Participants who provided consent to have their blood used in medical research had an ethylenediaminetetraacetic acid (EDTA plasma) tube of blood drawn and aliquots of plasma was stored at −80°C until protein quantification. Protein levels were quantified and quality controlled by SomaLogic using their SomaScan® version 4.0 (5.0K) assay for human plasma, which contains 5285 SOMAmers. This platform measures the relative abundance of 4776 unique human proteins. SomaLogic standardized the results per their protocol and COPDGene conducted additional data cleaning resulting in 5670 results available for use as previously reported.[17] SomaLogic standardized the results per their protocol, which included 1) controlling for variation across array signals by using within-plate hybridization, 2) controlling for technical variation within run replicates by using median signal normalization which corrects for sample differences in protein concentration, 3) using plate scaling and calibration to control for interassay variability between analytes and batch differences between plates, and 4) removal of edge effects and technical variance by using maximum likelihood adaptive normalization on quality control replicates.[17,18] Further details on the 5670 subjects with data are available.[19]

This report focuses on the 4693 study participants with data on diabetes status, proteomic measurements, and other covariates.

Unadjusted continuous data were analyzed by using the *t*-test or general linear models; categorical data were analyzed using the chi-square test. Logistic regression was used to determine the multivariable adjusted independent associations of plasma proteomic measurements of ferritin and transferrin collected at the Phase 2 follow-up visit with incident diabetes at the Phase 2 follow-up visit. Multivariable models included terms for age, sex, race (when not race-stratified), body mass index (BMI), smoking pack years, plasma proteomic measurements of ferritin, transferrin, hepcidin C-reactive protein (CRP), and interleukin 6 (IL-6). Non-normally distributed data such as ferritin were natural logarithmically transformed before analysis. Plasma proteomic measures were also natural logarithmically transformed before analysis. Tests for the interaction of these variables with either sex or race (NHB, NHW) were conducted by adding the corresponding cross-product terms to the models, and significant interactions are listed in the results section. All tests for statistical significance were two-tailed. Statistical analysis was conducted using SAS version 9.4 (Cary, North Carolina).

Results

Of the 4693 study participants with data on diabetes status, proteomic markers and covariate data, 348 developed diabetes during follow-up. Compared to those not developing diabetes, incident cases were younger at the study baseline (58.1 vs 59.9 years), more likely to be African American (42.2 Vs 26.4%), had a higher mean BMI (33.0 vs 28.3 kg/m^2) and significantly more smoking pack years at study entry (43.7 vs 41.9 years). They were also significantly more likely to have chronic obstructive pulmonary disease (58.8 vs 52.3%, $p < 0.05$). At the phase 2 follow-up visit, incident cases had higher ferritin and transferrin plasma proteomic levels, but there was no difference in hemoglobin or proteomic plasma measurement of hepcidin. Differences by sex were not observed between incident cases and those not developing diabetes during follow-up.

When stratified by race, no age differences between diabetes cases and non-cases were observed, but a sexual dimorphism by race emerged. Among African Americans, women were more likely to develop diabetes during follow-up, while the converse was true for NHW Americans, with incident diabetes cases more likely to be males. Hemoglobin was on average about half a gram per deciliter lower in African Americans compared to NHW Americans among incident diabetes cases and nearly a gram per deciliter lower in African American compared to NHW Americans among non-cases though differences by diabetes status were not observed in either race. Mean transferrin and hepcidin were significantly lower and ferritin significantly higher among African Americans compared to NHW Americans (data not depicted), however, of these three iron-related proteomic measured proteins, only transferrin demonstrated differences by diabetes status, with lower levels observed among incident cases among African Americans but higher levels observed for incident cases among NHW Americans. Characteristics of the study participants by incident diabetes status, stratified by race, are presented in Table 1 and Appendix Table 1.

Table 1 Characteristics of the COPDGene Study Population by Incident Diabetes Status, Stratified by Race, Mean (Std), or % (n)

Characteristics	African Americans		Non-Hispanic White Americans	
	Incident Diabetes (n=147)	No Diabetes (n=1148)	Incident Diabetes (n=201)	No Diabetes (n=3197)
Characteristics at Phase 1				
Age, years	55.5 (5.4)	54.2 (7.1)	61.4 (7.7)	62.0 (8.5)
Sex, female	57.8 (85)	48.3 (554)[a]	47.3 (95)	51.2(1637)
BMI, kg/m^2	32.2 (6.9)	28.4 (6.3)[d]	33.5 (7.0)	28.2 (5.4)[d]
Smoking pack years*	36.4 (20.3)	37.5 (20.8)	49.0 (24.0)	43.5 (23.6)[b]

(*Continued*)

Table 1 (Continued).

Characteristics	African Americans		Non-Hispanic White Americans	
	Incident Diabetes (n=147)	**No Diabetes (n=1148)**	**Incident Diabetes (n=201)**	**No Diabetes (n=3197)**
Proteomics and iron related indices at Phase 2				
Hemoglobin, g/dL	13.7 (1.5)	13.6 (1.5)	14.1 (1.5)	14.4 (1.4)
Natural log Ferritin, RFU	8.8 (8.6)	8.7 (8.7)	8.6 (0.81)	8.5 (0.80)
Natural log Transferrin, RFU	12.1 (0.11)	12.1 (0.11)	12.1 (0.10)	12.1 (0.10)[d]
Natural log Hepcidin, RFU	7.4 (0.84)	7.4 (0.87)	7.6 (0.86)	7.5 (0.89)
CRP, RFU	10.2 (0.80)	9.9 (0.97)[c]	10.1 (0.74)	9.8 (0.79)[d]
IL-6*, RFU	6.3 (0.49)	6.5 (0.56)	6.2 (0.51)	6.1 (0.53)[b]

Notes: *Natural log transformed before analyses. RFU= relative fluorescent units. a=p<0.05 b=p<0.0 c=p<0.001 d=p<0.0001.

Figure 1 shows the age and sex adjusted mean values plasma proteomic measures of ferritin, transferrin, and hepcidin, expressed in reflective fluorescent units (RFU) and serum hemoglobin expressed as g/dL. Values of all four iron biomarkers were significantly different by race. African Americans had significantly higher ferritin, but lower transferrin, hepcidin, and hemoglobin levels than NHW Americans.

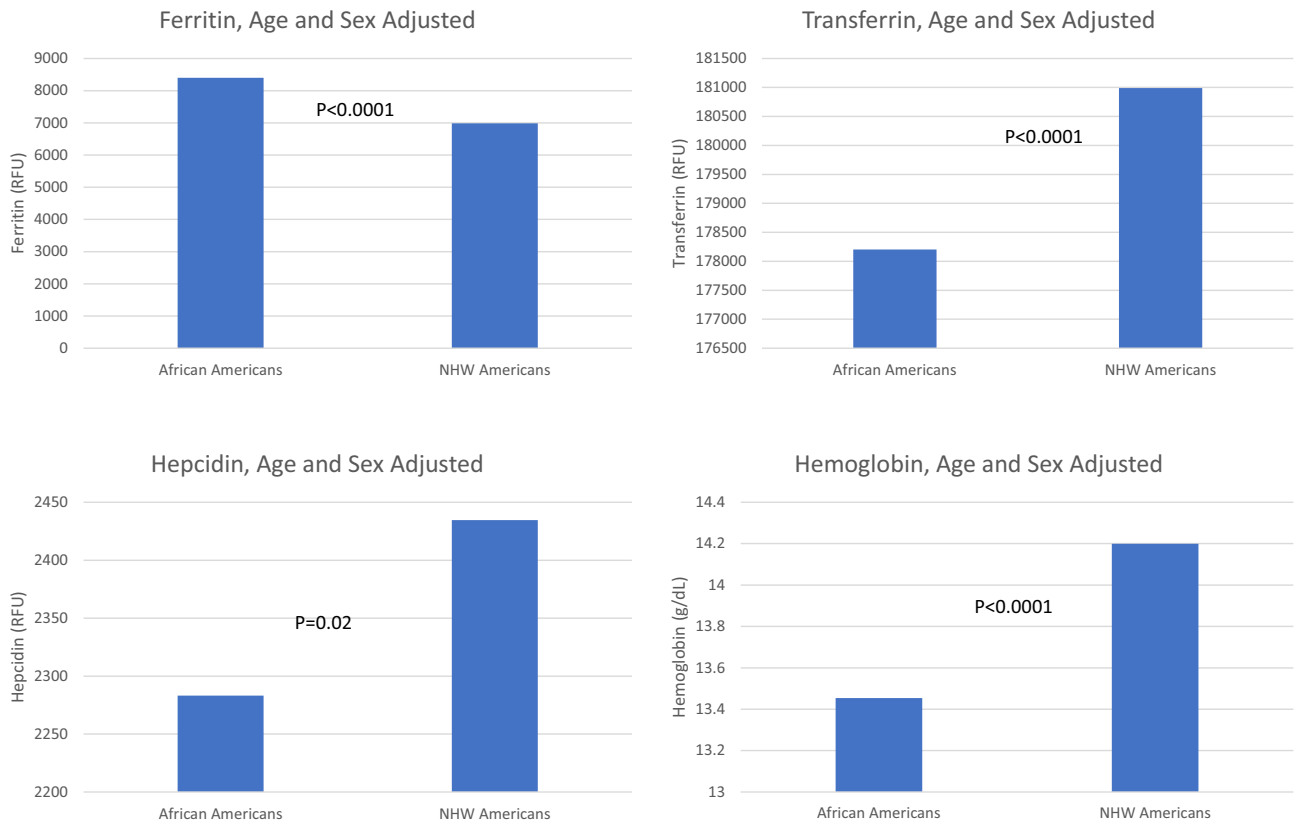

Figure 1 Age and sex adjusted mean iron biomarker values in African Americans and Non-Hispanic White (NHW) Americans.

The multivariable adjusted relationship of the iron-related proteomic measured plasma proteins with incident diabetes among the population as a whole is presented in Table 2. Hepcidin adjusted ferritin was associated with a modestly increased odds of being an incident diabetes case. This increased odds of incident diabetes associated with ferritin remained after further accounting for transferrin. Each log increase in transferrin relative fluorescent units was associated with an 83% decrease in the likelihood of being an incident diabetes case, a relationship that remained essentially unchanged after further control for hemoglobin and subsequently CRP and IL-6. Examination of these relationships by quintiles of ferritin and transferrin revealed that the highest risk was observed among those in the top quintile of ferritin, while the lowest risk was observed among those in the top quintile of transferrin (Appendix Table 2).

When stratified by race, the multivariable adjusted relationship of ferritin with the odds of incident diabetes remained in African Americans but showed no relationship among NHW Americans. By contrast, transferrin demonstrated a significant and highly inverse relationship with incident diabetes among NHW Americans but a non-significant and less strongly inverse relationship among African Americans. Hemoglobin was not associated with diabetes in either race. Further control for the inflammatory markers CRP and Il-6 modestly strengthened the relationship of ferritin with diabetes in both races, suggesting that these markers of inflammation were negative confounders, though the relationship in NHW Americans remained non-significant. The race-specific multivariable adjusted relationship of the iron-related proteomic plasma proteins with incident diabetes is presented in Table 3.

Table 2 Iron Somascan Biomarkers and Odds of Incident Diabetes at Phase 2 in the Overall Population

	Model 1	Model 2	Model 3	Model 4
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Race, African American vs NHS American	1.87 (1.44–2.43)	1.81 (1.40–2.36)	1.80 (1.37–2.36)	1.73 (1.31–2.27)
Ferritin	1.29 (1.03–1.60)	1.29 (1.04–1.61)	1.31 (1.05–1.64)	1.36 (1.08–1.70)
Hepcidin	0.86 (0.70–1.05)	0.82 (0.67–1.01)	0.82 (0.67–1.00)	0.80 (0.65–0.97)
Transferrin		0.17 (0.06–0.52)	0.19 (0.06–0.56)	0.25 (0.08–0.77)
Hemoglobin at follow-up			0.98 (0.90–1.07)	0.99 (0.91–1.08)
CRP				1.18 (1.00–1.38)
IL-6				1.21 (0.98–1.49)

Note: All models additionally controlled for sex, baseline BMI, and baseline natural log-transformed smoking pack years. Ferritin, hepcidin, transferrin, CRP, and IL-6 were natural logarithmically transformed before analyses.
Abbreviation: NHW, Non-Hispanic White.

Table 3 Iron Somascan Biomarkers and Odds of Incident Diabetes at Phase 2, Stratified by Race

	African Americans				Non-Hispanic White Americans			
	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Ferritin	1.44 (1.05–1.97)	1.46 (1.07–2.00)	1.42 (1.04–1.96)	1.56 (1.13–2.16)	1.13 (0.83–1.53)	1.12 (0.82–1.52)	1.19 (0.87–1.63)	1.22 (0.89–1.68)
Hepcidin	0.80 (0.59–1.07)	0.77 (0.57–1.04)	0.76 (0.56–1.04)	0.70 (0.51–0.95)	0.92 (0.70–1.20)	0.88 (0.67–1.14)	0.86 (0.66–1.13)	0.86 (0.66–1.12)
Transferrin		0.31 (0.06–1.57)	0.32 (0.06–1.60)	0.51 (0.10–2.73)		0.11 (0.02–0.49)	0.12 (0.03–0.55)	0.15 (0.03–0.67)
Hemoglobin			1.09 (0.96–1.24)	1.10 (0.96–1.25)			0.90 (0.80–1.02)	0.91 (0.81–1.03)
CRP				1.41 (1.11–1.81)				0.99 (0.79–1.23)
IL-6				1.03 (0.74–1.42)				1.40 (1.07–1.83)

Note: All models additionally controlled for age, sex, baseline BMI, and baseline natural log-transformed smoking pack years.

Further stratification by sex revealed similar relationships for African American men and women and NHW American women for ferritin and transferrin, with an approximately 50% increased risk associated with ferritin and an approximately 70 to 80% decreased risk associated with transferrin, though relationships were not significant (Appendix Table 3). No relationship between ferritin and incident diabetes risk was observed for NHW American men, but transferrin was associated with highly decreased odds of incident diabetes (Appendix Table 3). However, upon further control for CRP and IL-6 (Appendix Table 4), the relationship between ferritin and incident diabetes became significant in African American men and NHW American women and borderline significant in African American women ($p = 0.06$). Controlling for CRP and Il-6 strengthened the relationship between ferritin and diabetes by about 10% in African American men and women, suggesting that these inflammatory markers were negative confounders. By contrast, with the exception of NHW American men, controlling for CRP and Il-6 attenuated the relationship between transferrin and diabetes in all sex-race groups, suggesting that these inflammatory markers were positive confounders in the transferrin-diabetes relationship. Tests for interaction by sex with race in the ferritin-diabetes and the transferrin-diabetes relationships were not significant.

Finally, as menopausal status and certain medications may confound the relationship of iron-related markers with diabetes, we ran additional analyses controlling for menopausal status and the following medication classes: statins, antiplatelets, diuretics, ACE/ARBS, and proton pump inhibitors. Accounting for menopausal status and these medications appeared to strengthen the relationship of ferritin with diabetes in the overall population (Appendix Table 5) and race-specifically (Appendix Table 6). By contrast, accounting for these factors attenuated the relationship of transferrin with diabetes, particularly in NHW participants.

Discussion

Limited information is available on the relationship of iron with diabetes among African Americans and whether this differs from that in NHW Americans. In this population of approximately 5000 African American and NHW participants, we found that plasma proteomic markers of iron were associated with diabetes in both races, but that the strength of the association differed by race. Ferritin demonstrated a stronger association with diabetes among African Americans, while transferrin demonstrated a stronger association among NHW Americans, particularly NHW males. We also observed that the direction of the association varied by biomarker, with a positive association with diabetes for ferritin and an inverse association for transferrin. Our findings may have clinical significance for the prevention and treatment of diabetes, particularly for African Americans, a population little suspected of elevated iron stores.

Few studies have examined the relationship of iron with diabetes among African Americans. Hemoglobin and hematocrit, the most common routine measurements of iron status, are on average lower in African Americans than other racial/ethnic groups and anemia is more common, particularly compared to NHW Americans. Thus, low iron, rather than elevated iron stores, is more likely to be clinically suspected. Nevertheless, ferritin, the most reliable marker of body iron stores, is generally higher in African Americans than NHW Americans, despite their lower hemoglobin levels and lower transferrin and transferrin saturation. Consistent with this, we also found plasma proteomic measures of ferritin to be higher despite lower hemoglobin levels in our African American compared to NHW American participants. Iron loading anemias, sickle cell disease, and thalassemias, for example, are also over-represented among African Americans, and these anemias have a tendency for iron loading even in the absence of therapeutic iron supplementation,[20] with parenchymal iron loading similar to that observed in classical HFE-associated hemochromatosis. Mutations in a-thalassemia, present in 16–18% of the African American population,[21] were shown to account for a third of the difference in hemoglobin levels between iron sufficient African Americans and NHW Americans.[21] Mutations in the SLC40a1, which are present in about 20% of African Americans but uncommon among White Europeans and NHW Americans, are characterized by low hemoglobin but high ferritin levels and have also been posited as a reason the paradoxical low hemoglobin-high body iron stores status among African Americans.

The relationship between iron and diabetes has been extensively studied in Europeans and NHW Americans; however, few studies have examined this relationship among African Americans despite their on average higher ferritin levels. Consistent with other studies, we found that markers of iron status were associated with an increased likelihood of incident diabetes. We also found ferritin to be linked to incident diabetes among our African American participants. A study of African American and NHW American men recruited from the Veterans Affairs Medical Center in Jackson,

Mississippi, found ferritin levels were positively correlated with fasting blood glucose in HbA1c among both races.[22] In one of the only previous studies to evaluate the relationship of markers of iron status with diabetes risk in African Americans, Acton and colleagues found that high serum ferritin levels were associated with greater odds of having diabetes in women, but not men.[9] Our data, by contrast, indicated no difference between men and women in the association of ferritin with diabetes.

Contrary to other studies,[8,23] ferritin was not associated with diabetes among NHW men in our population. However, transferrin was associated with a decreased risk among NHW Americans, especially males, but showed no association with diabetes among African Americans in our population. While studies have been mixed on the relationship between transferrin saturation and diabetes, with some reporting positive[3] and others reporting inverse relationships,[9] the relationship of transferrin with diabetes risk has generally been null.[24] A meta-analysis by Orban and colleagues found no association between transferrin and type 2 diabetes risk, overall or in any of the individual studies making up the meta-analysis.[24] Transferrin, by itself, is usually not a sensitive marker of body iron stores, but it does go up in iron deficiency and down in pathological iron overload. Elevated transferrin is a marker of iron deficiency, and the combination of increased ferritin and lowered transferrin is confirmatory of increased iron stores in African Americans and of the relationship of increased iron stores to incident diabetes. The very strong inverse relationship we observed between transferrin and incident diabetes, particularly in NHW American men, may relate to this being the strongest marker of hemochromatosis among Europeans and NHW Americans, a condition most common among men of predominant European ancestry. Additionally, genetic downregulation of transferrin has been shown to cause insulin resistance,[25] and insulin resistance is thought to play a more dominant etiologic role among NHW than African Americans.

Multiple mechanisms by which iron contributes to diabetes risk have been identified[26] and include both insulin resistance[27] and beta cell ferroptosis leading to insulin insufficiency. Iron, one of the most common elements on earth and the most common human nutritional deficiency, has been called the soul of life on earth.[28] Iron has the capacity to readily accept and donate electrons. It is this capacity that also makes it dangerous, facilitating the conversion of hydrogen peroxide to free radicals and resulting oxidative stress to cellular proteins. Specifically, iron catalyzes the Haber-Weiss reaction in which the highly reactive hydroxyl radical (HO) free radical is generated from the interaction between superoxide and hydrogen peroxide. This iron catalyzed reaction is known as the Fenton reaction. Due to the Fenton reaction, excess iron in the beta cell leads to the generation of reactive oxygen species as a result of iron reacting with hydrogen peroxide, and free radicals. These in turn cause beta cell dysfunction and apoptosis. In murine models, McClain et al have demonstrated that while iron decreases insulin sensitivity,[29] the primary mechanism by which iron leads to diabetes in both animals and humans is through impaired insulin secretion.[30] Even within the normal range of iron, higher levels of iron have been shown to increase diabetes risk.[6,23] Supporting this, phlebotomy studies and iron chelation in humans have been shown to reduce HbA1c, glucose and glucose intolerance, and insulin resistance.

Strengths of our study include our large sample of both African American and NHW American men and women, our ability to account for hepcidin and markers of inflammation, our data on diabetes status at multiple time points, and our proteomics data. Hepcidin is the regulator of dietary iron absorption, functioning as a negative feedback regulator of iron absorption from the intestine. Low hepcidin levels cause an increase in dietary iron absorption, while higher hepcidin levels block intestinal iron absorption by the iron exporter ferroportin, resulting in iron-free ferritin.[31] By accounting for hepcidin, we were able to both control for inflammation associated with ferritin and strengthen the likelihood of ferritin being a marker of iron stores in our population.

A limitation of our data is that ferritin, in addition to being an iron storage protein, is also an acute phase reactant that can increase during inflammation. Thus, elevated ferritin can indicate either increased iron stores or inflammation, or both. However, data suggests that the relationship of ferritin with diabetes is independent of inflammation. Further, the relationship of diabetes to serum ferritin levels has been shown to be relatively minor, and even in cases of more severe inflammatory states such as sickle cell disease and biopsy-based studies of non-alcoholic steatohepatitis, ferritin still mainly reflects iron stores rather than inflammation.[32,33] Our findings support this. In our population even after further controlling for inflammation the relationship between ferritin and diabetes remained. In fact, accounting for inflammation, specifically CRP and Il-6, strengthened the association between ferritin and diabetes among African Americans in our population, while CRP also remained a significant correlate.

Another limitation of our study is that our population was a cohort of current and former smokers, a good proportion of whom had lung disease. Smoking is linked to abnormal iron metabolism in the lungs and thought to contribute to the pathology of lung disease among smokers.[34] Lung disease is also associated with an increased likelihood of diabetes;[35] This may have contributed to the apparently stronger relationship of smoking with diabetes among our NHW American than African American participants (data not depicted), who had a substantially higher number of smoking pack years. However, even minimizing any confounding by smoking in our population by controlling for the number of smoking pack years, the relationship of the iron biomarkers with diabetes remained. Our lack of data on dietary iron consumption or protein malabsorption status is also a limitation. Persons identifying as African American are known to consume less dietary iron and less overall protein than those of other races.[14,15] However, reduced iron consumption, and malabsorption of iron, would result in lower ferritin levels. Thus, any bias concerning dietary iron consumption or malabsorption status and would likely have biased the results towards the null, suggesting that the associations we observed were even stronger. Finally, with the exception of hemoglobin, our study was based on plasma proteomic measurers of iron biomarkers, and thus we do not have absolute values of these iron measures, only inter-participant relative measures. We cannot provide cut-off points at which levels these iron markers appear to be either pathogenic or protective. However, to our knowledge, this is the first study to investigate the association of iron with diabetes risk using plasma proteomic measures of iron biomarkers and provides evidence that higher iron stores also increase diabetes risk among African Americans.

Conclusion

Increased iron stores as a contributor to diabetes risk among African Americans are an understudied area of research and overlooked clinical risk factor. Our data suggest that despite having lower hemoglobin levels, iron stores are higher among African Americans and are at least as strong of a risk factor for diabetes as among NHW Americans, particularly among current and former smokers. While ferritin may be a stronger marker for African Americans and low levels of transferrin a stronger marker for NHW Americans, especially NHW American men, both suggest that monitoring for elevated iron levels among middle-aged and elderly African Americans and NHW Americans in order to decrease diabetes risk may be worthwhile. Intervention could be straightforward as iron levels are easily modified by diet and phlebotomy.

Data Sharing Statement

Although the parent study has a clinical trial identifier number, neither the parent study nor this ancillary study was a clinical trial. The COPDGene study is a longitudinal, observational cohort study. Both clinical trials and observational research studies can be listed in the ClinicalTrials.gov database. https://clinicaltrials.gov/about-site/about-ctg.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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