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Polygenic Risk Scores Point toward Potential Genetic Mechanisms of Type 2 Myocardial Infarction in People with HIV

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Author contributions

WJL, IP drafted and edited the manuscript. WJL, IP, HC, KH, BMW, RMN, SRW, KJ, SAR processed, analyzed, visualized and interpreted the data. HMC, PKC, CM, JAD, SL, GB, MMK, MSS, AWillig, JJE, JCK, JLMB, WCM, EC, MJF, MB, PWH, RDM, JK, MEM, GC, AWebel, KHM participated in cohort setup and data collection, sample processing, assisted with data acquisition, interpretation, and provided substantive comments and edits for the manuscript. All authors read and approved the final manuscript.

Author Statement

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Declaration of competing interest

The authors declare no conflict of interest.

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Abstract

Background—People with human immunodeficiency virus (HIV) infection (PWH) are at higher risk of myocardial infarction (MI) than those without HIV. About half of MIs in PWH are type 2 (T2MI), resulting from mismatch between myocardial oxygen supply and demand, in contrast to type 1 MI (T1MI), which is due to primary plaque rupture or coronary thrombosis. Despite worse survival and rising incidence in the general population, evidence-based treatment recommendations for T2MI are lacking. We used polygenic risk scores (PRS) to explore genetic mechanisms of T2MI compared to T1MI in PWH.

Methods—We derived 115 PRS for MI-related traits in 9,541 PWH enrolled in the Centers for AIDS Research Network of Integrated Clinical Systems cohort with adjudicated T1MI and T2MI. We applied multivariate logistic regression analyses to determine the association with T1MI and T2MI. Based on initial findings, we performed gene set enrichment analysis of the top variants composing PRS associated with T2MI.

Results—We found that T1MI was strongly associated with PRS for cardiovascular disease, lipid profiles, and metabolic traits. In contrast, PRS for alcohol dependence and cholecystitis, significantly enriched in energy metabolism pathways, were predictive of T2MI risk. The association remained after the adjustment for actual alcohol consumption.

Conclusions—We demonstrate distinct genetic traits associated with T1MI and T2MI among PWH further highlighting their etiological differences and supporting the role of energy regulation in T2MI pathogenesis.

Keywords

Type 1 myocardial infarction; type 2 myocardial infarction; HIV; polygenic risk score; energy metabolism

1. Introduction

Antiretroviral therapy (ART) has significantly improved the survival of people with human immunodeficiency virus (HIV) infection (PWH). Yet, the burden of cardiovascular disease (CVD), particularly myocardial infarction (MI), remains higher in PWH than in uninfected persons [1–3]. Several studies have identified HIV-related risk factors that contribute to elevated MI risk among PWH, including low CD4 cell counts, chronic inflammation, and ART-related dyslipidemia [3, 4]; however, to date, traditional and HIV-related CVD risk factors do not fully explain the increased MI rates among PWH. Moreover, ~50% of MIs among PWH are type 2 MI (T2MI) [5, 6], resulting from a mismatch between myocardial oxygen supply and demand [7, 8], rather than type 1 MI (T1MI) which are due to primary plaque rupture or coronary thrombosis. Importantly, the rates of T2MI are also increasing in the general non-HIV population reportedly consisting of up to 43% with an MI meeting the definition of T2MI [9]. Causes of the myocardial oxygen supply and demand mismatch of T2MI include severe anemia, sepsis, hypertensive emergency, arrhythmias, heart failure, and vasospasm such as due to use of cocaine or other illicit drugs, among others, and the relative contributions of each likely differs between PWH and the general population [5, 10]. Furthermore, T1MI has a clear set of guideline-based recommendations for treatment, focusing on thrombolysis and reperfusion of the myocardium. In contrast, optimal evaluation and therapeutic strategies for T2MI, including

its heterogeneous underlying disease contributors and risk factors for recurrence, have yet to be defined [11] and poorer long-term survival has been reported both among those with and without HIV [2, 12]. Accumulating evidence suggests that T1MI and related cardiometabolic traits, including lipid levels, body weight, insulin resistance, blood pressure, and many others, have a strong genetic component, with multiple common variants of small effect involved in risk variability [13–16]. Polygenic risk scores (PRS) have been implemented to evaluate cumulative genetic burden across multiple susceptibility loci based on genome-wide association studies (GWAS) [17, 18]. It has been shown that individuals at the top 10% of the PRS distribution for CVD [19] have a 2.9-fold increased risk and those at the top 1% had a 4.8-fold higher risk of developing the disease compared to people in the bottom 90% and 99%, respectively [20]. Furthermore, PRS based on the top 27 single nucleotide polymorphisms (SNPs) previously associated with CVD has been predictive of outcomes in primary and secondary prevention trials of statin therapy, demonstrating the largest benefit in individuals at the highest quintile of PRS [21]. Recent studies have shown the predictive value of a CVD-associated PRS in the risk of subclinical CVD in PWH, especially when combined with the clinical and HIV-related risk factors [22, 23]. However, to the best of our knowledge, while prior GWAS looked at CVD, stroke and MIs, predominantly T1MIs, no GWAS of T2MI or comparisons of T1MI and T2MI have been reported, limiting our ability to discern the genetic factors underlying T2MI etiology. Focusing on a high risk subgroup can help elicit biological underpinnings of T2MI and develop risk stratification strategies.

To understand the different risk factors, courses, and prognosis for MI types in PWH, we established an MI adjudication protocol in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort which enables the central adjudication and categorization of MIs by type in PWH [24]. The goal of the present study was to apply a set of PRS corresponding to various traits and diseases to identify major genetic determinants of T2MI and compare them to the known genetic risks for T1MI. We hypothesized that the CVD traits, key for T1MI, would not be important drivers for T2MI highlighting the differences in these outcomes. We further hypothesized that genetic contributors to T2MI risk among PWH would be heterogeneous, consistent with the wide range of causes of T2MI among PWH. A fuller understanding of the pathogenetic basis of T2MI occurrence may help identify individuals at risk and facilitate development of targeted interventions, regardless of HIV infection status.

2. Methods

2.1. Cohort description

CNICS is a prospective longitudinal observational cohort of PWH receiving routine clinical care at eight sites in the United States [25]. The CNICS data repository integrates comprehensive longitudinal data from outpatient and inpatient encounters. It captures standardized HIV-related information collected at enrollment (initial clinic visit); demographic characteristics; laboratory test results; prescription medications; and clinical diagnoses from each site’s electronic health record and other institutional data sources. This provides rich longitudinal phenotype data including laboratory data, medications such as

lipid-lowering therapies, antihypertensive medications, and ART; diagnoses; and vital status. Seven of eight sites have initiated centralized MI adjudication to not only improve the accuracy of identifying MIs over diagnoses alone, but also to categorize MIs by type based on the Universal Definition of MI [5, 24, 26, 27]. PWH also complete the CNICS clinical assessment of patient reported measures and outcomes (PROs) on touch-screen tablets at routine clinic visits every ~4–6 months [28, 29]. This provides rich phenotype data on domains such as drug and alcohol use for most PWH in CNICS. PWH who are medically unstable, appear intoxicated, have a cognitive impairment, or do not speak English, Spanish, or Amharic are not asked to complete the clinical assessment. The PRO clinical assessment was initiated at the first site in 2007, with most sites initiating around 2010, and the last site starting in 2018; therefore, this information is missing in a subset of CNICS participants.

2.2. Study eligibility

CNICS has an ongoing genetics project in which adult PWH across racial/ethnic backgrounds from all sites, who provided informed consent and contributed specimens to the CNICS biospecimen repository, are being genotyped. PWH were included in this study if they had been genotyped and were in care at one of the seven sites after MI adjudication began. While genotyping is ongoing, at the time this study was conducted, 9,541 PWH had been successfully genotyped from the seven sites and met study eligibility.

2.3. Covariates

Demographic and clinical covariates of interest included birth sex, age (calculated at index MI or study exit), race/ethnicity, ART status, and CD4 cell count, and other clinical values including body mass index (BMI), HIV viral load, hemoglobin A1c, total cholesterol (TC), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), triglycerides, systolic and diastolic blood pressure, and serum glucose. ART status (on versus off) was based on an ART regimen at the time of MI or study exit. The lab value closest to but before the index date was used. Index data was the date of the MI for PWH with a type 1 or type 2 MI or the study exit date for those who did not have an MI during follow-up. PROs such as smoking (measured using the National Institute of Drug Abuse-modified Alcohol, Smoking and Substance Involvement Test [30, 31]) and alcohol use (measured using the Alcohol Use Disorders Identification Test [32, 33]), were available from the subset of PWH who were in care after PRO initiation at their site [25].

2.4. Myocardial infarction classification

Potential MIs were identified retrospectively in the CNICS data repository by MI clinical diagnoses, cardiac biomarkers, and procedures [5, 24]. MI adjudication is ongoing and completion dates vary slightly by site but includes events from ~2000–2017. Sites prepare de-identified packets including provider notes, electrocardiograms, laboratory reports, and results of imaging and procedures. Potential MIs are centrally adjudicated by two expert physicians and discrepant results are reviewed by a third expert physician. Reviewers classify each MI as type 1 or type 2, and in the case of T2MI the suspected cause(s) is recorded [5, 24]. Other MI types (types 3, 4, and 5) were not included as they are rare. For example, there are less than 10 cardiac procedure-related MIs (type 4 and type 5) in CNICS to date.

2.3. Genotyping and Imputation

DNA was isolated from peripheral blood mononuclear cells or buffy coats using the FlexiGene DNA kit (Qiagen, #51206). We used Illumina high-density Infinium Multiethnic Global Array series BeadChips to generate genotype data. Variant calling was conducted using GenomeStudio® Genotyping Module v2.0 software (Illumina®, San Diego, California, USA) and zCall [34]. SNPs with call rates < 95%, minor allele frequency < 1%, and samples with call rates < 90%, sex discrepancies between genotype data and self-report, and pairwise identity-by-descent pi-hat > 0.9 were removed using PLINK v.1.9 [35]. For imputation, ancestry was inferred using GRAF-pop software [36] and genotype data imputed separately in each ancestral group (European, African, and other) using the Trans-Omics for Precision Medicine (TOPMed) reference panel. To retain variants with high quality, we used imputation quality score of $r^2 > 0.3$ and followed standard quality control procedures [37, 38]. Principal components analysis (PCA) was performed using PLINK v.1.9 with the derived principal components (PCs) included as covariates in the regression models to control for population stratification.

2.4. Polygenic risk score analysis

For each CNICS participant, we calculated 115 PRS representing 10 disease and trait categories known to be associated with MI based on previous studies. These categories include cardiovascular disease [39–42], hypertension [43], dyslipidemia [44], BMI [45], birth weight [46], kidney disease [47–49], substance use [50, 51], type 2 diabetes [52–54], and gall bladder disease [55, 56]. We used linear combinations of imputed genotype dosages [57] based on the association summary statistics of corresponding previously published formulas or trained on GWAS summary level data (Supplementary Table S1). Prior to PRS calculation, linkage disequilibrium-based pruning of SNPs was performed using 1000 Genomes using European and African reference panels in PLINK and highly redundant SNPs ($r^2 \geq 0.5$) were removed. Associations of PRS with T1MI and T2MI were evaluated using multivariable logistic regression adjusted for birth sex, age, race/ethnicity, top 5 PCs, study site, ART use, and CD4 cell counts. In subgroup analyses, the effects of lipid lowering drugs (statin use, ever versus never), as well as alcohol consumption (drinks per week), were also assessed. We used a study-wise statistical significance threshold of 0.005 (0.05/10 phenotypic categories) to correct for multiple hypothesis testing while accounting for correlated PRS derived for the same trait from different GWAS. We considered the results significant if consistent association was detected between MI status and PRS from at least two GWAS.

2.5. Expression quantitative trait loci and gene set enrichment analyses

Based on the initial findings, to explore potential genetic mechanisms linking T1MI and T2MI to the most significant PRS, we first sorted the SNPs composing respective PRS based on the GWAS of coronary artery disease (CAD) [58], alcohol dependence (FT12 cohort) [59], and cholecystitis [60] by absolute effect weights or GWAS p-values, whichever was available. We then examined if these SNPs were eQTLs (SNPs underlying expression quantitative trait loci) at false discovery rate (FDR) [61] < 0.1 in CAD-relevant tissues (atherosclerotic aortic root, liver, subcutaneous fat, skeletal muscle, and visceral abdominal

fat) from the Stockholm-Tartu Atherosclerosis Reverse Network Engineering Task study [62]. We allowed for each eQTL to map to one or more genes. The top 200 genes driving eQTLs for each of the three PRS were used to conduct a gene set enrichment analysis in Enrichr [63], a web server currently supporting 358,534 terms and 183 libraries (https://maayanlab.cloud/Enrichr/, Kyoto Encyclopedia of Genes and Genomes, or KEGG, database, last access August 2021) in each tissue separately, to identify biological pathways potentially associated with T1MI or T2MI.

3. Results

3.1. Cohort characteristics

Of the 9,541 PWH in CNICS who had genotype data available at the time of this analysis, there were 523 adjudicated MIs; 294 T1MI and 229 T2MI. The study cohort consisted of 79% males, 49% African Americans, 39% Europeans, 10% Hispanic/Latino, and 1% Asians (Table 1). The prevalence of T1MI and T2MI was 3.1% and 2.4%, with 2.9 T1MIs per 1000 person-years, and 2.3 T2MIs per 1000 person-years, respectively. PWH with T2MI were more likely to be of African American ancestry (70% versus 47%) and have lower BMI (26.3 kg/m^2 versus 27.5 kg/m^2; P=0.005), TC (162 mg/dL versus 188 mg/dL; $P=2.3\times10^{-9}$), LDL (85 mg/dL versus 109 mg/dL; $P=3.2\times10^{-11}$), and triglycerides (185 mg/dL versus 204 mg/dL; P=0.005), compared to T1MI. They also had significantly higher viral load (77,716 versus 22,194 copies/mL; P=0.0001) and lower CD4 counts (351 cells/mm^3 versus 530 cells/mm^3; $P=6.8\times10^{-10}$). PWH with either T1MI or T2MI had higher glucose levels, hemoglobin A1C, and systolic blood pressure and lower HDL compared to PWH with no MI. Also, PWH with T2MI were less likely to be on ART than those with T1MI or no MI (91%, 96%, and 97%, respectively; P=0.03 between T1MI and T2MI; Table 1).

3.2. PRS analysis

Of the 115 PRS (Supplementary Table 1), 31 were associated with T1MI, with 19 remaining significant after adjustment for multiple hypothesis testing. Several PRS for CAD, angina and stroke, lipoprotein levels such as TC, LDL, and apolipoprotein, and type 2 diabetes were associated with higher risk of T1MI, while PRS for birth weight showed an inverse correlation with T1MI (Fig. 1; Supplementary Table S1). For T2MI, the most consistent positive association was detected with PRS for alcohol dependence, quantified by three different PRS: (1) PRS-problematic alcohol use (PAU) derived from a GWAS on the problem subscale from the Collaborative Study on the Genetics of Alcoholism (COGA, PRS-PAU-COGA [59]; OR=1.23 [95%CI 1.01–1.49] per standard deviation of PRS, unadjusted P=0.04), (2) PRS-Alcohol Drink Per Week (ADPW) derived from the GWAS & Sequencing Consortium of Alcohol and Nicotine Use (GSCAN [64]; OR=1.24 [95%CI 1.03–1.51] per standard deviation of PRS, unadjusted P=0.04), and (3) PRS-PAU from the FinnTwin12 study (FT12, PRS-PAU-FT12 [59]; OR=1.36 [95%CI 1.12–1.65] per standard deviation of PRS, unadjusted P=0.002), the latter remaining statistically significant after adjustment for multiple testing (P=0.02; Fig. 1). Also, PWH with T2MI had higher PRS for cholecystitis, type 2 diabetes, and waist-hip ratio (Fig. 1; Supplementary Table S1). These associations did not substantially change after adjustment for statin use or type 2 diabetes (Supplementary Table S1). Moreover, PRS for type 2 diabetes was independently

associated with both T1MI and T2MI when included alongside PRS-CAD or PRS-PAU-F12, respectively (Supplementary Table S2). Also, ART use was associated with a significant reduction in T2MI (OR=0.25 [95%CI 0.15–0.43, P=1.3E-07) and to a lesser extend in T1MI (OR=0.53 [95%CI 0.29–1.08, P=0.06; Supplementary Table S2).

In the sub-cohort with PRO data (N=6,397), adding reported alcohol consumption per week to the model did not change the magnitude of the association between various alcohol-related PRS and T2MI, even though statistical significance was slightly weakened due to the reduction in the sample size (Table 2). These results suggest that genetic variants composing PRS for alcohol dependence, rather than actual drinking, contribute to the risk of T2MI. We did not observe genetic associations between PRS for atrial fibrillation, sepsis or anemia, previously reported in patients presenting with T2MI [10], and T2MI diagnosis (Supplementary Table 1).

3.3. Gene set enrichment analysis

To account for the variation in the sample size of original GWAS and different number of SNPs used in PRS derivation for various traits, we selected the top 200 genes regulated by the eQTLs comprising each PRS-PAU-FT12, PRS-cholecystitis or PRS-CAD. Metabolism of xenobiotics by cytochrome P450, drug metabolism, and bile secretion pathways were enriched in both PRS-PAU-FT12 and PRS-cholecystitis (all in the liver; Fig. 2). eQTLs from PRS-PAU-FT12 were also significantly enriched in the tyrosine metabolism (in the aortic root) and in ascorbate and aldarate metabolism, pentose and glucoronate interconversions, and retinol metabolism (in the liver; Fig. 2), whereas eQTLs from PRS-cholecystitis were also significantly enriched in the glutathione metabolism (in the liver). The cholesterol metabolism pathway was enriched in both PRS-cholecystitis (in the liver, foam cells and macrophages) and PRS-CAD (in the liver and visceral fat). In addition the PRS-CAD-associated eQTLs were enriched in the hepatocellular carcinoma and lysosome pathways.

4. Discussion

In this study, we applied a series of PRS linked to cardiovascular disease, metabolic and anthropometric traits, and risky behaviors, to a large, well-characterized cohort of PWH with adjudicated MIs to explore underlying mechanisms of T1MI and T2MI in a high risk population. We found that, as expected, T1MI was strongly associated with different PRS representing genetic risk burden for CVD and related risk factors. In contrast, PWH with T2MI had higher PRS for alcohol dependence and cholecystitis. PRS associated with T1MI were driven by genetic variants that are enriched in the lipid metabolism and lysosomal function, whereas those linked to T2MI controlled expression of genes enriched in energy metabolism. Our results highlight previously observed key clinical differences between T1MI and T2MI and the need for adjudication to allow them to be distinguished, especially in genetic studies.

T2MI is believed to result from mismatch between myocardial oxygen supply and demand [7, 8, 10, 65, 66], in contrast to T1MI, which is due to primary plaque rupture or coronary thrombosis. The ability of the heart to prioritize energy producing substrates between glucose metabolism and free fatty acids, especially during cardiac ischemia, is critical

and can be, at least in part, genetically determined. Apart from requiring higher oxygen expenditure than glucose metabolism, elevated free fatty acid uptake leads to reduced contractile function and arrhythmia generation, which is common in patients with T2MI [10]. We found that top loci comprising PRS-PAU-F16 were enriched for the ascorbate and aldarate metabolism, pentose and glucoronate interconverions, retinol metabolism, metabolism of xenobiotics by cytochrome P450, drug metabolism, and bile secretion in the liver and for tyrosine metabolism in the aortic root. Ascorbate and aldarate metabolism and pentose and glucoronate interconverions were among the 34 pathways disturbed during early stages of experimental myocardial ischemia.[67] Moreover, retinoids have been previously shown to regulate the expression of genes involved in hepatic glucose and lipid metabolism [68]. Certain xenobiotics particularly target the heart and promote toxicity. High levels of drugs of abuse, namely amphetamines, cocaine, and even the consumption of alcohol for long periods of time, are linked to cardiovascular abnormalities as oxidative stress may be one common link for cardiac toxicity associated with these compounds [69]. Furthermore, tyrosine kinases are critical in activating signaling pathways that regulate cell growth, differentiation, metabolism, migration, and apoptosis.

Given that the top variants composing the PRS that was associated with T2MI were derived from GWAS for alcohol dependence, we tested if the observed results were driven by genetic predisposition to alcohol addiction. We found no substantial differences after the adjustment for actual alcohol consumption in a sub-group analysis. Binge drinking has been previously associated with a higher risk for MI compared to no alcohol consumption [70, 71], though potential genetic mechanisms underlying this observation have not been fully elucidated. This finding suggests that PRS-PAU-FT16 may reflect the impaired genetic control of energy regulation and could be useful in the early recognition of myocardial ischemia regardless of alcohol intake.

PWH with T2MI were also more likely to have a higher PRS for cholecystitis. Interestingly, a large meta-analysis including nearly one million participants demonstrated a substantially higher risk of fatal and nonfatal CVD events among patients with a medical history of gallstone disease [56]. Beyond the observed clinical comorbidity, similar to PRS-PAU-FT16, the top variants contributing to PRS for cholecystitis were enriched in the energy metabolism pathways, including metabolism of xenobiotics by cytochrome P450, drug metabolism, bile secretion and, suggestively, retinol metabolism. Interestingly, excess bile acids have been shown to decrease fatty acid oxidation in cardiomyocytes and cause heart dysfunction, a cardiac syndrome termed cholecardia [72]. The cholecystitis PRS-related variants were also enriched in the glutathione and cholesterol metabolism. Glutathione plays an important role in the cell, regulating multiple vital functions and may serve as a biomarker for ischemic stroke in the blood [73], whereas cholesterol is a precursor of bile acids among numerous other functions. Further studies are warranted to determine if individuals at the top percentile of these two PRS may benefit from metabolic support to the ischemic heart – a promising strategy to reduce infarct size and improve T2MI outcomes [74].

Importantly, in contrast to T2MI, T1MI patients had consistently higher genetic risk for CAD based on multiple independent GWAS studies, as well as higher PRS for a number

of lipid traits, which is supported by prior clinical data demonstrating that T2MI patients had less dyslipidemia compared to PWH with T1MI [9, 75]. Moreover, the top variants composing the PRS for CAD were significantly enriched in the cholesterol metabolism, lysosomal function and hepatocellular carcinoma. Dyslipidemia is one of the major risk factors for T1MI, while previous studies have shown an early disruption of lysosomes in the setting of MI [76]. While the link between PRS for CAD and hepatocellular carcinoma is not obvious, a distant cardioprotective mechanism involving hepatic cell mobilization to the ischemic myocardium in response to experimental myocardial ischemia-reperfusion injury has been reported [77]. Also, T1MI, but not T2MI, was associated with lower birth weight as assessed by independent PRS [78, 79]. Previous epidemiological studies have linked lower birth weight to the higher risk of CVD in the general population [80, 81]. Future studies should be designed to determine the predictive value across multiple PRS identified in our study to enhance T2MI risk stratification and diagnosis.

It is important to emphasize that the contribution of genetic predisposition to MI risk may differ in PWH. However, direct assessment of the effect of genotype × HIV interactions on CVD morbidity is challenging due to the lack of sizable cohorts composing of people with and without HIV with adjudicated outcomes. Our previous study has identified novel genetic loci involved in immune cell regulation and previously linked to HIV control, body composition, and risky behaviors, which were associated with dyslipidemia in PWH but not in a large population-based GWAS [82]. These findings suggest that certain genetic variants may lead to further immune perturbations that contribute to cardiometabolic risk, especially, or uniquely, in the presence of HIV infection. Well-powered GWAS in PWH are warranted to further expand these results.

The major strengths of this study are the inclusion of the large, well-characterized cohort of PWH with genome-wide genotype data and centralized MI adjudication. We also adjusted for ART and CD4 counts known to be predictive of MI risk in PWH. Furthermore, we used PROs to test whether it is genetic determinants of alcohol dependence or actual alcohol intake that increase the risk of T2MI in PWH. There are also several limitations. Specifically, we calculated PRS using effect estimates from largely European GWAS, which are less generalizable, especially to the African-ancestry populations [83]. Further GWAS in diverse cohorts, as well as multi-ethnic PRS calculations, which have been shown to significantly improve disease prediction accuracy in cohorts of non-European ancestry [84], would allow us to refine our findings. Also, PRS accuracy heavily relies on the original GWAS size; smaller GWAS may be underpowered to properly select variants contributing to the PRS. That may explain the lack of association between T2MI and PRS for atrial fibrillation, sepsis or anemia, the phenotypes observed in patients presenting with T2MI [10]. Moreover, genetic determinants of other diseases or traits, which were not included in our PRS selection, could be involved in T2MI risk. Similarly, due to the lack of available GWAS, we were unable to confirm the contribution of genetic determinants to the principal mechanism shown to provoke T2MI, such as hypotension and hypoxia. In addition, we adjusted for the general ART use (yes vs. no), and did not differentiate between specific ART regimens. Moreover, despite being the largest genetic study reported in PWH, the number of T2MI cases was too small to conduct a GWAS to inform direct PRS-T2MI calculation. Future GWAS of adjudicated T2MI are needed to explore the genetic predictors

of disease pathogenesis. Lastly, we used Bonferroni correction to adjust for multiple testing for 10 traits and disease categories and not for each PRS, as PRS within each category were often highly correlated. We treated unadjusted significant associations between multiple PRS derived from different GWAS within the same phenotype category as a validation of our findings rather than a penalty. However, we could not completely rule out the overlap between the samples used in each independent GWAS. Further studies are warranted to replicate our findings.

4. Conclusions

In conclusion, using a set of PRS for various traits and diseases in a high risk cohort with adjudicated MI, we were able to reconstruct and expand on previously reported differences between T1MI and T2MI etiologies and identify potential genetic pathways associated with T2MI, whose incidence is high among PWH (~ half of MIs) and is increasing in the general population. Our approach might be useful to explore genetic determinants of other traits and diseases for which GWAS are not available.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- About half of myocardial infarction (MI) cases in people with HIV are type 2 (T2MI), resulting from mismatch between myocardial oxygen supply and demand, in contrast to type 1 MI (T1MI), which is due to primary plaque rupture or coronary thrombosis, and the incidence is significantly rising in the general non-HIV population.
- Despite worse survival, evidence-based treatment recommendations for T2MI are lacking partially due to a poor understanding of the disease pathogenesis.
- An unbiased analysis of polygenic risk scores associated with cardiometabolic traits and diseases implicated energy regulation and other metabolic pathways in T2MI risk, while confirming the role of lipid metabolism in the development of T1MI.
- Further research into the key genetic drivers of T2MI pathogenesis is warranted to help stratify those at risk and inform therapeutic strategies.

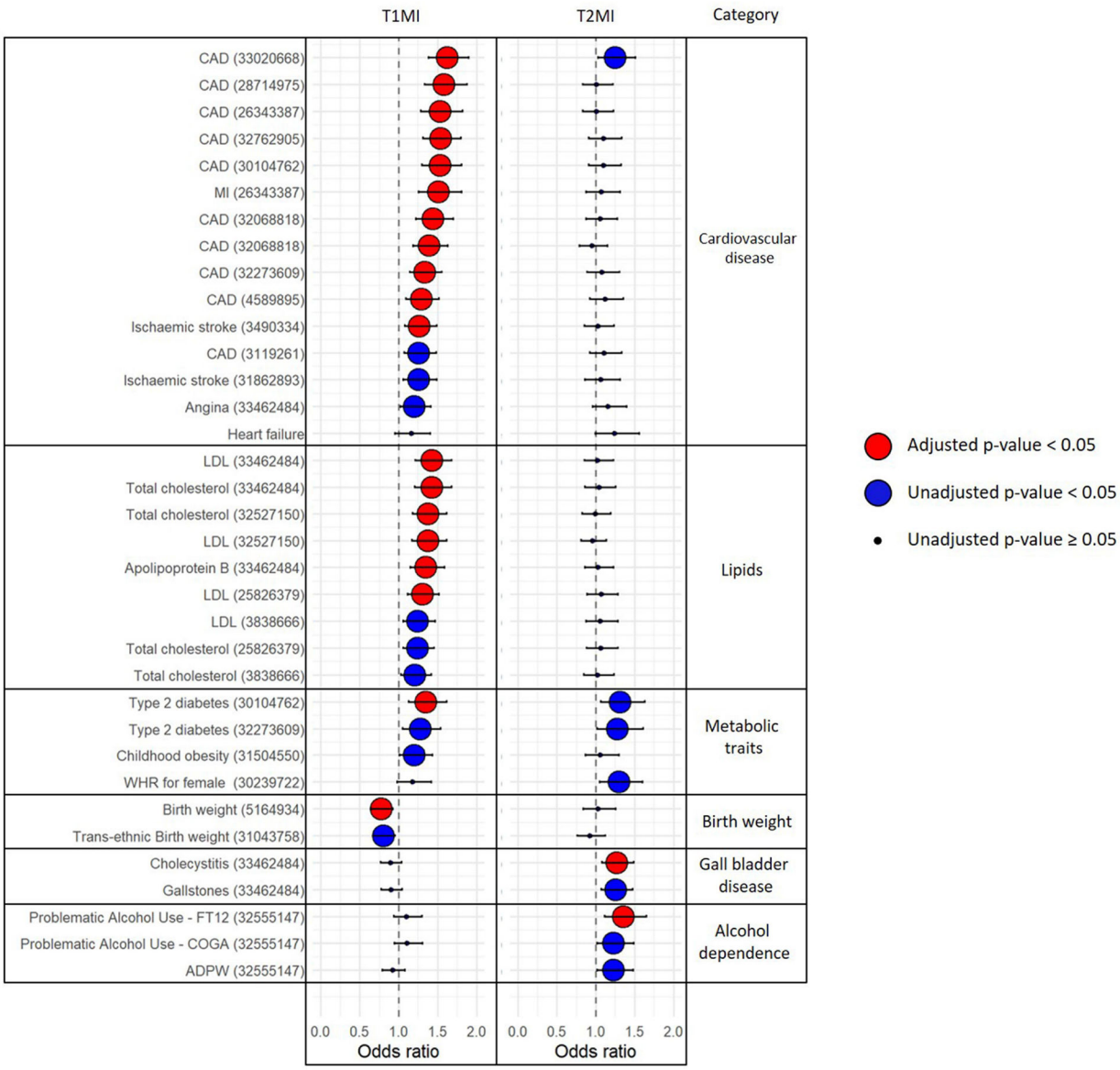

Fig. 1: Forest Plot of Association between Polygenic Risk Scores and Type 1 and Type 2 Myocardial Infarction.

CAD, coronary artery disease; T1MI, type 1 myocardial infarction; T2MI, type 2 MI; LDL, low-density lipoprotein; WHR, waist to hip ratio, ADPW, alcohol drink per week, COGA, the Collaborative Study on the Genetics of Alcoholism, FT12, the FinnTwin12 study. In parenthesis, PubMed identification numbers. Shown are the odds of T2MI or T1MI risk by 1-standard deviation increases of the risk scores using multivariate logistic regression models.

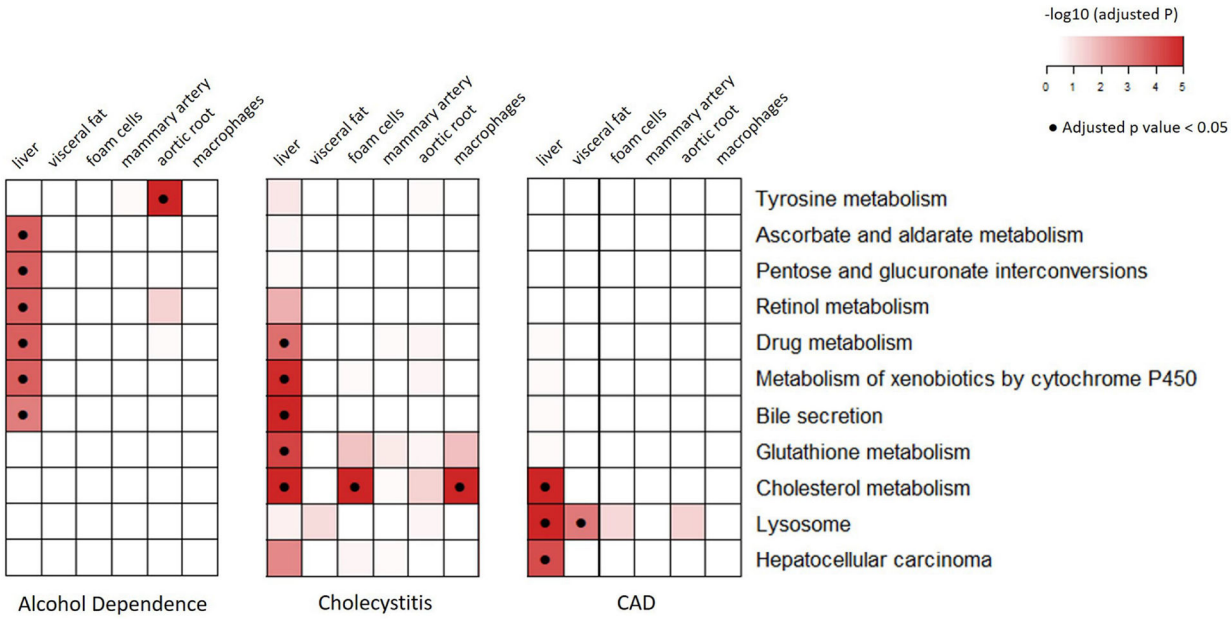

Fig. 2: Gene Set Enrichment Analysis of the Top Expression Quantitative Trait Loci Composing Polygenic Risk Scores for Alcohol Dependence, Cholecystitis, and Coronary Artery Disease.

P-values for enrichment are shown with and without adjustment for false discovery rate. Only the six tissues of nine tissues tested with at least one unadjusted P<0.05 for enrichment are shown. CAD, coronary artery disease.

Table 1.

Demographic and clinical characteristics of people with HIV by myocardial infarction status.

Variable	Total (n = 9,541)	No MI (n = 9,018)	T1MI (n = 294)	T2MI (n = 229)	P-value (T1MI vs. T2MI)	P-value (no MI vs. T1MI)	P-value (no MI vs. T2MI)
Sex					0.057	0.15	0.22
Male	7,510 (78.7%)	7,096 (78.7%)	242 (82.3%)	172 (75.1%)			
Female	2,031 (21.3%)	1,922 (21.3%)	52 (17.7%)	57 (24.9%)			
Age, years	54.7±11.1	54.3±11.1	62.5±9.3	60.7±9.6	0.05	**2.20E-35**	**5.70E-18**
Race / Ethnicity					**5.9E-07**	0.18	**1.41E-08**
African American	4,629 (48.5%)	4,333 (48.0%)	137 (46.6%)	159 (69.4%)			
European	3,695 (38.7%)	3,512 (38.9%)	127 (43.2%)	56 (24.5%)			
Hispanic	975 (10.2%)	937 (10.4%)	26 (8.8%)	12 (5.2%)			
Asian	125 (1.3%)	125 (1.4%)	0 (%)	0 (%)			
Other	117 (1.2%)	111 (1.2%)	4 (1.4%)	2 (0.9%)			
BMI, kg/m^2	27.3±6.5	27.3±6.4	27.5±6.7	26.3±6.9	**0.005**	0.49	**0.0018**
ART	9,255 (97.0%)	8,763 (97.2%)	283 (96.3%)	209 (91.3%)	**0.03**	0.45	**5.77E-07**
CD4 cell count	579±347	586±345	530±362	351±317	**6.78E-10**	**0.0007**	**2.89E-27**
Viral load	23,788±193,394	22,485±191,614	22,194±103,455	77,716±310,751	**0.0001**	**3.36E-11**	**3.43E-20**
Hemoglobin A1c, mmol/mol	5.9±1.4	5.9±1.4	6.2±1.7	6.1±1.6	0.52	**1.15E-05**	**0.002**
Total cholesterol, mg/dL	173.9±41.7	173.8±41.3	187.8±46.9	162.3±47.2	**2.29E-09**	**3.29E-07**	**4.02E-05**
HDL, mg/dL	46.6±17.1	46.8±17	41.2±13.9	45.3±20	0.055	**4.53E-09**	0.056
LDL, mg/dL	97.9±34.1	97.8±33.7	109.2±40.6	84.7±36.8	**3.15E-11**	**7.09E-06**	**1.90E-08**
Triglycerides, mg/dL	159.3±126	157.3±122.1	204.2±160.4	185.3±202.2	**0.005**	**1.49E-10**	0.05
Systolic blood pressure, mmHg	128.1±17.4	127.9±17	132.6±19.8	133.5±25.9	0.65	**8.61E-05**	**0.03**
Diastolic blood pressure, mmHg	79.6±10.9	79.5±10.8	81.6±11.5	80±15	0.14	**0.013**	0.92
Serum glucose, mmol/L	101.4±44.8	100.1±42.6	119.6±64.2	128.1±75.6	0.069	**1.22E-18**	**1.95E-20**

T1MI, type 1 myocardial infarction; T2MI, type 2 myocardial infarction; ART, antiretroviral therapy; BMI, body mass index; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol. Note hemoglobin A1c only ordered when clinically indicated so only available on 4,706 individuals.

Table 2.

Multivariate analysis of type 2 myocardial infarction with and without adjustment for alcohol consumption per week.

Cohort	Variable	OR (95% CI)	P value
Full cohort (n =9,541)	PRS-PAU (COGA)[59]	1.23 (1.01–1.49)	**0.036**
	PRS-PAU-FT12 [59]	1.36 (1.11–1.65)	**0.002**
	PRS-ADPW[64]	1.22 (1.01–1.48)	**0.037**
Subset with alcohol consumption data (n =6,397)	PRS-PAU (COGA)[59]	1.28 (1.07–1.11)	0.08
	Alcohol consumption (drinks per week)	1.00 (0.97–1.03)	0.71
	PRS-PAU-FT12 [59]	1.47 (1.11–1.96)	**0.008**
	Alcohol consumption (drinks per week)	1.00 (0.97–1.03)	0.72
	PRS-ADPW[64]	1.22 (1.02–3.61)	0.17
	Alcohol consumption (drinks per week)	1.00 (0.99–1.04)	0.76

OR, odds ratio, 95% confidence interval (CI), 95% confidence interval; PAU, problematic alcohol use; ADPW, alcohol drink per week. All models were also adjusted for birth sex, age, antiretroviral therapy, CD4 cell counts, self-reported ethnicity, first five principal components for population stratification, and study site.