BMJ open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005069
Article Type:	Research
Date Submitted by the Author:	17-Feb-2014
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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Public health
Keywords:	Cardiac Epidemiology < CARDIOLOGY, Epidemiology < INFECTIOUS DISEASES, PREVENTIVE MEDICINE

Low levels of high-density lipoprotein cholesterol is the most prevalent metabolic abnormality in urban Africans with newly diagnosed heart disease: The 'Heart of Soweto' hospital registry study

Short title: Lyons – HDLC in communicable heart disease

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Key Words: High-density lipoprotein, lipids, infection, epidemiologic transition, Africa.

Word count: 3247 not including 2 tables, 3 figures and 33 references.

ABSTRACT

Objectives: To investigate if urban Africans displayed abnormal lipid levels- in particular, lower levels of atheroprotective high-density lipoprotein cholesterol (HDLC) - when presenting with communicable versus non-communicable forms of heart disease (HD).

Design: Prospective clinical registry of 5328 *de novo* cases of HD over a 3-year period.

Setting: Cardiology Unit, Baragwanath Hospital in Soweto, South Africa.

Participants: A total of 1199 patients of African descent (59% female; 57.0±13.4 years) had fasting blood lipid levels (Total cholesterol [TC], triglyceride, HDLC, and low density lipoprotein [LDLC] cholesterol) documented on admission.

Main outcome measures: Lipid profiles were compared according to pre-specified classification of non-communicable (e.g. hypertensive heart disease) versus communicable (e.g. rheumatic heart disease;) HD.

Results: Overall 694 (58%) of those presenting with HD had low HDLC levels; 344 of 678 (51%) and 350 of 521 (67%) for non-communicable and communicable, respectively (p<0.001). By comparison, overall prevalence of high TC was 32%, high LDLC was 37%, and obesity (body mass index >30 kg/m^2) was 40%. On an adjusted basis, those with non-communicable HD were more likely to record a low HDLC relative to non-communicable presentations (OR 1.91, 95%CI 1.42, 2.57; p<0.001).

Conclusions: Despite largely favourable lipid profiles, there are clear differences according to aetiology of underlying HD in urban Africans. Younger Africans with communicable HD have particularly low levels of HDLC that, if persistent in the longer-term, may expose them to increased risk of atherosclerotic forms of cardiovascular disease.

ARTICLE SUMMARY

Article focus:

- In sub-Saharan Africa, the incidence of non-communicable cardiovascular disease is increasing while, simultaneously, communicable forms of heart disease continue to cause considerable levels of morbidity and mortality.
- In this study, we have sought to explore one heart disease risk factor, dyslipidaemia, in a well-defined clinical registry in Soweto, South Africa.
- Lipid profiles from 1199 de novo presentations of heart disease were compared according to pre-specified classification of non-communicable heart disease (e.g. hypertensive heart disease) versus communicable forms of heart disease (e.g. pericarditis or chronic rheumatic heart disease). We hypothesised that those diagnosed with communicable heart disease would display an adverse lipid profile, with low levels of atheroprotective high-density lipoprotein cholesterol (HDLC). We also investigated the potential interaction of the inflammatory marker C-reactive protein (CRP) and low HDLC in a subset of these patients.

Key messages:

- We describe distinct patterns of dyslipidaemia according to underlying heart disease aetiology: significantly decreased levels of HDLC, total cholesterol and low-density lipoprotein cholesterol in those with communicable heart disease (representing 43% of cohort) compared to those with non-communicable heart disease (57% of cohort).
- In adjusted analyses, low HDLC was more pronounced in those with communicable heart disease. In those with high CRP levels, we present novel data showing a sex-disparate relationship between CRP and low HDLC, with a strong relationship between high CRP and low HDLC in females only.
- The high prevalence of low HDLC in a relatively young population of urban Africans may, if persistent in the longer-term, confer greater risk of atherosclerotic heart disease

Strengths and limitations of the study:

- We report a high prevalence of low HDLC in *de novo* presentations of communicable heart disease compared with non-communicable heart disease.
- The study cohort is clinically very well defined; however the lipid data were obtained according to clinical presentation, which may impose systematic bias to the results.
- This hospital registry study has provided preliminary data that would support prospective investigation of longer-term dyslipidaemia patterns and their impact on heart disease incidence, both in South Africa and in other low-and-middle-income countries where the epidemiologic transition is currently underway.

INTRODUCTION

Heart diseases with infectious aetiology have long been the principal forms of cardiovascular disease (CVD) in Sub-Saharan Africa. However, epidemiological transition has seen increased prevalence of non-communicable forms of heart disease in these populations[1]. This phenomenon is largely driven by complex, population-wide changes in demographic, social and economic status, with associated changes in lifestyle habits[2, 3, 4]. Indicative of the tension between 'old' and 'new' forms of heart disease, the incidence of communicable heart disease (HD) is sustained by the devastating epidemics of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), tuberculosis (TB), rheumatic heart disease (RHD) and parasitic infections with cardiac involvement[5, 6, 7], while in parallel, the prevalence of risk factors for non-communicable HD increases[8].

Low serum levels of high-density lipoprotein cholesterol (HDLC) are consistently and independently associated with increased risk of atherosclerotic forms of CVD[9, 10]. However, it remains uncertain whether low HDLC is causal or just a cardiovascular risk marker[11]. There are several causes of low HDLC levels, including overweight, obesity, tobacco smoking, and insulin resistance/type 2 diabetes mellitus, indicative of the important role lifestyle factors have in mediating HDLC levels[9]. Additionally, low HDLC is a striking consequence of abnormal lipid metabolism in infection and inflammation[12]. Although it has been shown that those of African descent largely show a favourable lipid profile[13], it is unlikely that such lipid profiles remain athero-protective during an infected state[14]. Indeed, in this setting, it is probable that increasing prevalence of modifiable/ lifestyle risk factors contribute to a more advanced presentation in those with communicable HD[8]. We have previously reported that in the geographically compact townships that comprise Soweto in South Africa, 'old' and 'new' forms of HD are simultaneously present[8]. While this tension exists, we have a unique opportunity to explore lipid profiles in patients presenting with non-communicable versus communicable forms of HD.

STUDY HYPOTHESES

Having shown important ethnic differences in the lipid profiles of patients of African descent presenting with HD in the urban African enclave of Soweto[13], we hypothesised that independent of age and sex, urban Africans presenting with communicable HD will demonstrate patterns of dyslipidaemia associated with infection/inflammation, particularly sub-optimal levels of HDLC, versus non-communicable HD.

METHODS

Study Setting & Design

As described in detail previously[8, 15] the 3,500 bed Chris Hani Baragwanath Hospital (case load of > 125,000 in-patients per annum) services the tertiary care needs of Soweto (population of 1.1 million) and surrounding communities. All suspected cardiac presentations are referred to the hospital's Cardiology Unit for advanced diagnostic testing and gold-standard treatments. A prospective clinical registry of all *de novo* presentations of the same was established in 2006 as part of the Heart of Soweto Study and represents sub-Saharan Africa's largest and most detailed study of advanced forms of HD to date[15].

Participants

The 'Heart of Soweto' cohort of *de novo* case presentations comprised 5328 patients. Of these, 2185 patients (40%) had a documented fasting lipid profile (serum total cholesterol (TC) level, triglyceride, HDLC and calculated low-density lipoprotein cholesterol (LDLC)[16] undertaken at Baragwanath Hospital on-site pathology). None of the patients were on lipid lowering agents at the time of presentation, as this medication can only be prescribed at the tertiary institution. However some of the patients had been placed on anti-hypertensive medication prior to their first assessment at the Cardiac Clinic at Baragwanath Hospital. Moreover, only a small number of patients (39 cases) had been prescribed anti-retroviral therapy (ART) on presentation. The study was approved by the University of the Witwatersrand Ethical Committee and conforms to the principles outlined in the Declaration of Helsinki. All patients provided informed consent.

Study Data

A complete list of study data captured by the registry, comprising basic socio-demographic (including self-reported ethnicity, years of education and determining if the patient was born in Soweto) and advanced clinical profiling, has been described previously[8, 15] The registry captured all advanced clinical investigative procedures (e.g. coronary angiography, which was undertaken in all people diagnosed with coronary artery disease (CAD)). Echocardiography (performed on all patients) criteria used in the study has been described in detail previously[8, 15].

Case Classifications

Adjudication and classification of communicable and non-communicable presentations of HD in this cohort have been previously described[8]. After exclusion of those with uncomplicated hypertension (i.e. without evidence of cardiac dysfunction, n=380) or other non-modifiable aetiologies (e.g. congenital disorders), 1199 patients of African descent (22% of the total 'Heart of Soweto' cohort) were included in this analysis. Contributory diagnoses for non-communicable HD were predominantly hypertensive heart failure (HT-HF) and coronary artery disease (without HIV). Communicable heart disease was predominantly classified as HIV-dilated cardiomyopathy (HIV-DCMO), HIV-pulmonary hypertension, TB pericardial disease, and pericarditis due to other infection.

Risk factor definition

Optimum lipid levels and treatment goals with established CVD were defined according to international guidelines[9] adopted by the Lipid and Atherosclerosis Society of South Africa and the South African Heart Association - high TC: >4.5 mmol/L, high TGs: >1.7 mmol/L, high LDLC: >2.5 mmol/L and low HDLC: <1.0 for males and <1.2 mmol/L for females[17]. Other risk factors were measured on a clinical basis, as previously described[15]. Anthropometric measurements were available for calculation of body mass index (BMI, kg/m^2) in 854 (71%) cases, the low reporting rate restricted to ambulatory patients. Obesity was defined as BMI ≥ 30 kg/m^2. Serum C-reactive protein (CRP) was measured in a sub-set of 367 patients (31% of all cases) if clinically indicated (e.g. suspected infection). Patients were stratified into clinically relevant CRP categories[18], as defined by Dhingra and colleagues[19]. Patients with a CRP of 1 mg/L (n=19)

were used as reference group and compared to medium (1.1-3.0 mg/L, n=26), high (3.1-10.0 mg/L, n=83) and very high (>10.0 mg/L, n=239) CRP categories.

Statistical analyses

Normally distributed continuous data are presented as the mean ± standard deviation and non-Gaussian distributed variables as the median (inter-quartile range). Categorical data are presented as sample number and percentages. For group comparisons, we initially used Chi Square (χ^2) analysis with calculation of odds ratios (OR) with 95% confidence intervals (CI) presented where appropriate for discrete variables, and independent T-tests for normally distributed continuous variables and Mann-Whitney U test for nonparametric continuous variables. Multiple logistic regression analyses (entry model) were used to derive age and sex adjusted ORs (and BMI in some analyses, as described) for the risk of presenting with clinically relevant variables (primarily dyslipidaemia profiles), according to CD HD relative to NCD diagnosis. Significance was accepted at the two-sided level of $p<0.05$.

RESULTS

Clinical and Demographic Profile

Table 1 shows the socio-demographic and clinical profile of this cohort according to cardiac aetiology. Those presenting with non-communicable HD (n=678, 56.5% of cohort) were older and had higher BMI and mean SBP and DBP than those with communicable HD (n=521, 43.5%; all comparisons p<0.001). Overall, 76 (6%) were confirmed HIV-positive, with an expected significantly higher prevalence in those with communicable HD (n=61, 12%, p<0.001). Apart from higher BMIs in women (30.6 ± 6.9 vs. 26.7 ± 5.5 kg/m^2 in males, p<0.001) there were no significant differences between sexes in respect to other clinical parameters.

Aetiology of heart disease (primary diagnosis)

Overall, the most prevalent primary diagnoses were HT-HF (n=461, 38%), dilated cardiomyopathy (DCMO, n= 178, 15%) and CAD (n=157, 12%). In those classified as non-communicable HD, HT-HF was the main primary diagnosis (n=461, 68%), along with CAD (without concurrent HIV-infection; n=157, 23%). Dilated cardiomyopathy (n=178, 34%), right heart failure (n=92, 18%) and right heart disease (n=63, 12%) and other forms of primary valve disease (n=71, 14%), were the most common diagnoses in those classified with communicable forms of HD.

Lipid Profiles

There were significant reductions in TC, LDLC and HDLC in those with communicable forms of HD (**Table 1** and **Figure 1**, p<0.001 for all comparisons). Overall, women had significantly higher TC (4.2±1.3 mmol/L vs. 3.8±1.2 mmol/L, p<0.001); LDLC (2.4±1.0 mmol/L vs. 2.2±1.0 mmol/L, p<0.01), and HDLC compared to men (1.2±0.5 mmol/L vs. 1.0±0.5 mmol/L, p<0.001). This gender difference did not extend to triglycerides (1.1(0.4-1.8) mmol/L vs. 1.1(0.4-1.8), p=0.7) nor TC:HDLC ratio (4.2 ± 3.1 mmol/L vs. 4.3 ± 2.7 mmol/L, p=0.6).

Levels of TC (Figure 1A), HDLC (Figure 1B) and LDLC (Figure 1C) were significantly higher in females with non-communicable HD (**Figure 1**). However in those diagnosed with communicable HD, small, but significant, differences were observed only for TC and HDLC, not LDL (**Figure 1**). Overall, prevalence of dyslipidaemia varied from 18% of patients with high

triglycerides to 58% with low HDLC (**Table 1** and **Figure 2**). Consistent with the decrease observed with the actual levels, prevalence of high TC and high LDLC was increased in those with non-communicable HD aetiologies while low HDLC levels prevalence was higher in those with communicable HD **(Table 1 and Figure 2)**. There were no patients with TG levels > 4.5 mmol/L (range 0.1-3.8 mmol/L) which makes use of the Friedewald equation suitable for this cohort[16].

Table 2 shows independent associations between relevant socio-economic, demographic and clinical variables and communicable HD aetiology, relative to those presenting with non-communicable HD. The effect of HD aetiology on low HDLC dyslipidaemia was strong and consistent: adjusting for age, sex and BMI of patients, those with forms of communicable HD were significantly more likely to record a low HDLC relative to those presenting with non-communicable HD (**Table 2,** p<0.001) and less likely to record high TC and LDLC (**Table 2**). Patients with communicable HD were less likely to record high triglyceride levels (OR 0.65, 95%CI 0.51, 0.84, p<0.05) compared to those with non-communicable HD.

CRP subset analysis

Overall, there was no significant difference in CRP levels between aetiology groups (**Table 1**). The proportion of confirmed HIV cases in this CRP subset analysis was 7% (n=27). Of those, 23 were in the very high-risk category. There was also no association between CRP-derived risk categories and high TC, LDLC or triglycerides (data not shown). However the risk of having low HDLC increased with increasing CRP levels. In age and sex-adjusted analyses, those with medium risk (OR 2.73, 95% CI 0.68, 10.89, P=0.16), high risk (OR 4.98, 95% CI 1.46, 17.00, P=0.01) and very high risk (OR 6.37, 95% CI 1.97, 20.57, p<0.01) CRP levels were significantly more likely to record a low HDLC relative to those in the low risk CRP group. Also, when stratified by sex, a strong, positive association remained in females but was no longer apparent in males **(Figure 3)**. In females, the pattern was significant across all CRP risk categories: compared to low risk, those with medium risk (OR 12.1, 95% CI 1.21, 120, p=0.03), high risk (OR 14.4, 95% CI 1.64, 126, p=0.02) and very high risk (OR 23.5, 95% CI 2.81, 197, p=0.004)

CRP levels were all more likely to record a low HDLC. Moreover, the association was not weakened by addition of BMI into the model (BMI and CRP measurements available in only 230 cases) in overall and female-only (n=133) models: those with medium risk (OR 20.5, 95% CI 1.72, 246, p=0.02), high risk (OR 10.6, 95% CI 1.14, 98.8, p=0.04) and very high risk (OR 21.0, 95% CI 2.38, 185, p<0.01) CRP levels were all more likely to record a low HDLC.

DISCUSSION

We report significant decreases in lipid levels (TC, HDLC and LDLC) and age and BMI according to non-communicable and communicable manifestations of *de novo* HD in urban Africans, patterns that were observed in both sexes. The high prevalence of low HDLC in more than half of all cases, but much higher in those with communicable HD, is most striking. Also, it appears that gender is an effect modifier in the relationship between CRP and low HDLC in this cohort, but, importantly, the relationship remains even after adjustment for the significant confounder of adiposity.

While traditionally uncommon[20], dyslipidaemia, in particular low HDLC, is becoming more prevalent in sub-Saharan Africa[21]. The low lipid levels present in the majority of cases with communicable HD reflects the dramatic changes to lipid metabolism observed in infection and is therefore, anticipated. We acknowledge that atherogenic LDLC is also low in this setting and that low HDLC may not be indicative of particularly increased disease risk, at least in the short-term. However, we still deem this as highly clinically relevant given that low HDLC is associated with a higher risk of atherosclerotic forms of HD, even at very low LDLC levels[22]. Interestingly triglyceride levels were not significantly increased in those with communicable forms of HD, despite evidence that it can increase as part of the infectious/inflammatory metabolic milieu[12].

Our interest in this phenomenon predominantly relates to the longer-term effects of low HDLC, especially when observed together with the amplified vascular risk associated with chronic infection[12]. In Africa, where acute coronary syndromes are seen in a relatively young population[23], we predict the very high rates of myriad communicable disease[24, 25] will result in more complex cases, with potentially poorer outcomes in the long-term, given the critical role of HDLC in both innate and adaptive immunity[12]. While many infectious diseases (bacterial and viral) have contributed to the underlying pathology of HD reported here[5], dyslipidemia associated with HIV infection has been particularly well studied. HIV-related low HDLC is likely a consequence of both the viral infection and an adverse effect of some anti-retroviral treatment regimens[25, 26, 27, 28], however only 39 patients of the 76 (51%) confirmed HIV-positive were

on ART at time of presentation, representing 3% of entire subset sample, which possibly dilutes this effect.

Our CRP subset analysis found associations between low HDLC and the pro-inflammatory marker CRP in patients with newly diagnosed HD in a sex disparate manner, with a much stronger positive association in females. Median CRP levels were also very high across all categories of HD aetiology, and are much higher than previous reports in both early analyses of large cohorts[18] as well as South African studies[29], but reflect the clinical requirements at presentation. These high levels may also be the result of 'multi-morbidity' observed in the cohort, given the prevalence of infectious disease (such as HIV/AIDS) as well as other lifestyle factors that can also influence CRP levels[30]; all of which may have contributed to the high levels observed. Inflammatory stress may be having a more adverse effect on HDLC in women compared to men as a result of many causes. The prognostic value of stratifying CVD risk, even at very high CRP (>10 mg/L) levels, has been demonstrated in a very large female cohort[18], and there are reports of elevated CRP in female populations of African descent[31]. We also report females as having a significantly higher BMI; obesity itself can induce a low-grade inflammatory response, however the association between low HDLC and CRP in women remained even after adjusting for BMI. While we have assumed that the exaggerated drop in HDLC in women with acute forms of communicable HD is a consequence rather than a cause of infection, treatment of atherogenic dyslipidaemia and inflammatory markers in women are of particular clinical relevance in a setting where obesity and its antecedent behaviours are increasing.

These results underscore the need to consider multifactorial CVD risk burden that recognises that co-occurrence of infectious and non-communicable disease produces significant and complex health disparities. Certainly, the clinical strategies to protect the heart and vessels in acute infection differ from those required in chronic infection and it is unlikely that lipid measurements will form a cornerstone of treatment in such cases. However, it is important to recognise the benefits of early detection and treatment of dyslipidaemia in order to mitigate any double effect of infectious *and* 'lifestyle' HD risk factors in the longer term. While the

epidemiological evidence is clear, the precise mechanism by which HDLC decreases atherosclerotic CVD risk remains unclear[11]; indeed, efforts to develop pharmacological modalities to specifically increase HDLC levels to reduce cardiovascular risk, continues to be problematic[10] and we acknowledge that addressing the low HDLC observed in this cohort, in isolation, without commensurate improvements in HDLC functionality, will prove a difficult task. This does not, however, preclude use of other therapeutic interventions that address the greater, more complex risk presentation of cases that fall in the 'crossover' between communicable and non-communicable diseases. For example, the polypill, which includes lipid-lowering medications, has been proposed as a viable treatment option in secondary prevention, given its relative ease of use and efficacy in low-income settings[32]. More so, evidence that statins also exert immunomodulatory effects, along with suggestions they may prove useful in the treatment and prevention of infections[33], indicate they may have important, multi-faceted clinical implications in populations such as Soweto, especially given the substantial dyslipidaemic risk associated with highly-prevalent HIV infection and ART. Attempts to address prevention, management, cure and control of non-communicable and communicable forms of HD as entirely separate entities are likely to prove insufficient. This holds true on a per-patient basis as well as for any population-wide, public health approaches.

There are a number of limitations that require consideration. Clinical data (other than routine echocardiography and 12-lead ECG) were obtained according to presentation. This study was not specifically designed to comprehensively delineate between specific forms of HD (resulting in variable clinical data) although this is part of clinical investigation at Baragwanath Hospital; although it should be noted HIV status is not routinely determined. The arbitrary selection of disease states into the communicable versus non-communicable groups (e.g. primary valve disease) may be questioned; hence our further delineation of clearly identifiable cases of acute inflammation/infection at the point of admission. However, we would emphasise that classification was prospectively applied, the groupings are consistent with our previous reports that describe in detail the rigorous clinical criteria employed in profiling the 'Heart of Soweto' cohort, and expected gradients in lipid levels were subsequently found. Systematic bias

needs to be carefully considered before attributing broad patterns in lipid profiles, as those with suspected atherosclerotic disease were more likely to have had lipid levels measured, reflecting the low number of those presenting an acute infectious form of HD (for example, patients with pericarditis). Adiposity, a major confounder of both dyslipidaemia and HD, was recorded in 71% of the cohort. However, its inclusion in the regression analyses did not alter the significance of the associations. Central obesity measurements (e.g. waist-to-hip ratio) may have offered greater delineation of CVD risk but data were not available. CRP was measured in just under one third of cases and related data requires careful interpretation. Finally, we were not able to investigate the possible effect of the magnitude and timing of the contributing infection on lipid levels, beyond the data collected at admission. Given the transient, dynamic processes of lipid metabolism over the course of acute and chronic diseases, only longitudinal studies of lipid levels and subsequent outcomes can fully elucidate the clinical importance of our findings.

Conclusions

We have shown that despite largely favourable lipid profiles, there are clear differences according to underlying aetiology of HD in urban Africans. Younger Africans with communicable HD have particularly low levels of HDLC that, if maintained in the longer term, may leave them at increased risk of atherosclerotic disease. If proven, targeted prevention programs that identify and actively manage individuals with a history of CD (particularly an active case) and with low levels of HDLC may be indicated. The alternative is an increasing burden of non-communicable forms of HD in urban African communities that is supplemented (in origin and confluence) by historical cases of communicable disease that have adversely affected protective HDLC levels (particularly in women).

Acknowledgements

We thank all the doctors, nurses, and patients who participated in the registry; and Elisabeth Tshele, Bridget Phooko, Maureen Kubheka and Phutuma Mathusi who contributed to the meticulous collection and management of clinical data.

Competing interests

All authors declare: all authors had financial support from independent funding bodies, including University of the Witwatersrand and unconditional research grants from Adcock-Ingram, the Medtronic Foundation USA, Servier, Bayer-Schering and BHP Billiton, for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Funding

The 'Heart of Soweto Study' registry was supported by the University of the Witwatersrand and unconditional research grants from Adcock-Ingram, the Medtronic Foundation USA, Servier, Bayer-Schering and BHP Billiton. SS, MJC and JGL are supported by the National Health & Medical Research Council of Australia [Program Grants 320860 and 631947 and Postgraduate scholarship 586739]. JGL is supported by the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand. Baker IDI is supported by the Victorian Government's Operational Infrastructure Support Program. KS and SL are supported by the MRC South Africa and the University of Cape Town.

Author's contributions:

KS, MJC and SS participated in the original design of the study and supervised the collection of data. JGL prepared the first draft of the manuscript, with edits and revisions provided by all authors. FR and FT revised manuscript critically for important intellectual content. All authors

had full access to all the data and read and approved the final version of the manuscript. All authors had final responsibility for the decision to submit the manuscript for publication.

Data sharing statement

Study data will be available on request from the corresponding author.

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TABLE 1 Clinical and demographic profile according to heart disease aetiology

	ALL Cases	Non-communicable	Communicable	*P* value
	n=1199	n=678	n=521	
Demographic Profile				
Mean age (years)	58.3 ±14.0	60.1 ± 13.1	55.9 ± 14.9	<0.001
Female	701 (59%)	403 (59%)	298 (57%)	0.44
<6 years formal education	582 (49%)	335 (49%)	247 (47%)	0.52
Soweto origin	562 (47%)	327 (48%)	235 (45%)	0.29
Clinical Presentation				
Total cholesterol (mmol/L)	4.0 ± 1.4	4.3 ± 1.3	3.7 ± 1.2	<0.001
HDLC (mmol/L)	1.1 ± 0.5	1.2 ± 0.5	1.0 ± 0.5	<0.001
Median triglycerides (mmol/L)*	1.1 (0.8, 1.5)	1.1 (0.8,1.6)	1.0 (0.7, 1.3)	<0.001
LDLC (mmol/L)	2.4 ± 1.0	2.5 ± 1.0	2.2 ± 0.9	<0.001
TC:HDLC ratio	4.3 ± 3.0	4.2 ± 3.1	4.4 ± 2.7	0.27
Median serum CRP (mg/L)*	19 (7.0, 45.0)	16.8 (6.6,41.5)	20.5 (7.8, 55.9)	0.25
Systolic BP (mmHg)	135 ± 29	143 ± 29	126 ± 26	<0.001
Diastolic BP (mmHg)	78 ± 16	80 ± 16	74 ± 16	<0.001
BMI (kg/m^2)	29.0 ± 6.7	30.3 ± 6.7	27.2 ± 6.2	<0.001
Prevalence of dyslipidaemia (n, %)				
High total cholesterol (> 5mmol/L)	378 (32%)	266 (39%)	112 (22%)	<0.001
Low HDLC (< 1 in males and < 1.2 mmol/L in females)	694 (58%)	344 (51%)	350 (67%)	<0.001
High LDLC (> 2.5 mmol/L)	446 (37%)	291 (43%)	155 (30%)	<0.001

High triglycerides (> 1.7 mmol/l)	215 (18%)	143 (21%)	72 (14%)	0.001
Prevalence of other risk factors (n, %)				
Obese (BMI >30 kg/m^2)	344 (40%)	237 (48%)	107 (30%)	<0.001
Type 2 diabetes	98 (8%)	71 (11%)	27 (5%)	<0.001
Past or current smoker	566 (47%)	321(47%)	245 (47%)	0.95
Family history of CVD	466 (39%)	286 (42%)	180 (35%)	0.01
Confirmed HIV-positive cases	76 (6%)	15 (2%)	61 (12%)	<0.001

Table legend:

LDLC = low-density lipoprotein cholesterol; HDLC = high-density lipoprotein cholesterol; BMI = body mass index (available in 854 cases); CRP = C-reactive protein (available in 367 cases); CVD = cardiovascular disease; HIV = human immunodeficiency virus. *Median (interquartile range) values presented, differences tested by Mann-Whitney U test

TABLE 2 Independent correlates of communicable heart disease, relative to non-communicable heart disease

	Communicable disease	
	Odds Ratio	**95% CI**
Female sex	0.91	0.72, 1.15
Age	0.98	0.97, 0.99**
Obesity	0.50	0.37, 0.68***
< 6 years formal education	1.11	0.88, 1.42
Soweto origin	0.98	0.77, 1.24
Body mass index adjusted analysis		
High TC	0.52	0.37, 0.71***
High LDLC	0.56	0.41, 0.76***
Low HDLC	1.91	1.42, 2.57***
High TG	0.65	0.51, 0.84*

Table legend:

Obesity BMI >30kg/m^2; High total cholesterol (TC) > 4.5 mmol/L; High low density lipoprotein (LDLC) >2.5 mmol/L; Low high density lipoprotein (HDLC) (<1.0 mmol/L in males, <1.2 mmol/L in females). OR = odds ratio; CI = confidence intervals. Age and sex-adjusted analysis: * p<0.05; **p<0.01; ***p<0.001.

FIGURE 1 Sex specific lipid profiles according to heart disease aetiology

Figure legend:

Lipid values are shown as mean ± standard error. P values indicate between-sex comparisons per aetiology group (T-test), ** = P<0.01; * = P<0.05. NCD = non-communicable heart disease; CD = communicable heart disease; TC= total cholesterol; HDL= high-density lipoprotein cholesterol; LDL= low-density lipoprotein. Y-axis dotted lines show thresholds for high TC and LDL or low HDL (sex specific values).

FIGURE 2 Prevalence of low high-density lipoprotein cholesterol according to heart disease aetiology

Figure legend:

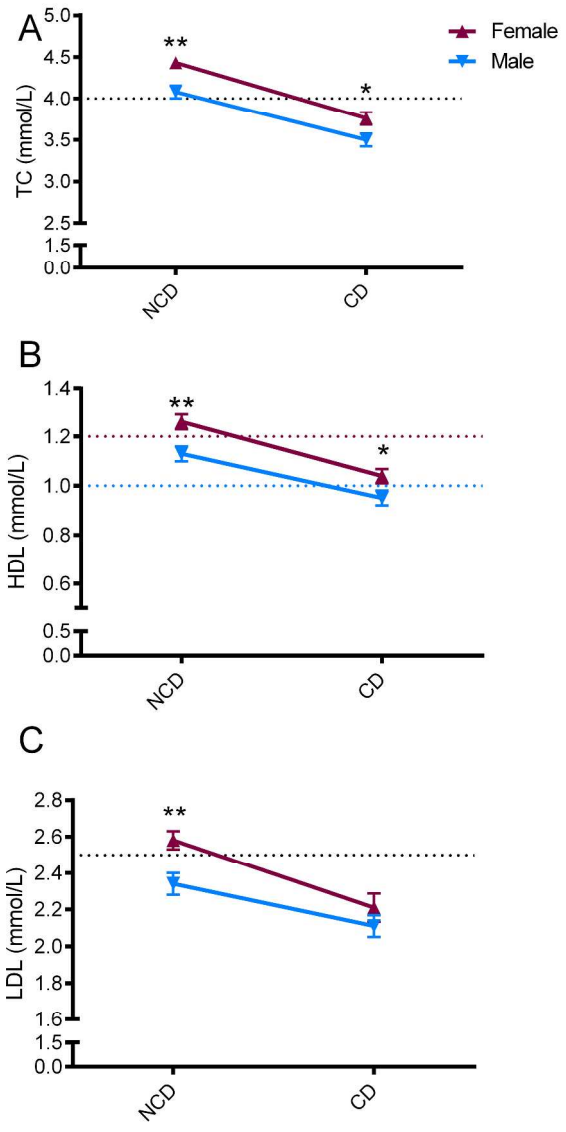
NCD = non-communicable heart disease; CD = communicable heart disease.

High total cholesterol (TC) > 4.5 mmol/L; Low high-density lipoprotein cholesterol (HDLC) (<1.0 mmol/L in males, <1.2 mmol/L in females). High low density lipoprotein cholesterol (LDLC) >2.5 mmol/L; High triglycerides (TGs) >1.7 mmol/L

FIGURE 3 Risk of low high-density lipoprotein cholesterol according to C-reactive protein risk group, relative to low-risk C-reactive protein group (n=367)

Figure legend:

Age-adjusted analysis. CRP = C-reactive protein. ** = P<0.01; * = P<0.05 relative to low CRP group. For confidence intervals, please refer to Results section.



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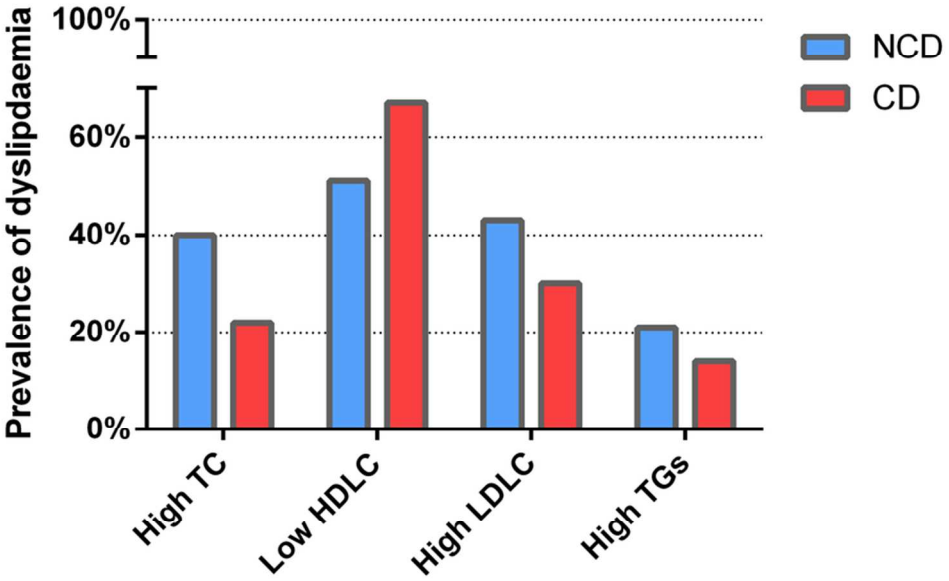

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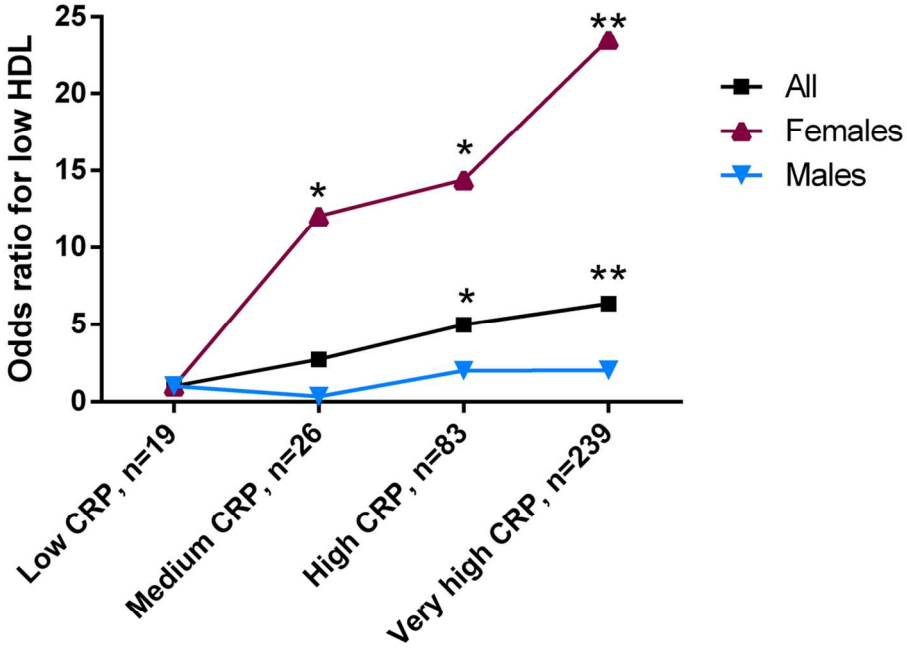

117x90mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

Completed for the article: ***Low levels of high-density lipoprotein cholesterol is the most prevalent metabolic abnormality in urban Africans with newly diagnosed heart disease: The 'Heart of Soweto' hospital registry study***
Date: 12 February 2014

	Item No	Recommendation	Complete
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	

		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for exposed and unexposed groups.

BMJ Open

Lower Levels of High-density Lipoprotein Cholesterol in Urban Africans Presenting with Communicable Versus Non-communicable Forms of Heart Disease: The 'Heart of Soweto' hospital registry study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005069.R1
Article Type:	Research
Date Submitted by the Author:	17-May-2014
Complete List of Authors:	Lyons, Jasmine; Baker IDI Heart and Diabetes Institute, Preventative Health Sliwa, Karen; University of the Witwatersrand, Soweto Cardiovascular Research Unit Carrington, Melinda; Baker IDI Heart and Diabetes Institute, Preventative Health; University of the Witwatersrand, Soweto Cardiovascular Research Unit Raal, Frederick; University of the Witwatersrand, Carbohydrate and Lipid Metabolism Research Unit Pretorius, Sandra; University of the Witwatersrand, Soweto Cardiovascular Research Unit Thienemann, Freidrich; University of Cape Town, Institute of Infectious Diseases and Molecular Medicine; University of Cape Town, Hatter Institute for Cardiovascular Research in Africa, Cape Heart Group amd IIDMM STEWART, SIMON; Baker IDI Heart and Diabetes Institute, Preventative Health; University of the Witwatersrand, Soweto Cardiovascular Research Unit
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Public health
Keywords:	Cardiac Epidemiology < CARDIOLOGY, Epidemiology < INFECTIOUS DISEASES, PREVENTIVE MEDICINE

Lower Levels of High-density Lipoprotein Cholesterol in Urban Africans Presenting with Communicable Versus Non-communicable Forms of Heart Disease: The 'Heart of Soweto' hospital registry study

Short title: Lyons – HDLC in communicable heart disease

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Key Words: High-density lipoprotein, lipids, infection, epidemiologic transition, Africa.

Word count: 3540 not including 2 tables, 3 figures and 35 references.

ABSTRACT

Objectives: To investigate if urban Africans displayed lower levels of atheroprotective high-density lipoprotein cholesterol (HDLC) when presenting with communicable versus non-communicable forms of heart disease (HD) as both acute infection and chronic inflammation reduce HDLC levels.

Design: Hospital registry of 5328 de novo cases of HD over a 3-year period.

Setting: Cardiology Unit, Baragwanath Hospital in Soweto, South Africa.

Participants: A total of 1199 patients of African descent (59% female; 57.0±13.4 years) had fasting blood lipid levels (Total cholesterol [TC], triglyceride, HDLC, and low-density lipoprotein [LDLC] cholesterol) documented on admission. Serum inflammatory marker C-reactive protein (CRP) was measured in a sub-set of 367 patients (31% of cases).

Main outcome measures: Lipid profiles were compared according to pre-specified classification of non-communicable (e.g. hypertensive HD) versus communicable (e.g. rheumatic HD) HD. Low HDLC was defined as <1.0 mmol/L for males and <1.2mmol/L for females, according to applicable South African Clinical Guidelines.

Results: Overall 694 (58%) of those presenting with HD had low HDLC levels; 344 of 678 (51%) and 350 of 521 (67%) for non-communicable and communicable, respectively (p<0.001). Comparatively, overall prevalence of high TC was 32% and high LDLC was 37%. On an adjusted basis, those with non-communicable HD were more likely to record a low HDLC relative to non-communicable presentations (OR 1.91, 95%CI 1.42, 2.57; p<0.001). There was a strong relationship between low HDLC and higher levels of CRP, but only in females.

Conclusions: Despite largely favourable lipid profiles, there are clear differences according to aetiology of underlying HD in urban Africans, with younger patients with communicable HD having particularly low levels of HDLC. Appropriate prospective evidence is needed to determine if persistent low levels of HDLC expose patients to increased, long-term risk of atherosclerotic forms of HD. The female-only inverse association between HDL-C and CRP warrants further investigation.

ARTICLE SUMMARY

Article focus:

- In sub-Saharan Africa, the incidence of non-communicable cardiovascular disease is increasing while, simultaneously, communicable forms of heart disease continue to cause considerable levels of morbidity and mortality.
- In this study, we have sought to explore one heart disease risk factor, dyslipidaemia, in a well-defined clinical registry in Soweto, South Africa.
- Lipid profiles from 1199 de novo presentations of heart disease were compared according to pre-specified classification of non-communicable heart disease (e.g. hypertensive heart disease) versus communicable forms of heart disease (e.g. pericarditis or chronic rheumatic heart disease). We hypothesised that those diagnosed with communicable heart disease would display an adverse lipid profile, with low levels of atheroprotective high-density lipoprotein cholesterol (HDLC). We also investigated the potential interaction of the inflammatory marker C-reactive protein (CRP) and low HDLC in a subset of these patients.

Key messages:

- We describe distinct patterns of dyslipidaemia according to underlying heart disease aetiology: significantly decreased levels of HDLC, total cholesterol and low-density lipoprotein cholesterol in those with communicable heart disease (representing 43% of cohort) compared to those with non-communicable heart disease (57% of cohort).
- In adjusted analyses, low HDLC was more pronounced in those with communicable heart disease. In those with high CRP levels, we present novel data showing a sex-disparate relationship between CRP and low HDLC, with a strong relationship between high CRP and low HDLC in females only.
- The high prevalence of low HDLC in a relatively young population of urban Africans may, if persistent in the longer-term, confer greater risk of atherosclerotic heart disease

Strengths and limitations of the study:

- We report a high prevalence of low HDLC in *de novo* presentations of both communicable heart disease and non-communicable heart disease, with a greater prevalence in those with communicable heart disease.
- The study cohort is clinically very well defined; however the lipid data were obtained according to clinical presentation, which may impose systematic bias to the results.
- This hospital registry study has provided preliminary data that would support prospective investigation of longer-term dyslipidaemia patterns and their impact on heart disease incidence, both in South Africa and in other low-and-middle-income countries where the epidemiologic transition is currently underway.

INTRODUCTION

Heart diseases with infectious aetiology have long been the principal forms of cardiovascular disease (CVD) in Sub-Saharan Africa. However, epidemiological transition has seen increased prevalence of non-communicable forms of heart disease in these populations[1]. This phenomenon is largely driven by complex, population-wide changes in demographic, social and economic status, with associated changes in lifestyle habits[2-4]. Indicative of the tension between 'old' and 'new' forms of heart disease, the incidence of communicable heart disease (HD) is sustained by the devastating epidemics of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), tuberculosis (TB), rheumatic heart disease (RHD) and parasitic infections with cardiac involvement[5-7], while in parallel, the prevalence of risk factors for non-communicable HD increases[8].

Low serum levels of high-density lipoprotein cholesterol (HDLC) are consistently and independently associated with increased risk of atherosclerotic forms of CVD[9 10]. However, it remains uncertain whether low HDLC is causal or just a cardiovascular risk marker[11]. If we are to extrapolate from studies in Western and Asian populations[12-14], isolated low HDLC is associated with increased risk for CVD in the long-term. There are several causes of low HDLC levels, including overweight, obesity, tobacco smoking, and insulin resistance/type 2 diabetes mellitus, indicative of the important role lifestyle factors have in mediating HDLC levels[9]. Additionally, low HDLC is a striking consequence of abnormal lipid metabolism in infection and inflammation[15]. Although it has been shown that those of African descent largely show a favourable lipid profile characterised by high HDLC levels [16], it is unlikely that they can remain athero-protective during an infected state[15]. Indeed, in this setting, it is probable that increasing prevalence of modifiable/ lifestyle risk factors contribute to a more advanced presentation in those with communicable HD[8]. We have previously reported that in the geographically compact townships that comprise Soweto in South Africa, 'old' and 'new' forms of HD are simultaneously present[8]. While this tension exists, we have a unique opportunity to explore lipid profiles in patients presenting with non-communicable versus communicable forms of HD.

STUDY HYPOTHESES

Having shown important ethnic differences in the lipid profiles of patients of African descent presenting with HD in the urban African enclave of Soweto[16], we hypothesised that independent of age and sex, urban Africans presenting with communicable HD will demonstrate patterns of dyslipidaemia associated with infection/inflammation, particularly sub-optimal levels of HDLC, versus non-communicable HD.

METHODS

Study Setting & Design

As described in detail previously[8 17] the 3,500 bed Chris Hani Baragwanath Hospital (case load of > 125,000 in-patients per annum) services the tertiary care needs of Soweto (population of 1.1 million) and surrounding communities. All suspected cardiac presentations are referred to the hospital's Cardiology Unit for advanced diagnostic testing and gold-standard treatments. A prospective clinical registry of all *de novo* presentations of the same was established in 2006 as part of the Heart of Soweto Study and represents sub-Saharan Africa's largest and most detailed study of advanced forms of HD to date[17].

Participants

The 'Heart of Soweto' cohort of *de novo* case presentations comprised 5328 patients. Of these, 2185 patients (40%) had a documented fasting lipid profile (serum total cholesterol (TC) level, triglyceride, HDLC and calculated low-density lipoprotein cholesterol (LDLC)[18] undertaken at Baragwanath Hospital on-site pathology). None of the patients were on lipid lowering agents at the time of presentation, as this medication can only be prescribed at the tertiary institution. However some of the patients had been placed on anti-hypertensive medication prior to their first assessment at the Cardiac Clinic at Baragwanath Hospital. Moreover, only a small number of patients (39 cases) had been prescribed anti-retroviral therapy (ART) on presentation. The study was approved by the University of the Witwatersrand Ethical Committee and conforms to the principles outlined in the Declaration of Helsinki. All patients provided informed consent.

Study Data

A complete list of study data captured by the registry, comprising basic socio-demographic (including self-reported ethnicity, years of education and determining if the patient was born in Soweto) and advanced clinical profiling, has been described previously[8 17] The registry captured all advanced clinical investigative procedures (e.g. coronary angiography, which was undertaken in all people diagnosed with coronary artery disease (CAD)). Echocardiography (performed on all patients) criteria used in the study has been described in detail previously[8 17].

Case Classifications

Adjudication and classification of communicable and non-communicable presentations of HD in this cohort have been previously described[8]. After exclusion of those with uncomplicated hypertension (i.e. without evidence of cardiac dysfunction, n=380) or other non-modifiable aetiologies (e.g. congenital disorders), 1199 patients of African descent (22% of the total 'Heart of Soweto' cohort) were included in this analysis. Contributory diagnoses for non-communicable HD were predominantly hypertensive heart failure (HT-HF) and coronary artery disease (without HIV). Communicable heart disease was predominantly classified as HIV-dilated cardiomyopathy (HIV-DCMO), HIV-pulmonary hypertension, TB pericardial disease, and pericarditis due to other infection.

Risk factor definition

Optimum lipid levels and treatment goals with established CVD were defined according to international guidelines[9] adopted by the Lipid and Atherosclerosis Society of South Africa and the South African Heart Association - high TC: >4.5 mmol/L, high TGs: >1.7 mmol/L, high LDLC: >2.5 mmol/L and low HDLC: <1.0 for males and <1.2 mmol/L for females[19]. Other risk factors were measured on a clinical basis, as previously described[17]. Anthropometric measurements were available for calculation of body mass index (BMI, kg/m^2) in 854 (71%) cases, the low reporting rate restricted to ambulatory patients. Obesity was defined as BMI ≥ 30 kg/m^2. Serum C-reactive protein (CRP) was measured in a sub-set of 367 patients (31% of all cases) if clinically indicated (e.g. suspected infection). Patients were stratified into clinically relevant CRP

categories[20], as defined by Dhingra and colleagues[21]. Patients with a CRP of 1 mg/L (n=19) were used as reference group and compared to medium (1.1-3.0 mg/L, n=26), high (3.1-10.0 mg/L, n=83) and very high (>10.0 mg/L, n=239) CRP categories.

Statistical analyses

Normally distributed continuous data are presented as the mean ± standard deviation and non-Gaussian distributed variables as the median (inter-quartile range). Categorical data are presented as sample number and percentages. For group comparisons, we initially used Chi Square (χ^2) analysis with calculation of odds ratios (OR) with 95% confidence intervals (CI) presented where appropriate for discrete variables, and independent T-tests for normally distributed continuous variables and Mann-Whitney U test for nonparametric continuous variables. Multiple logistic regression analyses (entry model) were used to derive age and sex adjusted ORs (and BMI in some analyses, as described) for the risk of presenting with clinically relevant variables (primarily dyslipidaemia profiles), according to CD HD relative to NCD diagnosis. Significance was accepted at the two-sided level of $p<0.05$.

RESULTS

Clinical and Demographic Profile

Table 1 shows the socio-demographic and clinical profile of this cohort according to cardiac aetiology. Those presenting with non-communicable HD (n=678, 56.5% of cohort) were older and had higher BMI and mean SBP and DBP than those with communicable HD (n=521, 43.5%; all comparisons p<0.001). Overall, 76 (6%) were confirmed HIV-positive: 15 (2%) and 61 (12%) patients were confirmed HIV-positive in non-communicable and communicable HD groups respectively (P<0.001). Apart from higher BMIs in women (30.6 ± 6.9 vs. 26.7 ± 5.5 kg/m^2 in males, p<0.001) there were no significant differences between sexes in respect to other clinical parameters. To this, the prevalence of obesity in women was 50% as compared to men (26%), P<0.001.

TABLE 1 Clinical and demographic profile according to heart disease aetiology

	ALL Cases n=1199	Non-communicable n=678 (57%)	Communicable n=521 (43%)	*P* value
Demographic Profile				
Mean age (years)	58.3 ±14.0	60.1 ± 13.1	55.9 ± 14.9	<0.001
Female	701 (59%)	403 (59%)	298 (57%)	0.44
<6 years formal education	582 (49%)	335 (49%)	247 (47%)	0.52
Soweto origin	562 (47%)	327 (48%)	235 (45%)	0.29
Clinical Presentation				
Total cholesterol (mmol/L)	4.0 ± 1.4	4.3 ± 1.3	3.7 ± 1.2	<0.001
HDLC (mmol/L)	1.1 ± 0.5	1.2 ± 0.5	1.0 ± 0.5	<0.001
Median triglycerides (mmol/L)*	1.1 (0.8, 1.5)	1.1 (0.8,1.6)	1.0 (0.7, 1.3)	<0.001
LDLC (mmol/L)	2.4 ± 1.0	2.5 ± 1.0	2.2 ± 0.9	<0.001
TC:HDLC ratio	4.3 ± 3.0	4.2 ± 3.1	4.4 ± 2.7	0.27
LDL:HDLC ratio	2.5 ± 1.1	2.5 ± 1.0	2.7 ± 1.1	0.36
TG:HDLC ratio*	1.1 (0.7, 1.7)	1.0 (0.7, 1.7)	1.1 (0.7, 1.8)	0.12
Median serum CRP (mg/L)*	19 (7.0, 45.0)	16.8 (6.6,41.5)	20.5 (7.8, 55.9)	0.25

Systolic BP (mmHg)	135 ± 29	143 ± 29	126 ± 26	<0.001
Diastolic BP (mmHg)	78 ± 16	80 ± 16	74 ± 16	<0.001
BMI (kg/m^2)	29.0 ± 6.7	30.3 ± 6.7	27.2 ± 6.2	<0.001
Prevalence of dyslipidaemia (n, %)				
High total cholesterol (> 5mmol/L)	378 (32%)	266 (39%)	112 (22%)	<0.001
Low HDLC (< 1 in males and < 1.2 mmol/L in females)	694 (58%)	344 (51%)	350 (67%)	<0.001
High LDLC (> 2.5 mmol/L)	446 (37%)	291 (43%)	155 (30%)	<0.001
High triglycerides (> 1.7 mmol/l)	215 (18%)	143 (21%)	72 (14%)	0.001
Prevalence of other risk factors (n, %)				
Obese (BMI >30 kg/m^2)	344 (40%)	237 (48%)	107 (30%)	<0.001
Type 2 diabetes	98 (8%)	71 (11%)	27 (5%)	<0.001
Past or current smoker	566 (47%)	321(47%)	245 (47%)	0.95
Family history of CVD	466 (39%)	286 (42%)	180 (35%)	0.01
Confirmed HIV-positive cases	76 (6%)	15 (2%)	61 (12%)	<0.001

Table legend:

LDLC = low-density lipoprotein cholesterol; HDLC = high-density lipoprotein cholesterol; TG = triglycerides; BMI = body mass index (available in 854 cases); CRP = C-reactive protein (available in 367 cases); CVD = cardiovascular disease; HIV = human immunodeficiency virus. *Median (interquartile range) values presented, differences tested by Mann-Whitney U test

Aetiology of heart disease (primary diagnosis)

Overall, the most prevalent primary diagnoses were HT-HF (n=461, 38%), dilated cardiomyopathy (DCMO, n= 178, 15%) and CAD (n=157, 12%). In those classified as non-communicable HD, HT-HF was the main primary diagnosis (n=461, 68%), along with CAD (without concurrent HIV-infection; n=157, 23%). Dilated cardiomyopathy (n=178, 34%), right heart failure (n=92, 18%) and right heart disease (n=63, 12%) and other forms of primary valve

disease (n=71, 14%), were the most common diagnoses in those classified with communicable forms of HD.

Lipid Profiles

Those with communicable HD had significantly lower TC, LDLC, and HDLC compared with patients with non-communicable HD (**Table 1** and **Figure 1**, p<0.001 for all comparisons). Overall, women had significantly higher TC (4.2±1.3 mmol/L vs. 3.8±1.2 mmol/L, p<0.001); LDLC (2.4±1.0 mmol/L vs. 2.2±1.0 mmol/L, p<0.01), and HDLC compared to men (1.2±0.5 mmol/L vs. 1.0±0.5 mmol/L, p<0.001). This gender difference did not extend to triglycerides (1.1(0.4-1.8) mmol/L vs. 1.1(0.4-1.8), p=0.7) nor TC:HDLC ratio (4.2 ± 3.1 mmol/L vs. 4.3 ± 2.7 mmol/L, p=0.6). Lipid ratios were calculated and compared (**Table 1**). There was no significant differences between aetiology groups for either TC:HDL or TG:HDL groups. However LDL:HDL ratios were significantly higher in the communicable group.

Levels of TC (Figure 1A), HDLC (Figure 1B) and LDLC (Figure 1C) were significantly higher in females with non-communicable HD (**Figure 1**). However in those diagnosed with communicable HD, small, but significant, differences were observed only for TC and HDLC, not LDL (**Figure 1**). Overall, prevalence of dyslipidaemia varied from 18% of patients with high triglycerides to 58% with low HDLC (**Table 1** and **Figure 2**). Consistent with the decrease observed with the actual levels, prevalence of high TC and high LDLC was increased in those with non-communicable HD aetiologies while low HDLC levels prevalence was higher in those with communicable HD **(Table 1 and Figure 2)**. There were no patients with TG levels > 4.5 mmol/L (range 0.1-3.8 mmol/L) which makes use of the Friedewald equation suitable for this cohort[18].

Table 2 shows independent associations between relevant socio-economic, demographic and clinical variables and communicable HD aetiology, relative to those presenting with non-communicable HD. The effect of HD aetiology on low HDLC dyslipidaemia was strong and consistent: adjusting for age, sex and BMI of patients, those with forms of communicable HD were significantly more likely to record a low HDLC relative to those presenting with non-communicable HD (**Table 2,** p<0.001) and less likely to record high TC and LDLC (**Table 2**).

Patients with communicable HD were less likely to record high triglyceride levels (OR 0.65, 95%CI 0.51, 0.84, p<0.05) compared to those with non-communicable HD.

TABLE 2 Independent correlates of communicable heart disease, relative to non-communicable heart disease

	Communicable disease	
	Odds Ratio	**95% CI**
Female sex	0.91	0.72, 1.15
Age	0.98	0.97, 0.99**
Obesity	0.50	0.37, 0.68***
< 6 years formal education	1.11	0.88, 1.42
Soweto origin	0.98	0.77, 1.24
Body mass index adjusted analysis		
High TC	0.52	0.37, 0.71***
High LDLC	0.56	0.41, 0.76***
Low HDLC	1.91	1.42, 2.57***
High TG	0.65	0.51, 0.84*

Table legend:

Obesity BMI >30kg/m^2; High total cholesterol (TC) > 4.5 mmol/L; High low density lipoprotein (LDLC) >2.5 mmol/L; Low high density lipoprotein (HDLC) (<1.0 mmol/L in males, <1.2 mmol/L in females). OR = odds ratio; CI = confidence intervals. Age and sex-adjusted analysis: * p<0.05; **p<0.01; ***p<0.001.

CRP subset analysis

Overall, there was no significant difference in CRP levels between aetiology groups (**Table 1**). The proportion of confirmed HIV cases in this CRP subset analysis was 7% (n=27). Of those, 23 were in the very high-risk category. There was also no association between CRP-derived risk categories and high TC, LDLC or triglycerides (data not shown). However the risk of having low HDLC increased with increasing CRP levels. In age and sex-adjusted analyses, those with

medium risk (OR 2.73, 95% CI 0.68, 10.89, P=0.16), high risk (OR 4.98, 95% CI 1.46, 17.00, P=0.01) and very high risk (OR 6.37, 95% CI 1.97, 20.57, p<0.01) CRP levels were significantly more likely to record a low HDLC relative to those in the low risk CRP group. Also, when stratified by sex, a strong, positive association remained in females but was no longer apparent in males **(Figure 3)**. In females, the pattern was significant across all CRP risk categories: compared to low risk, those with medium risk (OR 12.1, 95% CI 1.21, 120, p=0.03), high risk (OR 14.4, 95% CI 1.64, 126, p=0.02) and very high risk (OR 23.5, 95% CI 2.81, 197, p=0.004) CRP levels were all more likely to record a low HDLC. Moreover, the association was not weakened by addition of BMI into the model (BMI and CRP measurements available in only 230 cases) in overall and female-only (n=133) models: those with medium risk (OR 20.5, 95% CI 1.72, 246, p=0.02), high risk (OR 10.6, 95% CI 1.14, 98.8, p=0.04) and very high risk (OR 21.0, 95% CI 2.38, 185, p<0.01) CRP levels were all more likely to record a low HDLC.

DISCUSSION

We report significant decreases in lipid levels (TC, HDLC and LDLC) and age and BMI according to non-communicable and communicable manifestations of *de novo* HD in urban Africans, patterns that were observed in both sexes. The high prevalence of low HDLC in more than half of all cases, but much higher in those with communicable HD, is most striking. Also, it appears that gender is an effect modifier in the relationship between CRP and low HDLC in this cohort, but, importantly, the relationship remains even after adjustment for the significant confounder of adiposity.

While traditionally uncommon[22], dyslipidaemia, in particular low HDLC, is becoming more prevalent in sub-Saharan Africa[23]. The low lipid levels present in the majority of cases with communicable HD reflects the dramatic changes to lipid metabolism observed in infection and is therefore, anticipated. We acknowledge that atherogenic LDLC is also low in this setting and that low HDLC may not be indicative of particularly increased disease risk, at least in the short-term. However we still deem this as highly clinically relevant given that even isolated low HDLC is associated with a higher risk of atherosclerotic forms of HD, a finding that has been seen in diverse populations[12-14]. Interestingly triglyceride levels were not significantly increased in those with communicable forms of HD, despite evidence that it can increase as part of the infectious/inflammatory metabolic milieu[15]. Additionally, we speculate that the higher lipid levels in women may be the result of much higher rates of obesity (50% compared with 26% in men) as the driver of elevated total cholesterol, which has been suggested by authors of a worldwide systematic analysis on high TC [24].

Our interest in this phenomenon predominantly relates to the longer-term effects of low HDLC, especially when observed together with the amplified vascular risk associated with chronic infection[15]. In Africa, where acute coronary syndromes are seen in a relatively young population[25], we predict the very high rates of myriad communicable disease[26 27] will result in more complex cases, with potentially poorer outcomes in the long-term, given the critical role of HDLC in both innate and adaptive immunity[15]. While many infectious diseases (bacterial and viral) have contributed to the underlying pathology of HD reported here[5], dyslipidemia

associated with HIV infection has been particularly well studied. HIV-related low HDLC is likely a consequence of both the viral infection and an adverse effect of some anti-retroviral treatment regimens[27-30], however only 39 patients of the 76 (51%) confirmed HIV-positive were on ART at time of presentation, representing 3% of entire subset sample, which possibly dilutes this effect.

Our CRP subset analysis found associations between low HDLC and the pro-inflammatory marker CRP in patients with newly diagnosed HD in a sex disparate manner, with a much stronger positive association in females. Median CRP levels were also very high across all categories of HD aetiology, and are much higher than previous reports in both early analyses of large cohorts[20] as well as South African studies[31], but reflect the clinical requirements at presentation. These high levels may also be the result of 'multi-morbidity' observed in the cohort, given the prevalence of infectious disease (such as HIV/AIDS) as well as other lifestyle factors that can also influence CRP levels[32]; all of which may have contributed to the high levels observed. Inflammatory stress may be having a more adverse effect on HDLC in women compared to men as a result of many causes. The prognostic value of stratifying CVD risk, even at very high CRP (>10 mg/L) levels, has been demonstrated in a very large female cohort[20], and there are reports of elevated CRP in female populations of African descent[33]. We also report females as having a significantly higher BMI; obesity itself can induce a low-grade inflammatory response, however the association between low HDLC and CRP in women remained even after adjusting for BMI. While we have assumed that the exaggerated drop in HDLC in women with acute forms of communicable HD is a consequence rather than a cause of infection, treatment of atherogenic dyslipidaemia and inflammatory markers in women are of particular clinical relevance in a setting where obesity and its antecedent behaviours are increasing.

These results underscore the need to consider multifactorial CVD risk burden that recognises that co-occurrence of infectious and non-communicable disease produces significant and complex health disparities. Certainly, the clinical strategies to protect the heart and vessels in acute infection differ from those required in chronic infection and it is unlikely that lipid

measurements will form a cornerstone of treatment in such cases. However, it is important to recognise the benefits of early detection and treatment of dyslipidaemia in order to mitigate any double effect of infectious *and* 'lifestyle' HD risk factors in the longer term. While the epidemiological evidence is clear, the precise mechanism by which HDLC decreases atherosclerotic CVD risk remains unclear[11]; indeed, efforts to develop pharmacological modalities to specifically increase HDLC levels to reduce cardiovascular risk, continues to be problematic[10] and we acknowledge that addressing the low HDLC observed in this cohort, in isolation, without commensurate improvements in HDLC functionality, will prove a difficult task. This does not, however, preclude use of other therapeutic interventions that address the greater, more complex risk presentation of cases that fall in the 'crossover' between communicable and non-communicable diseases. For example, the polypill, which includes lipid-lowering medications, has been proposed as a viable treatment option in secondary prevention, given its relative ease of use and efficacy in low-income settings[34]. More so, evidence that statins also exert immunomodulatory effects, along with suggestions they may prove useful in the treatment and prevention of infections[35], indicate they may have important, multi-faceted clinical implications in populations such as Soweto, especially given the substantial dyslipidaemic risk associated with highly-prevalent HIV infection and ART. Attempts to address prevention, management, cure and control of non-communicable and communicable forms of HD as entirely separate entities are likely to prove insufficient. This holds true on a per-patient basis as well as for any population-wide, public health approaches.

There are a number of limitations that require consideration. Clinical data (other than routine echocardiography and 12-lead ECG) were obtained according to presentation. This study was not specifically designed to comprehensively delineate between specific forms of HD (resulting in variable clinical data) although this is part of clinical investigation at Baragwanath Hospital; although it should be noted HIV status is not routinely determined. The arbitrary selection of disease states into the communicable versus non-communicable groups (e.g. primary valve disease) may be questioned; hence our further delineation of clearly identifiable cases of acute inflammation/infection at the point of admission. However, we would emphasise

that classification was prospectively applied, the groupings are consistent with our previous reports that describe in detail the rigorous clinical criteria employed in profiling the 'Heart of Soweto' cohort, and expected gradients in lipid levels were subsequently found. Systematic bias needs to be carefully considered before attributing broad patterns in lipid profiles, as those with suspected atherosclerotic disease were more likely to have had lipid levels measured, reflecting the low number of those presenting an acute infectious form of HD (for example, patients with pericarditis). Adiposity, a major confounder of both dyslipidaemia and HD, was recorded in 71% of the cohort. However, its inclusion in the regression analyses did not alter the significance of the associations. Central obesity measurements (e.g. waist-to-hip ratio) may have offered greater delineation of CVD risk but data were not available. CRP was measured in just under one third of cases and related data requires careful interpretation. Finally, owing to the cross-sectional design of this study we were not able to investigate the possible effect of the magnitude and timing of the contributing infection on lipid levels, beyond the data collected at admission. Given the transient, dynamic processes of lipid metabolism over the course of acute and chronic diseases, only longitudinal studies of lipid levels and subsequent outcomes can fully elucidate the clinical importance of our findings.

Conclusions

We have shown that despite largely favourable lipid profiles, there are clear differences according to underlying aetiology of HD in urban Africans however, overall low HDLC was the most prevalent metabolic abnormality observed in this cohort. Younger Africans with communicable HD have particularly low levels of HDLC that, if maintained in the longer term, may leave them at increased risk of atherosclerotic disease. This is physiologically plausible in chronic infection; however low HDL at hospital admission could also simply reflect similarly low levels of TC/LDL and may not be indicative of increased long-term CVD risk. That uncertainty can only be resolved by well-powered studies with adequate follow-up, to provide sufficient evidence to address current gaps in evidence and, ultimately, guide clinical practice. Nevertheless if proven, targeted prevention programs that identify and actively manage individuals with a history of communicable HD (particularly an active case) and with low levels of

HDLC may be indicated. The alternative is an increasing burden of non-communicable forms of HD in urban African communities that is supplemented (in origin and confluence) by historical cases of communicable disease that have adversely affected protective HDLC levels (particularly in women).

Acknowledgements

We thank all the doctors, nurses, and patients who participated in the registry; and Elisabeth Tshele, Bridget Phooko, Maureen Kubheka and Phutuma Mathusi who contributed to the meticulous collection and management of clinical data.

Competing interests

All authors declare: all authors had financial support from independent funding bodies, including University of the Witwatersrand and unconditional research grants from Adcock-Ingram, the Medtronic Foundation USA, Servier, Bayer-Schering and BHP Billiton, for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Funding

The 'Heart of Soweto Study' registry was supported by the University of the Witwatersrand and unconditional research grants from Adcock-Ingram, the Medtronic Foundation USA, Servier, Bayer-Schering and BHP Billiton. SS, MJC and JGL are supported by the National Health & Medical Research Council of Australia [Program Grants 320860 and 631947 and Postgraduate scholarship 586739]. JGL is supported by the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand. Baker IDI is supported by the Victorian Government's Operational Infrastructure Support Program. KS and SL are supported by the MRC South Africa and the University of Cape Town.

Author's contributions:

KS, MJC and SS participated in the original design of the study and supervised the collection of data. JGL prepared the first draft of the manuscript, with edits and revisions provided by all authors. FR and FT revised manuscript critically for important intellectual content. All authors

had full access to all the data and read and approved the final version of the manuscript. All authors had final responsibility for the decision to submit the manuscript for publication.

Data sharing statement

Study data will be available on request from the corresponding author.

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FIGURE 1 Sex specific lipid profiles according to heart disease aetiology

Figure legend:

Lipid values are shown as mean ± standard error. P values indicate between-sex comparisons per aetiology group (T-test), ** = P<0.01; * = P<0.05. NCD = non-communicable heart disease; CD = communicable heart disease; TC= total cholesterol; HDL= high-density lipoprotein cholesterol; LDL= low-density lipoprotein. Y-axis dotted lines show thresholds for high TC and LDL or low HDL (sex specific values).

FIGURE 2 Prevalence of low high-density lipoprotein cholesterol according to heart disease aetiology

Figure legend:

NCD = non-communicable heart disease; CD = communicable heart disease.

High total cholesterol (TC) > 4.5 mmol/L; Low high-density lipoprotein cholesterol (HDLC) (<1.0 mmol/L in males, <1.2 mmol/L in females). High low density lipoprotein cholesterol (LDLC) >2.5 mmol/L; High triglycerides (TGs) >1.7 mmol/L

FIGURE 3 Risk of low high-density lipoprotein cholesterol according to C-reactive protein risk group, relative to low-risk C-reactive protein group (n=367)

Figure legend:

Age-adjusted analysis. CRP = C-reactive protein. ** = P<0.01; * = P<0.05 relative to low CRP group. For confidence intervals, please refer to Results section.

Lower Levels of High-density Lipoprotein Cholesterol in Urban Africans Presenting with Communicable Versus Non-communicable Forms of Heart Disease: The 'Heart of Soweto' hospital registry study

Short title: Lyons – HDLC in communicable heart disease

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Key Words: High-density lipoprotein, lipids, infection, epidemiologic transition, Africa.

Word count: 3540 not including 2 tables, 3 figures and 35 references.

ABSTRACT

Objectives: To investigate if urban Africans displayed lower levels of atheroprotective high-density lipoprotein cholesterol (HDLC) when presenting with communicable versus non-communicable forms of heart disease (HD) as both acute infection and chronic inflammation reduce HDLC levels.

Design: Hospital registry of 5328 de novo cases of HD over a 3-year period.

Setting: Cardiology Unit, Baragwanath Hospital in Soweto, South Africa.

Participants: A total of 1199 patients of African descent (59% female; 57.0±13.4 years) had fasting blood lipid levels (Total cholesterol [TC], triglyceride, HDLC, and low-density lipoprotein [LDLC] cholesterol) documented on admission. Serum inflammatory marker C-reactive protein (CRP) was measured in a sub-set of 367 patients (31% of cases).

Main outcome measures: Lipid profiles were compared according to pre-specified classification of non-communicable (e.g. hypertensive HD) versus communicable (e.g. rheumatic HD) HD. Low HDLC was defined as <1.0 mmol/L for males and <1.2mmol/L for females, according to applicable South African Clinical Guidelines.

Results: Overall 694 (58%) of those presenting with HD had low HDLC levels; 344 of 678 (51%) and 350 of 521 (67%) for non-communicable and communicable, respectively (p<0.001). Comparatively, overall prevalence of high TC was 32% and high LDLC was 37%. On an adjusted basis, those with non-communicable HD were more likely to record a low HDLC relative to non-communicable presentations (OR 1.91, 95%CI 1.42, 2.57; p<0.001). There was a strong relationship between low HDLC and higher levels of CRP, but only in females.

Conclusions: Despite largely favourable lipid profiles, there are clear differences according to aetiology of underlying HD in urban Africans, with younger patients with communicable HD having particularly low levels of HDLC. Appropriate prospective evidence is needed to determine if persistent low levels of HDLC expose patients to increased, long-term risk of atherosclerotic forms of HD. The female-only inverse association between HDL-C and CRP warrants further investigation.

ARTICLE SUMMARY

Article focus:

- In sub-Saharan Africa, the incidence of non-communicable cardiovascular disease is increasing while, simultaneously, communicable forms of heart disease continue to cause considerable levels of morbidity and mortality.
- In this study, we have sought to explore one heart disease risk factor, dyslipidaemia, in a well-defined clinical registry in Soweto, South Africa.
- Lipid profiles from 1199 de novo presentations of heart disease were compared according to pre-specified classification of non-communicable heart disease (e.g. hypertensive heart disease) versus communicable forms of heart disease (e.g. pericarditis or chronic rheumatic heart disease). We hypothesised that those diagnosed with communicable heart disease would display an adverse lipid profile, with low levels of atheroprotective high-density lipoprotein cholesterol (HDLC). We also investigated the potential interaction of the inflammatory marker C-reactive protein (CRP) and low HDLC in a subset of these patients.

Key messages:

- We describe distinct patterns of dyslipidaemia according to underlying heart disease aetiology: significantly decreased levels of HDLC, total cholesterol and low-density lipoprotein cholesterol in those with communicable heart disease (representing 43% of cohort) compared to those with non-communicable heart disease (57% of cohort).
- In adjusted analyses, low HDLC was more pronounced in those with communicable heart disease. In those with high CRP levels, we present novel data showing a sex-disparate relationship between CRP and low HDLC, with a strong relationship between high CRP and low HDLC in females only.
- The high prevalence of low HDLC in a relatively young population of urban Africans may, if persistent in the longer-term, confer greater risk of atherosclerotic heart disease

Strengths and limitations of the study:

- We report a high prevalence of low HDLC in *de novo* presentations of both communicable heart disease and non-communicable heart disease, with a greater prevalence in those with communicable heart disease.
- The study cohort is clinically very well defined; however the lipid data were obtained according to clinical presentation, which may impose systematic bias to the results.
- This hospital registry study has provided preliminary data that would support prospective investigation of longer-term dyslipidaemia patterns and their impact on heart disease incidence, both in South Africa and in other low-and-middle-income countries where the epidemiologic transition is currently underway.

INTRODUCTION

Heart diseases with infectious aetiology have long been the principal forms of cardiovascular disease (CVD) in Sub-Saharan Africa. However, epidemiological transition has seen increased prevalence of non-communicable forms of heart disease in these populations[1]. This phenomenon is largely driven by complex, population-wide changes in demographic, social and economic status, with associated changes in lifestyle habits[2-4]. Indicative of the tension between 'old' and 'new' forms of heart disease, the incidence of communicable heart disease (HD) is sustained by the devastating epidemics of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), tuberculosis (TB), rheumatic heart disease (RHD) and parasitic infections with cardiac involvement[5-7], while in parallel, the prevalence of risk factors for non-communicable HD increases[8].

Low serum levels of high-density lipoprotein cholesterol (HDLC) are consistently and independently associated with increased risk of atherosclerotic forms of CVD[9 10]. However, it remains uncertain whether low HDLC is causal or just a cardiovascular risk marker[11]. If we are to extrapolate from studies in Western and Asian populations[12-14], isolated low HDLC is associated with increased risk for CVD in the long-term. There are several causes of low HDLC levels, including overweight, obesity, tobacco smoking, and insulin resistance/type 2 diabetes mellitus, indicative of the important role lifestyle factors have in mediating HDLC levels[9]. Additionally, low HDLC is a striking consequence of abnormal lipid metabolism in infection and inflammation[15]. Although it has been shown that those of African descent largely show a favourable lipid profile characterised by high HDLC levels [16], it is unlikely that they can remain athero-protective during an infected state[15]. Indeed, in this setting, it is probable that increasing prevalence of modifiable/ lifestyle risk factors contribute to a more advanced presentation in those with communicable HD[8]. We have previously reported that in the geographically compact townships that comprise Soweto in South Africa, 'old' and 'new' forms of HD are simultaneously present[8]. While this tension exists, we have a unique opportunity to explore lipid profiles in patients presenting with non-communicable versus communicable forms of HD.

STUDY HYPOTHESES

Having shown important ethnic differences in the lipid profiles of patients of African descent presenting with HD in the urban African enclave of Soweto[16], we hypothesised that independent of age and sex, urban Africans presenting with communicable HD will demonstrate patterns of dyslipidaemia associated with infection/inflammation, particularly sub-optimal levels of HDLC, versus non-communicable HD.

METHODS

Study Setting & Design

As described in detail previously[8 17] the 3,500 bed Chris Hani Baragwanath Hospital (case load of > 125,000 in-patients per annum) services the tertiary care needs of Soweto (population of 1.1 million) and surrounding communities. All suspected cardiac presentations are referred to the hospital's Cardiology Unit for advanced diagnostic testing and gold-standard treatments. A prospective clinical registry of all *de novo* presentations of the same was established in 2006 as part of the Heart of Soweto Study and represents sub-Saharan Africa's largest and most detailed study of advanced forms of HD to date[17].

Participants

The 'Heart of Soweto' cohort of *de novo* case presentations comprised 5328 patients. Of these, 2185 patients (40%) had a documented fasting lipid profile (serum total cholesterol (TC) level, triglyceride, HDLC and calculated low-density lipoprotein cholesterol (LDLC)[18] undertaken at Baragwanath Hospital on-site pathology). None of the patients were on lipid lowering agents at the time of presentation, as this medication can only be prescribed at the tertiary institution. However some of the patients had been placed on anti-hypertensive medication prior to their first assessment at the Cardiac Clinic at Baragwanath Hospital. Moreover, only a small number of patients (39 cases) had been prescribed anti-retroviral therapy (ART) on presentation. The study was approved by the University of the Witwatersrand Ethical Committee and conforms to the principles outlined in the Declaration of Helsinki. All patients provided informed consent.

Study Data

A complete list of study data captured by the registry, comprising basic socio-demographic (including self-reported ethnicity, years of education and determining if the patient was born in Soweto) and advanced clinical profiling, has been described previously[8 17] The registry captured all advanced clinical investigative procedures (e.g. coronary angiography, which was undertaken in all people diagnosed with coronary artery disease (CAD)). Echocardiography (performed on all patients) criteria used in the study has been described in detail previously[8 17].

Case Classifications

Adjudication and classification of communicable and non-communicable presentations of HD in this cohort have been previously described[8]. After exclusion of those with uncomplicated hypertension (i.e. without evidence of cardiac dysfunction, n=380) or other non-modifiable aetiologies (e.g. congenital disorders), 1199 patients of African descent (22% of the total 'Heart of Soweto' cohort) were included in this analysis. Contributory diagnoses for non-communicable HD were predominantly hypertensive heart failure (HT-HF) and coronary artery disease (without HIV). Communicable heart disease was predominantly classified as HIV-dilated cardiomyopathy (HIV-DCMO), HIV-pulmonary hypertension, TB pericardial disease, and pericarditis due to other infection.

Risk factor definition

Optimum lipid levels and treatment goals with established CVD were defined according to international guidelines[9] adopted by the Lipid and Atherosclerosis Society of South Africa and the South African Heart Association - high TC: >4.5 mmol/L, high TGs: >1.7 mmol/L, high LDLC: >2.5 mmol/L and low HDLC: <1.0 for males and <1.2 mmol/L for females[19]. Other risk factors were measured on a clinical basis, as previously described[17]. Anthropometric measurements were available for calculation of body mass index (BMI, kg/m^2) in 854 (71%) cases, the low reporting rate restricted to ambulatory patients. Obesity was defined as BMI ≥ 30 kg/m^2. Serum C-reactive protein (CRP) was measured in a sub-set of 367 patients (31% of all cases) if clinically indicated (e.g. suspected infection). Patients were stratified into clinically relevant CRP

categories[20], as defined by Dhingra and colleagues[21]. Patients with a CRP of 1 mg/L (n=19) were used as reference group and compared to medium (1.1-3.0 mg/L, n=26), high (3.1-10.0 mg/L, n=83) and very high (>10.0 mg/L, n=239) CRP categories.

Statistical analyses

Normally distributed continuous data are presented as the mean ± standard deviation and non-Gaussian distributed variables as the median (inter-quartile range). Categorical data are presented as sample number and percentages. For group comparisons, we initially used Chi Square (χ^2) analysis with calculation of odds ratios (OR) with 95% confidence intervals (CI) presented where appropriate for discrete variables, and independent T-tests for normally distributed continuous variables and Mann-Whitney U test for nonparametric continuous variables. Multiple logistic regression analyses (entry model) were used to derive age and sex adjusted ORs (and BMI in some analyses, as described) for the risk of presenting with clinically relevant variables (primarily dyslipidaemia profiles), according to CD HD relative to NCD diagnosis. Significance was accepted at the two-sided level of $p<0.05$.

RESULTS

Clinical and Demographic Profile

Table 1 shows the socio-demographic and clinical profile of this cohort according to cardiac aetiology. Those presenting with non-communicable HD (n=678, 56.5% of cohort) were older and had higher BMI and mean SBP and DBP than those with communicable HD (n=521, 43.5%; all comparisons p<0.001). Overall, 76 (6%) were confirmed HIV-positive: 15 (2%) and 61 (12%) patients were confirmed HIV-positive in non-communicable and communicable HD groups respectively (P<0.001). Apart from higher BMIs in women (30.6 ± 6.9 vs. 26.7 ± 5.5 kg/m^2 in males, p<0.001) there were no significant differences between sexes in respect to other clinical parameters. To this, the prevalence of obesity in women was 50% as compared to men (26%), P<0.001.

TABLE 1 Clinical and demographic profile according to heart disease aetiology

	ALL Cases n=1199	Non-communicable n=678 (57%)	Communicable n=521 (43%)	*P* value
Demographic Profile				
Mean age (years)	58.3 ±14.0	60.1 ± 13.1	55.9 ± 14.9	<0.001
Female	701 (59%)	403 (59%)	298 (57%)	0.44
<6 years formal education	582 (49%)	335 (49%)	247 (47%)	0.52
Soweto origin	562 (47%)	327 (48%)	235 (45%)	0.29
Clinical Presentation				
Total cholesterol (mmol/L)	4.0 ± 1.4	4.3 ± 1.3	3.7 ± 1.2	<0.001
HDLC (mmol/L)	1.1 ± 0.5	1.2 ± 0.5	1.0 ± 0.5	<0.001
Median triglycerides (mmol/L)*	1.1 (0.8, 1.5)	1.1 (0.8,1.6)	1.0 (0.7, 1.3)	<0.001
LDLC (mmol/L)	2.4 ± 1.0	2.5 ± 1.0	2.2 ± 0.9	<0.001
TC:HDLC ratio	4.3 ± 3.0	4.2 ± 3.1	4.4 ± 2.7	0.27
LDL:HDLC ratio	2.5 ± 1.1	2.5 ± 1.0	2.7 ± 1.1	0.36
TG:HDLC ratio*	1.1 (0.7, 1.7)	1.0 (0.7, 1.7)	1.1 (0.7, 1.8)	0.12
Median serum CRP (mg/L)*	19 (7.0, 45.0)	16.8 (6.6,41.5)	20.5 (7.8, 55.9)	0.25

Systolic BP (mmHg)	135 ± 29	143 ± 29	126 ± 26	<0.001
Diastolic BP (mmHg)	78 ± 16	80 ± 16	74 ± 16	<0.001
BMI (kg/m^2)	29.0 ± 6.7	30.3 ± 6.7	27.2 ± 6.2	<0.001
Prevalence of dyslipidaemia (n, %)				
High total cholesterol (> 5mmol/L)	378 (32%)	266 (39%)	112 (22%)	<0.001
Low HDLC (< 1 in males and < 1.2 mmol/L in females)	694 (58%)	344 (51%)	350 (67%)	<0.001
High LDLC (> 2.5 mmol/L)	446 (37%)	291 (43%)	155 (30%)	<0.001
High triglycerides (> 1.7 mmol/l)	215 (18%)	143 (21%)	72 (14%)	0.001
Prevalence of other risk factors (n, %)				
Obese (BMI >30 kg/m^2)	344 (40%)	237 (48%)	107 (30%)	<0.001
Type 2 diabetes	98 (8%)	71 (11%)	27 (5%)	<0.001
Past or current smoker	566 (47%)	321(47%)	245 (47%)	0.95
Family history of CVD	466 (39%)	286 (42%)	180 (35%)	0.01
Confirmed HIV-positive cases	76 (6%)	15 (2%)	61 (12%)	<0.001

Table legend:

LDLC = low-density lipoprotein cholesterol; HDLC = high-density lipoprotein cholesterol; TG = triglycerides; BMI = body mass index (available in 854 cases); CRP = C-reactive protein (available in 367 cases); CVD = cardiovascular disease; HIV = human immunodeficiency virus.

*Median (interquartile range) values presented, differences tested by Mann-Whitney U test

Aetiology of heart disease (primary diagnosis)

Overall, the most prevalent primary diagnoses were HT-HF (n=461, 38%), dilated cardiomyopathy (DCMO, n= 178, 15%) and CAD (n=157, 12%). In those classified as non-communicable HD, HT-HF was the main primary diagnosis (n=461, 68%), along with CAD (without concurrent HIV-infection; n=157, 23%). Dilated cardiomyopathy (n=178, 34%), right heart failure (n=92, 18%) and right heart disease (n=63, 12%) and other forms of primary valve

disease (n=71, 14%), were the most common diagnoses in those classified with communicable forms of HD.

Lipid Profiles

Those with communicable HD had significantly lower TC, LDLC, and HDLC compared with patients with non-communicable HD (**Table 1** and **Figure 1**, p<0.001 for all comparisons). Overall, women had significantly higher TC (4.2±1.3 mmol/L vs. 3.8±1.2 mmol/L, p<0.001); LDLC (2.4±1.0 mmol/L vs. 2.2±1.0 mmol/L, p<0.01), and HDLC compared to men (1.2±0.5 mmol/L vs. 1.0±0.5 mmol/L, p<0.001). This gender difference did not extend to triglycerides (1.1(0.4-1.8) mmol/L vs. 1.1(0.4-1.8), p=0.7) nor TC:HDLC ratio (4.2 ± 3.1 mmol/L vs. 4.3 ± 2.7 mmol/L, p=0.6). Lipid ratios were calculated and compared (**Table 1**). There was no significant differences between aetiology groups for either TC:HDL or TG:HDL groups. However LDL:HDL ratios were significantly higher in the communicable group.

Levels of TC (Figure 1A), HDLC (Figure 1B) and LDLC (Figure 1C) were significantly higher in females with non-communicable HD (**Figure 1**). However in those diagnosed with communicable HD, small, but significant, differences were observed only for TC and HDLC, not LDL (**Figure 1**). Overall, prevalence of dyslipidaemia varied from 18% of patients with high triglycerides to 58% with low HDLC (**Table 1** and **Figure 2**). Consistent with the decrease observed with the actual levels, prevalence of high TC and high LDLC was increased in those with non-communicable HD aetiologies while low HDLC levels prevalence was higher in those with communicable HD **(Table 1 and Figure 2)**. There were no patients with TG levels > 4.5 mmol/L (range 0.1-3.8 mmol/L) which makes use of the Friedewald equation suitable for this cohort[18].

Table 2 shows independent associations between relevant socio-economic, demographic and clinical variables and communicable HD aetiology, relative to those presenting with non-communicable HD. The effect of HD aetiology on low HDLC dyslipidaemia was strong and consistent: adjusting for age, sex and BMI of patients, those with forms of communicable HD were significantly more likely to record a low HDLC relative to those presenting with non-communicable HD (**Table 2,** p<0.001) and less likely to record high TC and LDLC (**Table 2**).

Patients with communicable HD were less likely to record high triglyceride levels (OR 0.65, 95%CI 0.51, 0.84, p<0.05) compared to those with non-communicable HD.

TABLE 2 Independent correlates of communicable heart disease, relative to non-communicable heart disease

	Communicable disease	
	Odds Ratio	**95% CI**
Female sex	0.91	0.72, 1.15
Age	0.98	0.97, 0.99**
Obesity	0.50	0.37, 0.68***
< 6 years formal education	1.11	0.88, 1.42
Soweto origin	0.98	0.77, 1.24
Body mass index adjusted analysis		
High TC	0.52	0.37, 0.71***
High LDLC	0.56	0.41, 0.76***
Low HDLC	1.91	1.42, 2.57***
High TG	0.65	0.51, 0.84*

Table legend:

Obesity BMI >30kg/m^2; High total cholesterol (TC) > 4.5 mmol/L; High low density lipoprotein (LDLC) >2.5 mmol/L; Low high density lipoprotein (HDLC) (<1.0 mmol/L in males, <1.2 mmol/L in females). OR = odds ratio; CI = confidence intervals. Age and sex-adjusted analysis: * p<0.05; **p<0.01; ***p<0.001.

CRP subset analysis

Overall, there was no significant difference in CRP levels between aetiology groups (**Table 1**). The proportion of confirmed HIV cases in this CRP subset analysis was 7% (n=27). Of those, 23 were in the very high-risk category. There was also no association between CRP-derived risk categories and high TC, LDLC or triglycerides (data not shown). However the risk of having low HDLC increased with increasing CRP levels. In age and sex-adjusted analyses, those with

medium risk (OR 2.73, 95% CI 0.68, 10.89, P=0.16), high risk (OR 4.98, 95% CI 1.46, 17.00, P=0.01) and very high risk (OR 6.37, 95% CI 1.97, 20.57, p<0.01) CRP levels were significantly more likely to record a low HDLC relative to those in the low risk CRP group. Also, when stratified by sex, a strong, positive association remained in females but was no longer apparent in males **(Figure 3)**. In females, the pattern was significant across all CRP risk categories: compared to low risk, those with medium risk (OR 12.1, 95% CI 1.21, 120, p=0.03), high risk (OR 14.4, 95% CI 1.64, 126, p=0.02) and very high risk (OR 23.5, 95% CI 2.81, 197, p=0.004) CRP levels were all more likely to record a low HDLC. Moreover, the association was not weakened by addition of BMI into the model (BMI and CRP measurements available in only 230 cases) in overall and female-only (n=133) models: those with medium risk (OR 20.5, 95% CI 1.72, 246, p=0.02), high risk (OR 10.6, 95% CI 1.14, 98.8, p=0.04) and very high risk (OR 21.0, 95% CI 2.38, 185, p<0.01) CRP levels were all more likely to record a low HDLC.

DISCUSSION

We report significant decreases in lipid levels (TC, HDLC and LDLC) and age and BMI according to non-communicable and communicable manifestations of *de novo* HD in urban Africans, patterns that were observed in both sexes. The high prevalence of low HDLC in more than half of all cases, but much higher in those with communicable HD, is most striking. Also, it appears that gender is an effect modifier in the relationship between CRP and low HDLC in this cohort, but, importantly, the relationship remains even after adjustment for the significant confounder of adiposity.

While traditionally uncommon[22], dyslipidaemia, in particular low HDLC, is becoming more prevalent in sub-Saharan Africa[23]. The low lipid levels present in the majority of cases with communicable HD reflects the dramatic changes to lipid metabolism observed in infection and is therefore, anticipated. We acknowledge that atherogenic LDLC is also low in this setting and that low HDLC may not be indicative of particularly increased disease risk, at least in the short-term. However we still deem this as highly clinically relevant given that even isolated low HDLC is associated with a higher risk of atherosclerotic forms of HD, a finding that has been seen in diverse populations[12-14]. Interestingly triglyceride levels were not significantly increased in those with communicable forms of HD, despite evidence that it can increase as part of the infectious/inflammatory metabolic milieu[15]. Additionally, we speculate that the higher lipid levels in women may be the result of much higher rates of obesity (50% compared with 26% in men) as the driver of elevated total cholesterol, which has been suggested by authors of a worldwide systematic analysis on high TC [24].

Our interest in this phenomenon predominantly relates to the longer-term effects of low HDLC, especially when observed together with the amplified vascular risk associated with chronic infection[15]. In Africa, where acute coronary syndromes are seen in a relatively young population[25], we predict the very high rates of myriad communicable disease[26 27] will result in more complex cases, with potentially poorer outcomes in the long-term, given the critical role of HDLC in both innate and adaptive immunity[15]. While many infectious diseases (bacterial and viral) have contributed to the underlying pathology of HD reported here[5], dyslipidemia

associated with HIV infection has been particularly well studied. HIV-related low HDLC is likely a consequence of both the viral infection and an adverse effect of some anti-retroviral treatment regimens[27-30], however only 39 patients of the 76 (51%) confirmed HIV-positive were on ART at time of presentation, representing 3% of entire subset sample, which possibly dilutes this effect.

Our CRP subset analysis found associations between low HDLC and the pro-inflammatory marker CRP in patients with newly diagnosed HD in a sex disparate manner, with a much stronger positive association in females. Median CRP levels were also very high across all categories of HD aetiology, and are much higher than previous reports in both early analyses of large cohorts[20] as well as South African studies[31], but reflect the clinical requirements at presentation. These high levels may also be the result of 'multi-morbidity' observed in the cohort, given the prevalence of infectious disease (such as HIV/AIDS) as well as other lifestyle factors that can also influence CRP levels[32]; all of which may have contributed to the high levels observed. Inflammatory stress may be having a more adverse effect on HDLC in women compared to men as a result of many causes. The prognostic value of stratifying CVD risk, even at very high CRP (>10 mg/L) levels, has been demonstrated in a very large female cohort[20], and there are reports of elevated CRP in female populations of African descent[33]. We also report females as having a significantly higher BMI; obesity itself can induce a low-grade inflammatory response, however the association between low HDLC and CRP in women remained even after adjusting for BMI. While we have assumed that the exaggerated drop in HDLC in women with acute forms of communicable HD is a consequence rather than a cause of infection, treatment of atherogenic dyslipidaemia and inflammatory markers in women are of particular clinical relevance in a setting where obesity and its antecedent behaviours are increasing.

These results underscore the need to consider multifactorial CVD risk burden that recognises that co-occurrence of infectious and non-communicable disease produces significant and complex health disparities. Certainly, the clinical strategies to protect the heart and vessels in acute infection differ from those required in chronic infection and it is unlikely that lipid

measurements will form a cornerstone of treatment in such cases. However, it is important to recognise the benefits of early detection and treatment of dyslipidaemia in order to mitigate any double effect of infectious *and* 'lifestyle' HD risk factors in the longer term. While the epidemiological evidence is clear, the precise mechanism by which HDLC decreases atherosclerotic CVD risk remains unclear[11]; indeed, efforts to develop pharmacological modalities to specifically increase HDLC levels to reduce cardiovascular risk, continues to be problematic[10] and we acknowledge that addressing the low HDLC observed in this cohort, in isolation, without commensurate improvements in HDLC functionality, will prove a difficult task. This does not, however, preclude use of other therapeutic interventions that address the greater, more complex risk presentation of cases that fall in the 'crossover' between communicable and non-communicable diseases. For example, the polypill, which includes lipid-lowering medications, has been proposed as a viable treatment option in secondary prevention, given its relative ease of use and efficacy in low-income settings[34]. More so, evidence that statins also exert immunomodulatory effects, along with suggestions they may prove useful in the treatment and prevention of infections[35], indicate they may have important, multi-faceted clinical implications in populations such as Soweto, especially given the substantial dyslipidaemic risk associated with highly-prevalent HIV infection and ART. Attempts to address prevention, management, cure and control of non-communicable and communicable forms of HD as entirely separate entities are likely to prove insufficient. This holds true on a per-patient basis as well as for any population-wide, public health approaches.

There are a number of limitations that require consideration. Clinical data (other than routine echocardiography and 12-lead ECG) were obtained according to presentation. This study was not specifically designed to comprehensively delineate between specific forms of HD (resulting in variable clinical data) although this is part of clinical investigation at Baragwanath Hospital; although it should be noted HIV status is not routinely determined. The arbitrary selection of disease states into the communicable versus non-communicable groups (e.g. primary valve disease) may be questioned; hence our further delineation of clearly identifiable cases of acute inflammation/infection at the point of admission. However, we would emphasise

that classification was prospectively applied, the groupings are consistent with our previous reports that describe in detail the rigorous clinical criteria employed in profiling the 'Heart of Soweto' cohort, and expected gradients in lipid levels were subsequently found. Systematic bias needs to be carefully considered before attributing broad patterns in lipid profiles, as those with suspected atherosclerotic disease were more likely to have had lipid levels measured, reflecting the low number of those presenting an acute infectious form of HD (for example, patients with pericarditis). Adiposity, a major confounder of both dyslipidaemia and HD, was recorded in 71% of the cohort. However, its inclusion in the regression analyses did not alter the significance of the associations. Central obesity measurements (e.g. waist-to-hip ratio) may have offered greater delineation of CVD risk but data were not available. CRP was measured in just under one third of cases and related data requires careful interpretation. Finally, owing to the cross-sectional design of this study we were not able to investigate the possible effect of the magnitude and timing of the contributing infection on lipid levels, beyond the data collected at admission. Given the transient, dynamic processes of lipid metabolism over the course of acute and chronic diseases, only longitudinal studies of lipid levels and subsequent outcomes can fully elucidate the clinical importance of our findings.

Conclusions

We have shown that despite largely favourable lipid profiles, there are clear differences according to underlying aetiology of HD in urban Africans however, overall low HDLC was the most prevalent metabolic abnormality observed in this cohort. Younger Africans with communicable HD have particularly low levels of HDLC that, if maintained in the longer term, may leave them at increased risk of atherosclerotic disease. This is physiologically plausible in chronic infection; however low HDL at hospital admission could also simply reflect similarly low levels of TC/LDL and may not be indicative of increased long-term CVD risk. That uncertainty can only be resolved by well-powered studies with adequate follow-up, to provide sufficient evidence to address current gaps in evidence and, ultimately, guide clinical practice. Nevertheless if proven, targeted prevention programs that identify and actively manage individuals with a history of communicable HD (particularly an active case) and with low levels of

HDLC may be indicated. The alternative is an increasing burden of non-communicable forms of HD in urban African communities that is supplemented (in origin and confluence) by historical cases of communicable disease that have adversely affected protective HDLC levels (particularly in women).

Acknowledgements

We thank all the doctors, nurses, and patients who participated in the registry; and Elisabeth Tshele, Bridget Phooko, Maureen Kubheka and Phutuma Mathusi who contributed to the meticulous collection and management of clinical data.

Competing interests

All authors declare: all authors had financial support from independent funding bodies, including University of the Witwatersrand and unconditional research grants from Adcock-Ingram, the Medtronic Foundation USA, Servier, Bayer-Schering and BHP Billiton, for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Funding

The 'Heart of Soweto Study' registry was supported by the University of the Witwatersrand and unconditional research grants from Adcock-Ingram, the Medtronic Foundation USA, Servier, Bayer-Schering and BHP Billiton. SS, MJC and JGL are supported by the National Health & Medical Research Council of Australia [Program Grants 320860 and 631947 and Postgraduate scholarship 586739]. JGL is supported by the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand. Baker IDI is supported by the Victorian Government's Operational Infrastructure Support Program. KS and SL are supported by the MRC South Africa and the University of Cape Town.

Author's contributions:

KS, MJC and SS participated in the original design of the study and supervised the collection of data. JGL prepared the first draft of the manuscript, with edits and revisions provided by all authors. FR and FT revised manuscript critically for important intellectual content. All authors

had full access to all the data and read and approved the final version of the manuscript. All authors had final responsibility for the decision to submit the manuscript for publication.

Data sharing statement

Study data will be available on request from the corresponding author.

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FIGURE 1 Sex specific lipid profiles according to heart disease aetiology

Figure legend:

Lipid values are shown as mean ± standard error. P values indicate between-sex comparisons per aetiology group (T-test), ** = P<0.01; * = P<0.05. NCD = non-communicable heart disease; CD = communicable heart disease; TC= total cholesterol; HDL= high-density lipoprotein cholesterol; LDL= low-density lipoprotein. Y-axis dotted lines show thresholds for high TC and LDL or low HDL (sex specific values).

FIGURE 2 Prevalence of low high-density lipoprotein cholesterol according to heart disease aetiology

Figure legend:

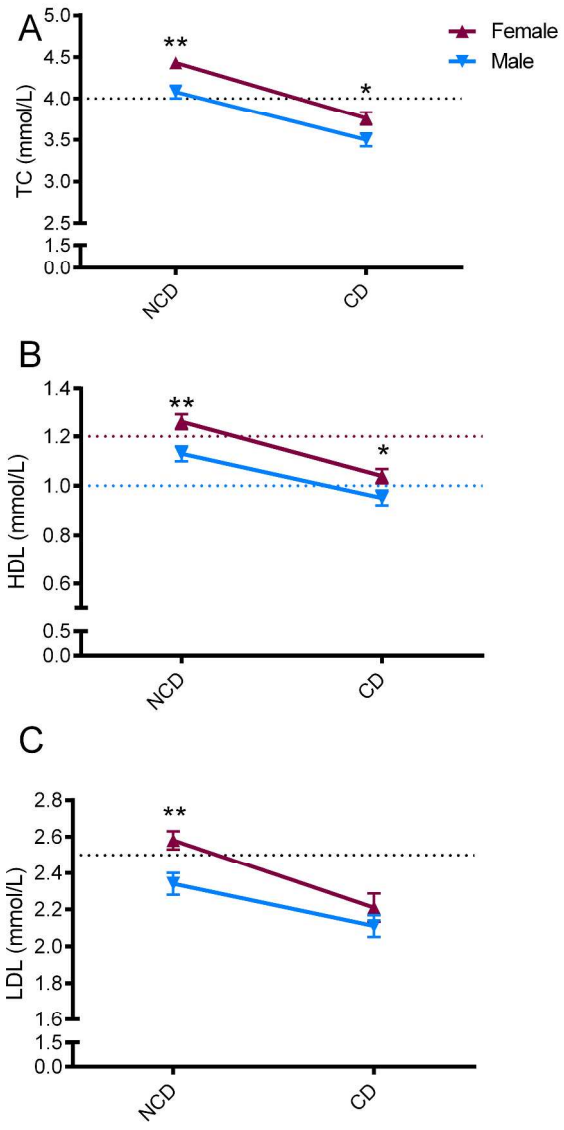
NCD = non-communicable heart disease; CD = communicable heart disease.

High total cholesterol (TC) > 4.5 mmol/L; Low high-density lipoprotein cholesterol (HDLC) (<1.0 mmol/L in males, <1.2 mmol/L in females). High low density lipoprotein cholesterol (LDLC) >2.5 mmol/L; High triglycerides (TGs) >1.7 mmol/L

FIGURE 3 Risk of low high-density lipoprotein cholesterol according to C-reactive protein risk group, relative to low-risk C-reactive protein group (n=367)

Figure legend:

Age-adjusted analysis. CRP = C-reactive protein. ** = P<0.01; * = P<0.05 relative to low CRP group. For confidence intervals, please refer to Results section.



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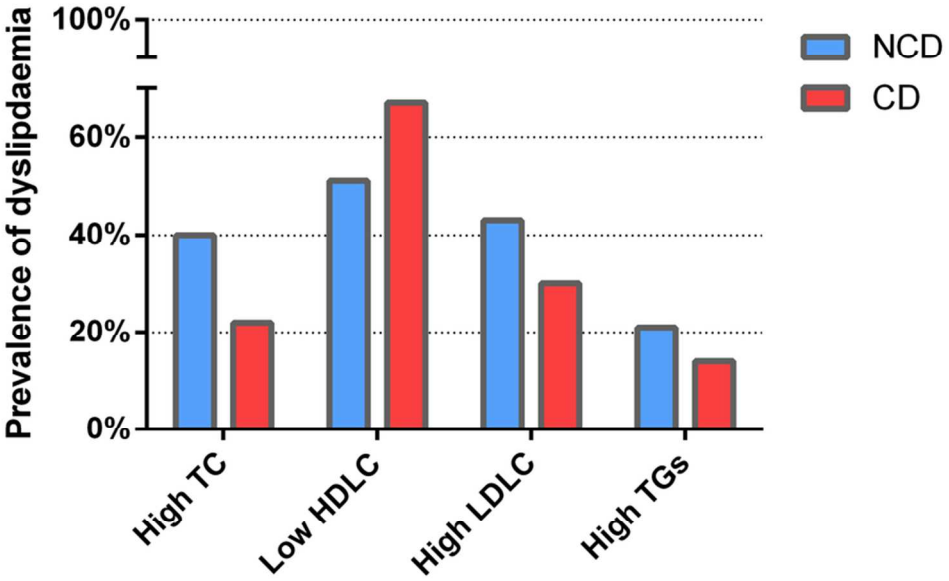

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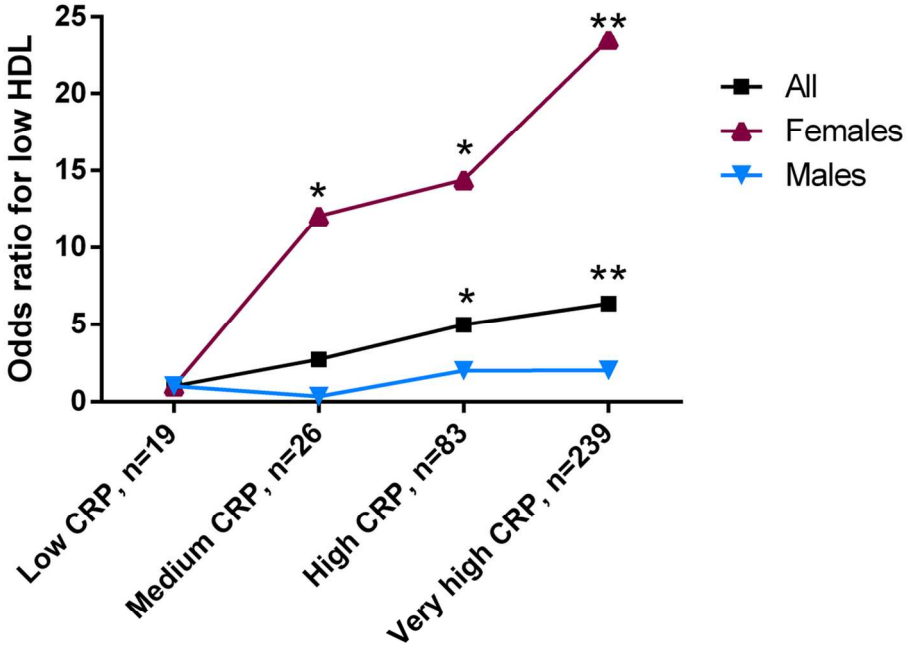

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

Completed for the article: ***Low levels of high-density lipoprotein cholesterol is the most prevalent metabolic abnormality in urban Africans with newly diagnosed heart disease: The 'Heart of Soweto' hospital registry study***
Date: 12 February 2014

	Item No	Recommendation	Complete
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	

		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for exposed and unexposed groups.

BMJ Open

Lower Levels of High-density Lipoprotein Cholesterol in Urban Africans Presenting with Communicable Versus Non-communicable Forms of Heart Disease: The 'Heart of Soweto' hospital registry study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005069.R2
Article Type:	Research
Date Submitted by the Author:	22-Jun-2014
Complete List of Authors:	Lyons, Jasmine; Baker IDI Heart and Diabetes Institute, Preventative Health Sliwa, Karen; University of the Witwatersrand, Soweto Cardiovascular Research Unit Carrington, Melinda; Baker IDI Heart and Diabetes Institute, Preventative Health; University of the Witwatersrand, Soweto Cardiovascular Research Unit Raal, Frederick; University of the Witwatersrand, Carbohydrate and Lipid Metabolism Research Unit Pretorius, Sandra; University of the Witwatersrand, Soweto Cardiovascular Research Unit Thienemann, Freidrich; University of Cape Town, Institute of Infectious Diseases and Molecular Medicine; University of Cape Town, Hatter Institute for Cardiovascular Research in Africa, Cape Heart Group amd IIDMM STEWART, SIMON; Baker IDI Heart and Diabetes Institute, Preventative Health; University of the Witwatersrand, Soweto Cardiovascular Research Unit
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Public health, Epidemiology
Keywords:	Cardiac Epidemiology < CARDIOLOGY, Epidemiology < INFECTIOUS DISEASES, PREVENTIVE MEDICINE

Lower Levels of High-density Lipoprotein Cholesterol in Urban Africans Presenting with Communicable Versus Non-communicable Forms of Heart Disease: The 'Heart of Soweto' hospital registry study

Short title: Lyons – HDLC in communicable heart disease

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Key Words: High-density lipoprotein, lipids, infection, epidemiologic transition, Africa.

Word count: 3540 not including 2 tables, 3 figures and 36 references.

ABSTRACT

Objectives: To investigate if urban Africans displayed lower levels of atheroprotective high-density lipoprotein cholesterol (HDLC) when presenting with communicable versus non-communicable forms of heart disease (HD) as both acute infection and chronic inflammation reduce HDLC levels.

Design: Hospital registry of 5328 de novo cases of HD over a 3-year period.

Setting: Cardiology Unit, Baragwanath Hospital in Soweto, South Africa.

Participants: A total of 1199 patients of African descent (59% women; 57.0±13.4 years) had fasting blood lipid levels (Total cholesterol [TC], triglyceride, HDLC, and low-density lipoprotein [LDLC] cholesterol) documented on admission. Serum inflammatory marker C-reactive protein (CRP) was measured in a sub-set of 367 patients (31% of cases).

Main outcome measures: Lipid profiles were compared according to pre-specified classification of non-communicable (e.g. hypertensive HD) versus communicable (e.g. rheumatic HD) HD. Low HDLC was defined as <1.0 mmol/L for men and <1.2mmol/L for women, according to applicable South African Clinical Guidelines.

Results: Overall 694 (58%) of those presenting with HD had low HDLC levels; 344 of 678 (51%) and 350 of 521 (67%) for non-communicable and communicable, respectively (p<0.001). Comparatively, overall prevalence of high TC was 32% and high LDLC was 37%. On an adjusted basis, those with non-communicable HD were more likely to record a low HDLC relative to non-communicable presentations (OR 1.91, 95%CI 1.42, 2.57; p<0.001). There was a strong relationship between low HDLC and higher levels of CRP, but only in women.

Conclusions: Despite largely favourable lipid profiles, there are clear differences according to aetiology of underlying HD in urban Africans, with younger patients with communicable HD having particularly low levels of HDLC. Appropriate prospective evidence is needed to determine if persistent low levels of HDLC expose patients to increased, long-term risk of atherosclerotic forms of HD. The women-only inverse association between HDL-C and CRP warrants further investigation.

ARTICLE SUMMARY

Article focus:

- In sub-Saharan Africa, the incidence of non-communicable cardiovascular disease is increasing while, simultaneously, communicable forms of heart disease continue to cause considerable levels of morbidity and mortality.
- In this study, we have sought to explore one heart disease risk factor, dyslipidaemia, in a well-defined clinical registry in Soweto, South Africa.
- Lipid profiles from 1199 de novo presentations of heart disease were compared according to pre-specified classification of non-communicable heart disease (e.g. hypertensive heart disease) versus communicable forms of heart disease (e.g. pericarditis or chronic rheumatic heart disease). We hypothesised that those diagnosed with communicable heart disease would display an adverse lipid profile, with low levels of atheroprotective high-density lipoprotein cholesterol (HDLC). We also investigated the potential interaction of the inflammatory marker C-reactive protein (CRP) and low HDLC in a subset of these patients.

Key messages:

- We describe distinct patterns of dyslipidaemia according to underlying heart disease aetiology: significantly decreased levels of HDLC, total cholesterol and low-density lipoprotein cholesterol in those with communicable heart disease (representing 43% of cohort) compared to those with non-communicable heart disease (57% of cohort).
- In adjusted analyses, low HDLC was more pronounced in those with communicable heart disease. In those with high CRP levels, we present novel data showing a sex-disparate relationship between CRP and low HDLC, with a strong relationship between high CRP and low HDLC in women only.
- The high prevalence of low HDLC in a relatively young population of urban Africans may, if persistent in the longer-term, confer greater risk of atherosclerotic heart disease

Strengths and limitations of the study:

- We report a high prevalence of low HDLC in *de novo* presentations of both communicable heart disease and non-communicable heart disease, with a greater prevalence in those with communicable heart disease.
- The study cohort is clinically very well defined; however the lipid data were obtained according to clinical presentation, which may impose systematic bias to the results.
- This hospital registry study has provided preliminary data that would support prospective investigation of longer-term dyslipidaemia patterns and their impact on heart disease incidence, both in South Africa and in other low-and-middle-income countries where the epidemiologic transition is currently underway.

INTRODUCTION

Heart diseases with infectious aetiology have long been the principal forms of cardiovascular disease (CVD) in Sub-Saharan Africa. However, epidemiological transition has seen increased prevalence of non-communicable forms of heart disease in these populations[1]. This phenomenon is largely driven by complex, population-wide changes in demographic, social and economic status, with associated changes in lifestyle habits[2-4]. Indicative of the tension between 'old' and 'new' forms of heart disease, the incidence of communicable heart disease (HD) is sustained by the devastating epidemics of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), tuberculosis (TB), rheumatic heart disease (RHD) and parasitic infections with cardiac involvement[5-7], while in parallel, the prevalence of risk factors for non-communicable HD increases[8].

Low serum levels of high-density lipoprotein cholesterol (HDLC) are consistently and independently associated with increased risk of atherosclerotic forms of CVD[9 10]. However, it remains uncertain whether low HDLC is causal or just a cardiovascular risk marker[11]. If we are to extrapolate from studies in Western and Asian populations[12-14], isolated low HDLC is associated with increased risk for CVD in the long-term. There are several causes of low HDLC levels, including overweight, obesity, tobacco smoking, and insulin resistance/type 2 diabetes mellitus, indicative of the important role lifestyle factors have in mediating HDLC levels[9]. Additionally, low HDLC is a striking consequence of abnormal lipid metabolism in infection and inflammation[15]. Although it has been shown that those of African descent largely show a favourable lipid profile characterised by high HDLC levels [16], it is unlikely that they can remain athero-protective during an infected state[15]. Indeed, in this setting, it is probable that increasing prevalence of modifiable/ lifestyle risk factors contribute to a more advanced presentation in those with communicable HD[8]. We have previously reported that in the geographically compact townships that comprise Soweto in South Africa, 'old' and 'new' forms of HD are simultaneously present[8]. While this tension exists, we have a unique opportunity to explore lipid profiles in patients presenting with non-communicable versus communicable forms of HD.

STUDY HYPOTHESES

Having shown important ethnic differences in the lipid profiles of patients of African descent presenting with HD in the urban African enclave of Soweto[16], we hypothesised that independent of age and sex, urban Africans presenting with communicable HD will demonstrate patterns of dyslipidaemia associated with infection/inflammation, particularly sub-optimal levels of HDLC, versus non-communicable HD.

METHODS

Study Setting & Design

As described in detail previously[8 17] the 3,500 bed Chris Hani Baragwanath Hospital (case load of > 125,000 in-patients per annum) services the tertiary care needs of Soweto (population of 1.1 million) and surrounding communities. All suspected cardiac presentations are referred to the hospital's Cardiology Unit for advanced diagnostic testing and gold-standard treatments. A prospective clinical registry of all *de novo* presentations of the same was established in 2006 as part of the Heart of Soweto Study and represents sub-Saharan Africa's largest and most detailed study of advanced forms of HD to date[17].

Participants

The 'Heart of Soweto' cohort of *de novo* case presentations comprised 5328 patients. Of these, 2185 patients (40%) had a documented fasting lipid profile (serum total cholesterol (TC) level, triglyceride, HDLC and calculated low-density lipoprotein cholesterol (LDLC)[18] undertaken at Baragwanath Hospital on-site pathology). None of the patients were on lipid lowering agents at the time of presentation, as this medication can only be prescribed at the tertiary institution. However some of the patients had been placed on anti-hypertensive medication prior to their first assessment at the Cardiac Clinic at Baragwanath Hospital. Moreover, only a small number of patients (39 cases) had been prescribed anti-retroviral therapy (ART) on presentation. The study was approved by the University of the Witwatersrand Ethical Committee and conforms to the principles outlined in the Declaration of Helsinki. All patients provided informed consent.

Study Data

A complete list of study data captured by the registry, comprising basic socio-demographic (including self-reported ethnicity, years of education and determining if the patient was born in Soweto) and advanced clinical profiling, has been described previously[8 17] The registry captured all advanced clinical investigative procedures (e.g. coronary angiography, which was undertaken in all people diagnosed with coronary artery disease (CAD)). Echocardiography (performed on all patients) criteria used in the study has been described in detail previously[8 17].

Case Classifications

Adjudication and classification of communicable and non-communicable presentations of HD in this cohort have been previously described[8]. After exclusion of those with uncomplicated hypertension (i.e. without evidence of cardiac dysfunction, n=380) or other non-modifiable aetiologies (e.g. congenital disorders), 1199 patients of African descent (22% of the total 'Heart of Soweto' cohort) were included in this analysis. Contributory diagnoses for non-communicable HD were predominantly hypertensive heart failure (HT-HF) and coronary artery disease (without HIV). Communicable heart disease was predominantly classified as HIV-dilated cardiomyopathy (HIV-DCMO), HIV-pulmonary hypertension, TB pericardial disease, and pericarditis due to other infection.

Risk factor definition

Optimum lipid levels and treatment goals with established CVD were defined according to international guidelines[9] adopted by the Lipid and Atherosclerosis Society of South Africa and the South African Heart Association - high TC: >4.5 mmol/L, high TGs: >1.7 mmol/L, high LDLC: >2.5 mmol/L and low HDLC: <1.0 for men and <1.2 mmol/L for women[19]. Other risk factors were measured on a clinical basis, as previously described[17]. Anthropometric measurements were available for calculation of body mass index (BMI, kg/m^2) in 854 (71%) cases, the low reporting rate restricted to ambulatory patients. Obesity was defined as BMI ≥ 30 kg/m^2. Serum C-reactive protein (CRP) was measured in a sub-set of 367 patients (31% of all cases) if clinically indicated (e.g. suspected infection). Patients were stratified into clinically relevant CRP

categories[20], as defined by Dhingra and colleagues[21]. Patients with a CRP of 1 mg/L (n=19) were used as reference group and compared to medium (1.1-3.0 mg/L, n=26), high (3.1-10.0 mg/L, n=83) and very high (>10.0 mg/L, n=239) CRP categories.

Statistical analyses

Normally distributed continuous data are presented as the mean ± standard deviation and non-Gaussian distributed variables as the median (inter-quartile range). Categorical data are presented as sample number and percentages. For group comparisons, we initially used Chi Square (χ^2) analysis with calculation of odds ratios (OR) with 95% confidence intervals (CI) presented where appropriate for discrete variables, and independent T-tests for normally distributed continuous variables and Mann-Whitney U test for nonparametric continuous variables. Multiple logistic regression analyses (entry model) were used to derive age and sex adjusted ORs (and BMI in some analyses, as described) for the risk of presenting with clinically relevant variables (primarily dyslipidaemia profiles), according to CD HD relative to NCD diagnosis. Significance was accepted at the two-sided level of $p<0.05$.

RESULTS

Clinical and Demographic Profile

Table 1 shows the socio-demographic and clinical profile of this cohort according to cardiac aetiology. Those presenting with non-communicable HD (n=678, 56.5% of cohort) were older and had higher BMI and mean SBP and DBP than those with communicable HD (n=521, 43.5%; all comparisons p<0.001). Overall, 76 (6%) were confirmed HIV-positive: 15 (2%) and 61 (12%) patients were confirmed HIV-positive in non-communicable and communicable HD groups respectively (P<0.001). Apart from higher BMIs in women (30.6 ± 6.9 vs. 26.7 ± 5.5 kg/m^2 in men, p<0.001) there were no significant differences between sexes in respect to other clinical parameters. To this, the prevalence of obesity in women was 50% as compared to men (26%), P<0.001.

TABLE 1 Clinical and demographic profile according to heart disease aetiology

	ALL Cases	Non-communicable	Communicable	*P* value
	n=1199	n=678 (57%)	n=521 (43%)	
Demographic Profile				
Mean age (years)	58.3 ±14.0	60.1 ± 13.1	55.9 ± 14.9	<0.001
Women	701 (59%)	403 (59%)	298 (57%)	0.44
<6 years formal education	582 (49%)	335 (49%)	247 (47%)	0.52
Soweto origin	562 (47%)	327 (48%)	235 (45%)	0.29
Clinical Presentation				
Total cholesterol (mmol/L)	4.0 ± 1.4	4.3 ± 1.3	3.7 ± 1.2	<0.001
HDLC (mmol/L)	1.1 ± 0.5	1.2 ± 0.5	1.0 ± 0.5	<0.001
Median triglycerides (mmol/L)*	1.1 (0.8, 1.5)	1.1 (0.8,1.6)	1.0 (0.7, 1.3)	<0.001
LDLC (mmol/L)	2.4 ± 1.0	2.5 ± 1.0	2.2 ± 0.9	<0.001
TC:HDLC ratio	4.3 ± 3.0	4.2 ± 3.1	4.4 ± 2.7	0.27
LDL:HDLC ratio	2.5 ± 1.1	2.5 ± 1.0	2.7 ± 1.1	0.36
TG:HDLC ratio*	1.1 (0.7, 1.7)	1.0 (0.7, 1.7)	1.1 (0.7, 1.8)	0.12
Median serum CRP (mg/L)*	19 (7.0, 45.0)	16.8 (6.6,41.5)	20.5 (7.8, 55.9)	0.25

Systolic BP (mmHg)	135 ± 29	143 ± 29	126 ± 26	<0.001
Diastolic BP (mmHg)	78 ± 16	80 ± 16	74 ± 16	<0.001
BMI (kg/m^2)	29.0 ± 6.7	30.3 ± 6.7	27.2 ± 6.2	<0.001
Prevalence of dyslipidaemia (n, %)				
High total cholesterol (> 5mmol/L)	378 (32%)	266 (39%)	112 (22%)	<0.001
Low HDLC (< 1 in men and < 1.2 mmol/L in women)	694 (58%)	344 (51%)	350 (67%)	<0.001
High LDLC (> 2.5 mmol/L)	446 (37%)	291 (43%)	155 (30%)	<0.001
High triglycerides (> 1.7 mmol/l)	215 (18%)	143 (21%)	72 (14%)	0.001
Prevalence of other risk factors (n, %)				
Obese (BMI >30 kg/m^2)	344 (40%)	237 (48%)	107 (30%)	<0.001
Type 2 diabetes	98 (8%)	71 (11%)	27 (5%)	<0.001
Past or current smoker	566 (47%)	321(47%)	245 (47%)	0.95
Family history of CVD	466 (39%)	286 (42%)	180 (35%)	0.01
Confirmed HIV-positive cases	76 (6%)	15 (2%)	61 (12%)	<0.001

Table legend:

LDLC = low-density lipoprotein cholesterol; HDLC = high-density lipoprotein cholesterol; TG = triglycerides; BMI = body mass index (available in 854 cases); CRP = C-reactive protein (available in 367 cases); CVD = cardiovascular disease; HIV = human immunodeficiency virus. *Median (interquartile range) values presented, differences tested by Mann-Whitney U test

Aetiology of heart disease (primary diagnosis)

Overall, the most prevalent primary diagnoses were HT-HF (n=461, 38%), dilated cardiomyopathy (DCMO, n= 178, 15%) and CAD (n=157, 12%). In those classified as non-communicable HD, HT-HF was the main primary diagnosis (n=461, 68%), along with CAD (without concurrent HIV-infection; n=157, 23%). Dilated cardiomyopathy (n=178, 34%), right heart failure (n=92, 18%) and right heart disease (n=63, 12%) and other forms of primary valve

disease (n=71, 14%), were the most common diagnoses in those classified with communicable forms of HD.

Lipid Profiles

Those with communicable HD had significantly lower TC, LDLC, and HDLC compared with patients with non-communicable HD (**Table 1** and **Figure 1**, p<0.001 for all comparisons). Overall, women had significantly higher TC (4.2±1.3 mmol/L vs. 3.8±1.2 mmol/L, p<0.001); LDLC (2.4±1.0 mmol/L vs. 2.2±1.0 mmol/L, p<0.01), and HDLC compared to men (1.2±0.5 mmol/L vs. 1.0±0.5 mmol/L, p<0.001). This gender difference did not extend to triglycerides (1.1(0.4-1.8) mmol/L vs. 1.1(0.4-1.8), p=0.7) nor TC:HDLC ratio (4.2 ± 3.1 mmol/L vs. 4.3 ± 2.7 mmol/L, p=0.6). Lipid ratios were calculated and compared (**Table 1**). There was no significant differences between aetiology groups for either TC:HDL or TG:HDL groups. However LDL:HDL ratios were significantly higher in the communicable group.

Levels of TC (Figure 1A), HDLC (Figure 1B) and LDLC (Figure 1C) were significantly higher in women with non-communicable HD (**Figure 1**). However in those diagnosed with communicable HD, small, but significant, differences were observed only for TC and HDLC, not LDL (**Figure 1**). Overall, prevalence of dyslipidaemia varied from 18% of patients with high triglycerides to 58% with low HDLC (**Table 1** and **Figure 2**). Consistent with the decrease observed with the actual levels, prevalence of high TC and high LDLC was increased in those with non-communicable HD aetiologies while low HDLC levels prevalence was higher in those with communicable HD **(Table 1 and Figure 2)**. There were no patients with TG levels > 4.5 mmol/L (range 0.1-3.8 mmol/L) which makes use of the Friedewald equation suitable for this cohort[18].

Table 2 shows independent associations between relevant socio-economic, demographic and clinical variables and communicable HD aetiology, relative to those presenting with non-communicable HD. The effect of HD aetiology on low HDLC dyslipidaemia was strong and consistent: adjusting for age, sex and BMI of patients, those with forms of communicable HD were significantly more likely to record a low HDLC relative to those presenting with non-communicable HD (**Table 2,** p<0.001) and less likely to record high TC and LDLC (**Table 2**).

Patients with communicable HD were less likely to record high triglyceride levels (OR 0.65, 95%CI 0.51, 0.84, p<0.05) compared to those with non-communicable HD.

TABLE 2 Independent correlates of communicable heart disease, relative to non-communicable heart disease

	Communicable disease	
	Odds Ratio	**95% CI**
Women	0.91	0.72, 1.15
Age	0.98	0.97, 0.99**
Obesity	0.50	0.37, 0.68***
< 6 years formal education	1.11	0.88, 1.42
Soweto origin	0.98	0.77, 1.24
Body mass index adjusted analysis		
High TC	0.52	0.37, 0.71***
High LDLC	0.56	0.41, 0.76***
Low HDLC	1.91	1.42, 2.57***
High TG	0.65	0.51, 0.84*

Table legend:

Obesity BMI >30kg/m^2; High total cholesterol (TC) > 4.5 mmol/L; High low density lipoprotein (LDLC) >2.5 mmol/L; Low high density lipoprotein (HDLC) (<1.0 mmol/L in men, <1.2 mmol/L in women). OR = odds ratio; CI = confidence intervals. Age and sex-adjusted analysis: * p<0.05; **p<0.01; ***p<0.001.

CRP subset analysis

Overall, there was no significant difference in CRP levels between aetiology groups (**Table 1**). The proportion of confirmed HIV cases in this CRP subset analysis was 7% (n=27). Of those, 23 were in the very high-risk category. There was also no association between CRP-derived risk categories and high TC, LDLC or triglycerides (data not shown). However the risk of having low HDLC increased with increasing CRP levels. In age and sex-adjusted analyses, those with

medium risk (OR 2.73, 95% CI 0.68, 10.89, P=0.16), high risk (OR 4.98, 95% CI 1.46, 17.00, P=0.01) and very high risk (OR 6.37, 95% CI 1.97, 20.57, p<0.01) CRP levels were significantly more likely to record a low HDLC relative to those in the low risk CRP group. Also, when stratified by sex, a strong, positive association remained in women but was no longer apparent in men **(Figure 3)**. In women, the pattern was significant across all CRP risk categories: compared to low risk, those with medium risk (OR 12.1, 95% CI 1.21, 120, p=0.03), high risk (OR 14.4, 95% CI 1.64, 126, p=0.02) and very high risk (OR 23.5, 95% CI 2.81, 197, p=0.004) CRP levels were all more likely to record a low HDLC. Moreover, the association was not weakened by addition of BMI into the model (BMI and CRP measurements available in only 230 cases) in overall and women-only (n=133) models: those with medium risk (OR 20.5, 95% CI 1.72, 246, p=0.02), high risk (OR 10.6, 95% CI 1.14, 98.8, p=0.04) and very high risk (OR 21.0, 95% CI 2.38, 185, p<0.01) CRP levels were all more likely to record a low HDLC.

DISCUSSION

We report significant decreases in lipid levels (TC, HDLC and LDLC) and age and BMI according to non-communicable and communicable manifestations of *de novo* HD in urban Africans, patterns that were observed in both sexes. The high prevalence of low HDLC in more than half of all cases, but much higher in those with communicable HD, is most striking. Also, it appears that gender is an effect modifier in the relationship between CRP and low HDLC in this cohort, but, importantly, the relationship remains even after adjustment for the significant confounder of adiposity.

While traditionally uncommon[22], dyslipidaemia, in particular low HDLC, is becoming more prevalent in sub-Saharan Africa[23 24]. The low lipid levels present in the majority of cases with communicable HD reflects the dramatic changes to lipid metabolism observed in infection and is therefore, anticipated. We acknowledge that atherogenic LDLC is also low in this setting and that low HDLC may not be indicative of particularly increased disease risk, at least in the short-term. However we still deem this as highly clinically relevant given that even isolated low HDLC is associated with a higher risk of atherosclerotic forms of HD, a finding that has been seen in diverse populations[12-14]. Interestingly triglyceride levels were not significantly increased in those with communicable forms of HD, despite evidence that it can increase as part of the infectious/inflammatory metabolic milieu[15]. Additionally, we speculate that the higher lipid levels in women may be the result of much higher rates of obesity (50% compared with 26% in men) as the driver of elevated total cholesterol, which has been suggested by authors of a worldwide systematic analysis on high TC [25].

Our interest in this phenomenon predominantly relates to the longer-term effects of low HDLC, especially when observed together with the amplified vascular risk associated with chronic infection[15]. In Africa, where acute coronary syndromes are seen in a relatively young population[26], we predict the very high rates of myriad communicable disease[27 28] will result in more complex cases, with potentially poorer outcomes in the long-term, given the critical role of HDLC in both innate and adaptive immunity[15]. While many infectious diseases (bacterial and viral) have contributed to the underlying pathology of HD reported here[5], dyslipidemia

associated with HIV infection has been particularly well studied. HIV-related low HDLC is likely a consequence of both the viral infection and an adverse effect of some anti-retroviral treatment regimens[28-31], however only 39 patients of the 76 (51%) confirmed HIV-positive were on ART at time of presentation, representing 3% of entire subset sample, which possibly dilutes this effect.

Our CRP subset analysis found associations between low HDLC and the pro-inflammatory marker CRP in patients with newly diagnosed HD in a sex disparate manner, with a much stronger positive association in women. Median CRP levels were also very high across all categories of HD aetiology, and are much higher than previous reports in both early analyses of large cohorts[20] as well as South African studies[32], but reflect the clinical requirements at presentation. These high levels may also be the result of 'multi-morbidity' observed in the cohort, given the prevalence of infectious disease (such as HIV/AIDS) as well as other lifestyle factors that can also influence CRP levels[33]; all of which may have contributed to the high levels observed. Inflammatory stress may be having a more adverse effect on HDLC in women compared to men as a result of many causes. The prognostic value of stratifying CVD risk, even at very high CRP (>10 mg/L) levels, has been demonstrated in a very large cohort of women[20], and there are reports of elevated CRP in women of African descent[34]. We also report women as having a significantly higher BMI; obesity itself can induce a low-grade inflammatory response, however the association between low HDLC and CRP in women remained even after adjusting for BMI. While we have assumed that the exaggerated drop in HDLC in women with acute forms of communicable HD is a consequence rather than a cause of infection, treatment of atherogenic dyslipidaemia and inflammatory markers in women are of particular clinical relevance in a setting where obesity and its antecedent behaviours are increasing.

These results underscore the need to consider multifactorial CVD risk burden that recognises that co-occurrence of infectious and non-communicable disease produces significant and complex health disparities. Certainly, the clinical strategies to protect the heart and vessels in acute infection differ from those required in chronic infection and it is unlikely that lipid

measurements will form a cornerstone of treatment in such cases. However, it is important to recognise the benefits of early detection and treatment of dyslipidaemia in order to mitigate any double effect of infectious *and* 'lifestyle' HD risk factors in the longer term. While the epidemiological evidence is clear, the precise mechanism by which HDLC decreases atherosclerotic CVD risk remains unclear[11]; indeed, efforts to develop pharmacological modalities to specifically increase HDLC levels to reduce cardiovascular risk, continues to be problematic[10] and we acknowledge that addressing the low HDLC observed in this cohort, in isolation, without commensurate improvements in HDLC functionality, will prove a difficult task. This does not, however, preclude use of other therapeutic interventions that address the greater, more complex risk presentation of cases that fall in the 'crossover' between communicable and non-communicable diseases. For example, the polypill, which includes lipid-lowering medications, has been proposed as a viable treatment option in secondary prevention, given its relative ease of use and efficacy in low-income settings[35]. More so, evidence that statins also exert immunomodulatory effects, along with suggestions they may prove useful in the treatment and prevention of infections[36], indicate they may have important, multi-faceted clinical implications in populations such as Soweto, especially given the substantial dyslipidaemic risk associated with highly-prevalent HIV infection and ART. Attempts to address prevention, management, cure and control of non-communicable and communicable forms of HD as entirely separate entities are likely to prove insufficient. This holds true on a per-patient basis as well as for any population-wide, public health approaches.

There are a number of limitations that require consideration. Clinical data (other than routine echocardiography and 12-lead ECG) were obtained according to presentation. This study was not specifically designed to comprehensively delineate between specific forms of HD (resulting in variable clinical data) although this is part of clinical investigation at Baragwanath Hospital; although it should be noted HIV status is not routinely determined. The arbitrary selection of disease states into the communicable versus non-communicable groups (e.g. primary valve disease) may be questioned; hence our further delineation of clearly identifiable cases of acute inflammation/infection at the point of admission. However, we would emphasise

that classification was prospectively applied, the groupings are consistent with our previous reports that describe in detail the rigorous clinical criteria employed in profiling the 'Heart of Soweto' cohort, and expected gradients in lipid levels were subsequently found. Systematic bias needs to be carefully considered before attributing broad patterns in lipid profiles, as those with suspected atherosclerotic disease were more likely to have had lipid levels measured, reflecting the low number of those presenting an acute infectious form of HD (for example, patients with pericarditis). Adiposity, a major confounder of both dyslipidaemia and HD, was recorded in 71% of the cohort. However, its inclusion in the regression analyses did not alter the significance of the associations. Central obesity measurements (e.g. waist-to-hip ratio) may have offered greater delineation of CVD risk but data were not available. CRP was measured in just under one third of cases and related data requires careful interpretation. Finally, owing to the cross-sectional design of this study we were not able to investigate the possible effect of the magnitude and timing of the contributing infection on lipid levels, beyond the data collected at admission. Given the transient, dynamic processes of lipid metabolism over the course of acute and chronic diseases, only longitudinal studies of lipid levels and subsequent outcomes can fully elucidate the clinical importance of our findings.

Conclusions

We have shown that despite largely favourable lipid profiles, there are clear differences according to underlying aetiology of HD in urban Africans however, overall low HDLC was the most prevalent metabolic abnormality observed in this cohort. Younger Africans with communicable HD have particularly low levels of HDLC that, if maintained in the longer term, may leave them at increased risk of atherosclerotic disease. This is physiologically plausible in chronic infection; however low HDL at hospital admission could also simply reflect similarly low levels of TC/LDL and may not be indicative of increased long-term CVD risk. That uncertainty can only be resolved by well-powered studies with adequate follow-up, to provide sufficient evidence to address current gaps in evidence and, ultimately, guide clinical practice. Nevertheless if proven, targeted prevention programs that identify and actively manage individuals with a history of communicable HD (particularly an active case) and with low levels of

HDLC may be indicated. The alternative is an increasing burden of non-communicable forms of HD in urban African communities that is supplemented (in origin and confluence) by historical cases of communicable disease that have adversely affected protective HDLC levels (particularly in women).

Acknowledgements

We thank all the doctors, nurses, and patients who participated in the registry; and Elisabeth Tshele, Bridget Phooko, Maureen Kubheka and Phutuma Mathusi who contributed to the meticulous collection and management of clinical data.

Competing interests

All authors declare: all authors had financial support from independent funding bodies, including University of the Witwatersrand and unconditional research grants from Adcock-Ingram, the Medtronic Foundation USA, Servier, Bayer-Schering and BHP Billiton, for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Funding

The 'Heart of Soweto Study' registry was supported by the University of the Witwatersrand and unconditional research grants from Adcock-Ingram, the Medtronic Foundation USA, Servier, Bayer-Schering and BHP Billiton. SS, MJC and JGL are supported by the National Health & Medical Research Council of Australia [Program Grants 320860 and 631947 and Postgraduate scholarship 586739]. JGL is supported by the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand. Baker IDI is supported by the Victorian Government's Operational Infrastructure Support Program. KS and SL are supported by the MRC South Africa and the University of Cape Town.

Author's contributions:

KS, MJC and SS participated in the original design of the study and supervised the collection of data. JGL prepared the first draft of the manuscript, with edits and revisions provided by all authors. FR and FT revised manuscript critically for important intellectual content. All authors

had full access to all the data and read and approved the final version of the manuscript. All authors had final responsibility for the decision to submit the manuscript for publication.

Data sharing statement

Study data will be available on request from the corresponding author.

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FIGURE 1 Sex specific lipid profiles according to heart disease aetiology

Figure legend:

Lipid values are shown as mean ± standard error. P values indicate between-sex comparisons per aetiology group (T-test), ** = P<0.01; * = P<0.05. NCD = non-communicable heart disease; CD = communicable heart disease; TC= total cholesterol; HDL= high-density lipoprotein cholesterol; LDL= low-density lipoprotein. Y-axis dotted lines show thresholds for high TC and LDL or low HDL (sex specific values).

FIGURE 2 Prevalence of low high-density lipoprotein cholesterol according to heart disease aetiology

Figure legend:

NCD = non-communicable heart disease; CD = communicable heart disease.

High total cholesterol (TC) > 4.5 mmol/L; Low high-density lipoprotein cholesterol (HDLC) (<1.0 mmol/L in men, <1.2 mmol/L in women). High low density lipoprotein cholesterol (LDLC) >2.5 mmol/L; High triglycerides (TGs) >1.7 mmol/L

FIGURE 3 Risk of low high-density lipoprotein cholesterol according to C-reactive protein risk group, relative to low-risk C-reactive protein group (n=367)

Figure legend:

Age-adjusted analysis. CRP = C-reactive protein. ** = P<0.01; * = P<0.05 relative to low CRP group. For confidence intervals, please refer to Results section.

Lower Levels of High-density Lipoprotein Cholesterol in Urban Africans Presenting with Communicable Versus Non-communicable Forms of Heart Disease: The 'Heart of Soweto' hospital registry study

Short title: Lyons – HDLC in communicable heart disease

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Key Words: High-density lipoprotein, lipids, infection, epidemiologic transition, Africa.

Word count: 3540 not including 2 tables, 3 figures and 3~~5~~6 references.

ABSTRACT

Objectives: To investigate if urban Africans displayed lower levels of atheroprotective high-density lipoprotein cholesterol (HDLC) when presenting with communicable versus non-communicable forms of heart disease (HD) as both acute infection and chronic inflammation reduce HDLC levels.

Design: Hospital registry of 5328 de novo cases of HD over a 3-year period.

Setting: Cardiology Unit, Baragwanath Hospital in Soweto, South Africa.

Participants: A total of 1199 patients of African descent (59% ~~female~~women; 57.0±13.4 years) had fasting blood lipid levels (Total cholesterol [TC], triglyceride, HDLC, and low-density lipoprotein [LDLC] cholesterol) documented on admission. Serum inflammatory marker C-reactive protein (CRP) was measured in a sub-set of 367 patients (31% of cases).

Main outcome measures: Lipid profiles were compared according to pre-specified classification of non-communicable (e.g. hypertensive HD) versus communicable (e.g. rheumatic HD) HD. Low HDLC was defined as <1.0 mmol/L for ~~males~~men and <1.2mmol/L for ~~females~~women, according to applicable South African Clinical Guidelines.

Results: Overall 694 (58%) of those presenting with HD had low HDLC levels; 344 of 678 (51%) and 350 of 521 (67%) for non-communicable and communicable, respectively (p<0.001). Comparatively, overall prevalence of high TC was 32% and high LDLC was 37%. On an adjusted basis, those with non-communicable HD were more likely to record a low HDLC relative to non-communicable presentations (OR 1.91, 95%CI 1.42, 2.57; p<0.001). There was a strong relationship between low HDLC and higher levels of CRP, but only in ~~females~~women.

Conclusions: Despite largely favourable lipid profiles, there are clear differences according to aetiology of underlying HD in urban Africans, with younger patients with communicable HD having particularly low levels of HDLC. Appropriate prospective evidence is needed to determine if persistent low levels of HDLC expose patients to increased, long-term risk of atherosclerotic forms of HD. The ~~female~~women-only inverse association between HDL-C and CRP warrants further investigation.

ARTICLE SUMMARY

Article focus:

- In sub-Saharan Africa, the incidence of non-communicable cardiovascular disease is increasing while, simultaneously, communicable forms of heart disease continue to cause considerable levels of morbidity and mortality.
- In this study, we have sought to explore one heart disease risk factor, dyslipidaemia, in a well-defined clinical registry in Soweto, South Africa.
- Lipid profiles from 1199 de novo presentations of heart disease were compared according to pre-specified classification of non-communicable heart disease (e.g. hypertensive heart disease) versus communicable forms of heart disease (e.g. pericarditis or chronic rheumatic heart disease). We hypothesised that those diagnosed with communicable heart disease would display an adverse lipid profile, with low levels of atheroprotective high-density lipoprotein cholesterol (HDLC). We also investigated the potential interaction of the inflammatory marker C-reactive protein (CRP) and low HDLC in a subset of these patients.

Key messages:

- We describe distinct patterns of dyslipidaemia according to underlying heart disease aetiology: significantly decreased levels of HDLC, total cholesterol and low-density lipoprotein cholesterol in those with communicable heart disease (representing 43% of cohort) compared to those with non-communicable heart disease (57% of cohort).
- In adjusted analyses, low HDLC was more pronounced in those with communicable heart disease. In those with high CRP levels, we present novel data showing a sex-disparate relationship between CRP and low HDLC, with a strong relationship between high CRP and low HDLC in ~~females~~women only.
- The high prevalence of low HDLC in a relatively young population of urban Africans may, if persistent in the longer-term, confer greater risk of atherosclerotic heart disease

Strengths and limitations of the study:

- We report a high prevalence of low HDLC in *de novo* presentations of both communicable heart disease and non-communicable heart disease, with a greater prevalence in those with communicable heart disease.
- The study cohort is clinically very well defined; however the lipid data were obtained according to clinical presentation, which may impose systematic bias to the results.
- This hospital registry study has provided preliminary data that would support prospective investigation of longer-term dyslipidaemia patterns and their impact on heart disease incidence, both in South Africa and in other low-and-middle-income countries where the epidemiologic transition is currently underway.

INTRODUCTION

Heart diseases with infectious aetiology have long been the principal forms of cardiovascular disease (CVD) in Sub-Saharan Africa. However, epidemiological transition has seen increased prevalence of non-communicable forms of heart disease in these populations[1]. This phenomenon is largely driven by complex, population-wide changes in demographic, social and economic status, with associated changes in lifestyle habits[2-4]. Indicative of the tension between 'old' and 'new' forms of heart disease, the incidence of communicable heart disease (HD) is sustained by the devastating epidemics of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), tuberculosis (TB), rheumatic heart disease (RHD) and parasitic infections with cardiac involvement[5-7], while in parallel, the prevalence of risk factors for non-communicable HD increases[8].

Low serum levels of high-density lipoprotein cholesterol (HDLC) are consistently and independently associated with increased risk of atherosclerotic forms of CVD[9 10]. However, it remains uncertain whether low HDLC is causal or just a cardiovascular risk marker[11]. If we are to extrapolate from studies in Western and Asian populations[12-14], isolated low HDLC is associated with increased risk for CVD in the long-term. There are several causes of low HDLC levels, including overweight, obesity, tobacco smoking, and insulin resistance/type 2 diabetes mellitus, indicative of the important role lifestyle factors have in mediating HDLC levels[9]. Additionally, low HDLC is a striking consequence of abnormal lipid metabolism in infection and inflammation[15]. Although it has been shown that those of African descent largely show a favourable lipid profile characterised by high HDLC levels [16], it is unlikely that they can remain athero-protective during an infected state[15]. Indeed, in this setting, it is probable that increasing prevalence of modifiable/ lifestyle risk factors contribute to a more advanced presentation in those with communicable HD[8]. We have previously reported that in the geographically compact townships that comprise Soweto in South Africa, 'old' and 'new' forms of HD are simultaneously present[8]. While this tension exists, we have a unique opportunity to explore lipid profiles in patients presenting with non-communicable versus communicable forms of HD.

STUDY HYPOTHESES

Having shown important ethnic differences in the lipid profiles of patients of African descent presenting with HD in the urban African enclave of Soweto[16], we hypothesised that independent of age and sex, urban Africans presenting with communicable HD will demonstrate patterns of dyslipidaemia associated with infection/inflammation, particularly sub-optimal levels of HDLC, versus non-communicable HD.

METHODS

Study Setting & Design

As described in detail previously[8 17] the 3,500 bed Chris Hani Baragwanath Hospital (case load of > 125,000 in-patients per annum) services the tertiary care needs of Soweto (population of 1.1 million) and surrounding communities. All suspected cardiac presentations are referred to the hospital's Cardiology Unit for advanced diagnostic testing and gold-standard treatments. A prospective clinical registry of all *de novo* presentations of the same was established in 2006 as part of the Heart of Soweto Study and represents sub-Saharan Africa's largest and most detailed study of advanced forms of HD to date[17].

Participants

The 'Heart of Soweto' cohort of *de novo* case presentations comprised 5328 patients. Of these, 2185 patients (40%) had a documented fasting lipid profile (serum total cholesterol (TC) level, triglyceride, HDLC and calculated low-density lipoprotein cholesterol (LDLC)[18] undertaken at Baragwanath Hospital on-site pathology). None of the patients were on lipid lowering agents at the time of presentation, as this medication can only be prescribed at the tertiary institution. However some of the patients had been placed on anti-hypertensive medication prior to their first assessment at the Cardiac Clinic at Baragwanath Hospital. Moreover, only a small number of patients (39 cases) had been prescribed anti-retroviral therapy (ART) on presentation. The study was approved by the University of the Witwatersrand Ethical Committee and conforms to the principles outlined in the Declaration of Helsinki. All patients provided informed consent.

Study Data

A complete list of study data captured by the registry, comprising basic socio-demographic (including self-reported ethnicity, years of education and determining if the patient was born in Soweto) and advanced clinical profiling, has been described previously[8 17] The registry captured all advanced clinical investigative procedures (e.g. coronary angiography, which was undertaken in all people diagnosed with coronary artery disease (CAD)). Echocardiography (performed on all patients) criteria used in the study has been described in detail previously[8 17].

Case Classifications

Adjudication and classification of communicable and non-communicable presentations of HD in this cohort have been previously described[8]. After exclusion of those with uncomplicated hypertension (i.e. without evidence of cardiac dysfunction, n=380) or other non-modifiable aetiologies (e.g. congenital disorders), 1199 patients of African descent (22% of the total 'Heart of Soweto' cohort) were included in this analysis. Contributory diagnoses for non-communicable HD were predominantly hypertensive heart failure (HT-HF) and coronary artery disease (without HIV). Communicable heart disease was predominantly classified as HIV-dilated cardiomyopathy (HIV-DCMO), HIV-pulmonary hypertension, TB pericardial disease, and pericarditis due to other infection.

Risk factor definition

Optimum lipid levels and treatment goals with established CVD were defined according to international guidelines[9] adopted by the Lipid and Atherosclerosis Society of South Africa and the South African Heart Association - high TC: >4.5 mmol/L, high TGs: >1.7 mmol/L, high LDLC: >2.5 mmol/L and low HDLC: <1.0 for ~~males~~men and <1.2 mmol/L for ~~females~~women[19]. Other risk factors were measured on a clinical basis, as previously described[17]. Anthropometric measurements were available for calculation of body mass index (BMI, kg/m^2) in 854 (71%) cases, the low reporting rate restricted to ambulatory patients. Obesity was defined as BMI ≥ 30 kg/m^2. Serum C-reactive protein (CRP) was measured in a sub-set of 367 patients (31% of all cases) if clinically indicated (e.g. suspected infection). Patients were stratified into clinically

relevant CRP categories[20], as defined by Dhingra and colleagues[21]. Patients with a CRP of 1 mg/L (n=19) were used as reference group and compared to medium (1.1-3.0 mg/L, n=26), high (3.1-10.0 mg/L, n=83) and very high (>10.0 mg/L, n=239) CRP categories.

Statistical analyses

Normally distributed continuous data are presented as the mean ± standard deviation and non-Gaussian distributed variables as the median (inter-quartile range). Categorical data are presented as sample number and percentages. For group comparisons, we initially used Chi Square (χ^2) analysis with calculation of odds ratios (OR) with 95% confidence intervals (CI) presented where appropriate for discrete variables, and independent T-tests for normally distributed continuous variables and Mann-Whitney U test for nonparametric continuous variables. Multiple logistic regression analyses (entry model) were used to derive age and sex adjusted ORs (and BMI in some analyses, as described) for the risk of presenting with clinically relevant variables (primarily dyslipidaemia profiles), according to CD HD relative to NCD diagnosis. Significance was accepted at the two-sided level of $p<0.05$.

RESULTS

Clinical and Demographic Profile

Table 1 shows the socio-demographic and clinical profile of this cohort according to cardiac aetiology. Those presenting with non-communicable HD (n=678, 56.5% of cohort) were older and had higher BMI and mean SBP and DBP than those with communicable HD (n=521, 43.5%; all comparisons p<0.001). Overall, 76 (6%) were confirmed HIV-positive: 15 (2%) and 61 (12%) patients were confirmed HIV-positive in non-communicable and communicable HD groups respectively (P<0.001). Apart from higher BMIs in women (30.6 ± 6.9 vs. 26.7 ± 5.5 kg/m^2 in ~~males~~men, p<0.001) there were no significant differences between sexes in respect to other clinical parameters. To this, the prevalence of obesity in women was 50% as compared to men (26%), P<0.001.

TABLE 1 Clinical and demographic profile according to heart disease aetiology

	ALL Cases n=1199	Non-communicable n=678 (57%)	Communicable n=521 (43%)	*P* value
Demographic Profile				
Mean age (years)	58.3 ±14.0	60.1 ± 13.1	55.9 ± 14.9	<0.001
~~Female~~Women	701 (59%)	403 (59%)	298 (57%)	0.44
<6 years formal education	582 (49%)	335 (49%)	247 (47%)	0.52
Soweto origin	562 (47%)	327 (48%)	235 (45%)	0.29
Clinical Presentation				
Total cholesterol (mmol/L)	4.0 ± 1.4	4.3 ± 1.3	3.7 ± 1.2	<0.001
HDLC (mmol/L)	1.1 ± 0.5	1.2 ± 0.5	1.0 ± 0.5	<0.001
Median triglycerides (mmol/L)*	1.1 (0.8, 1.5)	1.1 (0.8,1.6)	1.0 (0.7, 1.3)	<0.001
LDLC (mmol/L)	2.4 ± 1.0	2.5 ± 1.0	2.2 ± 0.9	<0.001
TC:HDLC ratio	4.3 ± 3.0	4.2 ± 3.1	4.4 ± 2.7	0.27
LDL:HDLC ratio	2.5 ± 1.1	2.5 ± 1.0	2.7 ± 1.1	0.36
TG:HDLC ratio*	1.1 (0.7, 1.7)	1.0 (0.7, 1.7)	1.1 (0.7, 1.8)	0.12
Median serum CRP (mg/L)*	19 (7.0, 45.0)	16.8 (6.6,41.5)	20.5 (7.8, 55.9)	0.25

Systolic BP (mmHg)	135 ± 29	143 ± 29	126 ± 26	<0.001
Diastolic BP (mmHg)	78 ± 16	80 ± 16	74 ± 16	<0.001
BMI (kg/m^2)	29.0 ± 6.7	30.3 ± 6.7	27.2 ± 6.2	<0.001
Prevalence of dyslipidaemia (n, %)				
High total cholesterol (> 5mmol/L)	378 (32%)	266 (39%)	112 (22%)	<0.001
Low HDLC (< 1 in ~~males~~men and < 1.2 mmol/L in ~~females~~women)	694 (58%)	344 (51%)	350 (67%)	<0.001
High LDLC (> 2.5 mmol/L)	446 (37%)	291 (43%)	155 (30%)	<0.001
High triglycerides (> 1.7 mmol/l)	215 (18%)	143 (21%)	72 (14%)	0.001
Prevalence of other risk factors (n, %)				
Obese (BMI >30 kg/m^2)	344 (40%)	237 (48%)	107 (30%)	<0.001
Type 2 diabetes	98 (8%)	71 (11%)	27 (5%)	<0.001
Past or current smoker	566 (47%)	321(47%)	245 (47%)	0.95
Family history of CVD	466 (39%)	286 (42%)	180 (35%)	0.01
Confirmed HIV-positive cases	76 (6%)	15 (2%)	61 (12%)	<0.001

Table legend:

LDLC = low-density lipoprotein cholesterol; HDLC = high-density lipoprotein cholesterol; TG = triglycerides; BMI = body mass index (available in 854 cases); CRP = C-reactive protein (available in 367 cases); CVD = cardiovascular disease; HIV = human immunodeficiency virus. *Median (interquartile range) values presented, differences tested by Mann-Whitney U test

Aetiology of heart disease (primary diagnosis)

Overall, the most prevalent primary diagnoses were HT-HF (n=461, 38%), dilated cardiomyopathy (DCMO, n= 178, 15%) and CAD (n=157, 12%). In those classified as non-communicable HD, HT-HF was the main primary diagnosis (n=461, 68%), along with CAD (without concurrent HIV-infection; n=157, 23%). Dilated cardiomyopathy (n=178, 34%), right heart failure (n=92, 18%) and right heart disease (n=63, 12%) and other forms of primary valve

disease (n=71, 14%), were the most common diagnoses in those classified with communicable forms of HD.

Lipid Profiles

Those with communicable HD had significantly lower TC, LDLC, and HDLC compared with patients with non-communicable HD (**Table 1** and **Figure 1**, p<0.001 for all comparisons). Overall, women had significantly higher TC (4.2±1.3 mmol/L vs. 3.8±1.2 mmol/L, p<0.001); LDLC (2.4±1.0 mmol/L vs. 2.2±1.0 mmol/L, p<0.01), and HDLC compared to men (1.2±0.5 mmol/L vs. 1.0±0.5 mmol/L, p<0.001). This gender difference did not extend to triglycerides (1.1(0.4-1.8) mmol/L vs. 1.1(0.4-1.8), p=0.7) nor TC:HDLC ratio (4.2 ± 3.1 mmol/L vs. 4.3 ± 2.7 mmol/L, p=0.6). Lipid ratios were calculated and compared (**Table 1**). There was no significant differences between aetiology groups for either TC:HDL or TG:HDL groups. However LDL:HDL ratios were significantly higher in the communicable group.

Levels of TC (Figure 1A), HDLC (Figure 1B) and LDLC (Figure 1C) were significantly higher in ~~females~~women with non-communicable HD (**Figure 1**). However in those diagnosed with communicable HD, small, but significant, differences were observed only for TC and HDLC, not LDL (**Figure 1**). Overall, prevalence of dyslipidaemia varied from 18% of patients with high triglycerides to 58% with low HDLC (**Table 1** and **Figure 2**). Consistent with the decrease observed with the actual levels, prevalence of high TC and high LDLC was increased in those with non-communicable HD aetiologies while low HDLC levels prevalence was higher in those with communicable HD **(Table 1 and Figure 2)**. There were no patients with TG levels > 4.5 mmol/L (range 0.1-3.8 mmol/L) which makes use of the Friedewald equation suitable for this cohort[18].

Table 2 shows independent associations between relevant socio-economic, demographic and clinical variables and communicable HD aetiology, relative to those presenting with non-communicable HD. The effect of HD aetiology on low HDLC dyslipidaemia was strong and consistent: adjusting for age, sex and BMI of patients, those with forms of communicable HD were significantly more likely to record a low HDLC relative to those presenting with non-communicable HD (**Table 2,** p<0.001) and less likely to record high TC and LDLC (**Table 2**).

Patients with communicable HD were less likely to record high triglyceride levels (OR 0.65, 95%CI 0.51, 0.84, p<0.05) compared to those with non-communicable HD.

TABLE 2 Independent correlates of communicable heart disease, relative to non-communicable heart disease

	Communicable disease	
	Odds Ratio	**95% CI**
~~Female~~Women ~~sex~~	0.91	0.72, 1.15
Age	0.98	0.97, 0.99**
Obesity	0.50	0.37, 0.68***
< 6 years formal education	1.11	0.88, 1.42
Soweto origin	0.98	0.77, 1.24
Body mass index adjusted analysis		
High TC	0.52	0.37, 0.71***
High LDLC	0.56	0.41, 0.76***
Low HDLC	1.91	1.42, 2.57***
High TG	0.65	0.51, 0.84*

Table legend:

Obesity BMI >30kg/m^2; High total cholesterol (TC) > 4.5 mmol/L; High low density lipoprotein (LDLC) >2.5 mmol/L; Low high density lipoprotein (HDLC) (<1.0 mmol/L in ~~males~~men, <1.2 mmol/L in ~~females~~women). OR = odds ratio; CI = confidence intervals. Age and sex-adjusted analysis: * p<0.05; **p<0.01; ***p<0.001.

CRP subset analysis

Overall, there was no significant difference in CRP levels between aetiology groups (**Table 1**). The proportion of confirmed HIV cases in this CRP subset analysis was 7% (n=27). Of those, 23 were in the very high-risk category. There was also no association between CRP-derived risk categories and high TC, LDLC or triglycerides (data not shown). However the risk of having low HDLC increased with increasing CRP levels. In age and sex-adjusted analyses, those with

medium risk (OR 2.73, 95% CI 0.68, 10.89, P=0.16), high risk (OR 4.98, 95% CI 1.46, 17.00, P=0.01) and very high risk (OR 6.37, 95% CI 1.97, 20.57, p<0.01) CRP levels were significantly more likely to record a low HDLC relative to those in the low risk CRP group. Also, when stratified by sex, a strong, positive association remained in ~~females~~women but was no longer apparent in ~~males~~men **(Figure 3)**. In ~~females~~women, the pattern was significant across all CRP risk categories: compared to low risk, those with medium risk (OR 12.1, 95% CI 1.21, 120, p=0.03), high risk (OR 14.4, 95% CI 1.64, 126, p=0.02) and very high risk (OR 23.5, 95% CI 2.81, 197, p=0.004) CRP levels were all more likely to record a low HDLC. Moreover, the association was not weakened by addition of BMI into the model (BMI and CRP measurements available in only 230 cases) in overall and ~~female~~women-only (n=133) models: those with medium risk (OR 20.5, 95% CI 1.72, 246, p=0.02), high risk (OR 10.6, 95% CI 1.14, 98.8, p=0.04) and very high risk (OR 21.0, 95% CI 2.38, 185, p<0.01) CRP levels were all more likely to record a low HDLC.

DISCUSSION

We report significant decreases in lipid levels (TC, HDLC and LDLC) and age and BMI according to non-communicable and communicable manifestations of *de novo* HD in urban Africans, patterns that were observed in both sexes. The high prevalence of low HDLC in more than half of all cases, but much higher in those with communicable HD, is most striking. Also, it appears that gender is an effect modifier in the relationship between CRP and low HDLC in this cohort, but, importantly, the relationship remains even after adjustment for the significant confounder of adiposity.

While traditionally uncommon[22], dyslipidaemia, in particular low HDLC, is becoming more prevalent in sub-Saharan Africa[23 24]. The low lipid levels present in the majority of cases with communicable HD reflects the dramatic changes to lipid metabolism observed in infection and is therefore, anticipated. We acknowledge that atherogenic LDLC is also low in this setting and that low HDLC may not be indicative of particularly increased disease risk, at least in the short-term. However we still deem this as highly clinically relevant given that even isolated low HDLC is associated with a higher risk of atherosclerotic forms of HD, a finding that has been seen in diverse populations[12-14]. Interestingly triglyceride levels were not significantly increased in those with communicable forms of HD, despite evidence that it can increase as part of the infectious/inflammatory metabolic milieu[15]. Additionally, we speculate that the higher lipid levels in women may be the result of much higher rates of obesity (50% compared with 26% in men) as the driver of elevated total cholesterol, which has been suggested by authors of a worldwide systematic analysis on high TC [25].

Our interest in this phenomenon predominantly relates to the longer-term effects of low HDLC, especially when observed together with the amplified vascular risk associated with chronic infection[15]. In Africa, where acute coronary syndromes are seen in a relatively young population[26], we predict the very high rates of myriad communicable disease[27 28] will result in more complex cases, with potentially poorer outcomes in the long-term, given the critical role of HDLC in both innate and adaptive immunity[15]. While many infectious diseases (bacterial and viral) have contributed to the underlying pathology of HD reported here[5], dyslipidemia

associated with HIV infection has been particularly well studied. HIV-related low HDLC is likely a consequence of both the viral infection and an adverse effect of some anti-retroviral treatment regimens[28-31], however only 39 patients of the 76 (51%) confirmed HIV-positive were on ART at time of presentation, representing 3% of entire subset sample, which possibly dilutes this effect.

Our CRP subset analysis found associations between low HDLC and the pro-inflammatory marker CRP in patients with newly diagnosed HD in a sex disparate manner, with a much stronger positive association in ~~females~~women. Median CRP levels were also very high across all categories of HD aetiology, and are much higher than previous reports in both early analyses of large cohorts[20] as well as South African studies[32], but reflect the clinical requirements at presentation. These high levels may also be the result of 'multi-morbidity' observed in the cohort, given the prevalence of infectious disease (such as HIV/AIDS) as well as other lifestyle factors that can also influence CRP levels[33]; all of which may have contributed to the high levels observed. Inflammatory stress may be having a more adverse effect on HDLC in women compared to men as a result of many causes. The prognostic value of stratifying CVD risk, even at very high CRP (>10 mg/L) levels, has been demonstrated in a very large ~~female~~ cohort of women[20], and there are reports of elevated CRP in women~~female populations~~ of African descent[34]. We also report ~~females~~women as having a significantly higher BMI; obesity itself can induce a low-grade inflammatory response, however the association between low HDLC and CRP in women remained even after adjusting for BMI. While we have assumed that the exaggerated drop in HDLC in women with acute forms of communicable HD is a consequence rather than a cause of infection, treatment of atherogenic dyslipidaemia and inflammatory markers in women are of particular clinical relevance in a setting where obesity and its antecedent behaviours are increasing.

These results underscore the need to consider multifactorial CVD risk burden that recognises that co-occurrence of infectious and non-communicable disease produces significant and complex health disparities. Certainly, the clinical strategies to protect the heart and vessels in acute infection differ from those required in chronic infection and it is unlikely that lipid

measurements will form a cornerstone of treatment in such cases. However, it is important to recognise the benefits of early detection and treatment of dyslipidaemia in order to mitigate any double effect of infectious *and* 'lifestyle' HD risk factors in the longer term. While the epidemiological evidence is clear, the precise mechanism by which HDLC decreases atherosclerotic CVD risk remains unclear[11]; indeed, efforts to develop pharmacological modalities to specifically increase HDLC levels to reduce cardiovascular risk, continues to be problematic[10] and we acknowledge that addressing the low HDLC observed in this cohort, in isolation, without commensurate improvements in HDLC functionality, will prove a difficult task. This does not, however, preclude use of other therapeutic interventions that address the greater, more complex risk presentation of cases that fall in the 'crossover' between communicable and non-communicable diseases. For example, the polypill, which includes lipid-lowering medications, has been proposed as a viable treatment option in secondary prevention, given its relative ease of use and efficacy in low-income settings[35]. More so, evidence that statins also exert immunomodulatory effects, along with suggestions they may prove useful in the treatment and prevention of infections[36], indicate they may have important, multi-faceted clinical implications in populations such as Soweto, especially given the substantial dyslipidaemic risk associated with highly-prevalent HIV infection and ART. Attempts to address prevention, management, cure and control of non-communicable and communicable forms of HD as entirely separate entities are likely to prove insufficient. This holds true on a per-patient basis as well as for any population-wide, public health approaches.

There are a number of limitations that require consideration. Clinical data (other than routine echocardiography and 12-lead ECG) were obtained according to presentation. This study was not specifically designed to comprehensively delineate between specific forms of HD (resulting in variable clinical data) although this is part of clinical investigation at Baragwanath Hospital; although it should be noted HIV status is not routinely determined. The arbitrary selection of disease states into the communicable versus non-communicable groups (e.g. primary valve disease) may be questioned; hence our further delineation of clearly identifiable cases of acute inflammation/infection at the point of admission. However, we would emphasise

that classification was prospectively applied, the groupings are consistent with our previous reports that describe in detail the rigorous clinical criteria employed in profiling the 'Heart of Soweto' cohort, and expected gradients in lipid levels were subsequently found. Systematic bias needs to be carefully considered before attributing broad patterns in lipid profiles, as those with suspected atherosclerotic disease were more likely to have had lipid levels measured, reflecting the low number of those presenting an acute infectious form of HD (for example, patients with pericarditis). Adiposity, a major confounder of both dyslipidaemia and HD, was recorded in 71% of the cohort. However, its inclusion in the regression analyses did not alter the significance of the associations. Central obesity measurements (e.g. waist-to-hip ratio) may have offered greater delineation of CVD risk but data were not available. CRP was measured in just under one third of cases and related data requires careful interpretation. Finally, owing to the cross-sectional design of this study we were not able to investigate the possible effect of the magnitude and timing of the contributing infection on lipid levels, beyond the data collected at admission. Given the transient, dynamic processes of lipid metabolism over the course of acute and chronic diseases, only longitudinal studies of lipid levels and subsequent outcomes can fully elucidate the clinical importance of our findings.

Conclusions

We have shown that despite largely favourable lipid profiles, there are clear differences according to underlying aetiology of HD in urban Africans however, overall low HDLC was the most prevalent metabolic abnormality observed in this cohort. Younger Africans with communicable HD have particularly low levels of HDLC that, if maintained in the longer term, may leave them at increased risk of atherosclerotic disease. This is physiologically plausible in chronic infection; however low HDL at hospital admission could also simply reflect similarly low levels of TC/LDL and may not be indicative of increased long-term CVD risk. That uncertainty can only be resolved by well-powered studies with adequate follow-up, to provide sufficient evidence to address current gaps in evidence and, ultimately, guide clinical practice. Nevertheless if proven, targeted prevention programs that identify and actively manage individuals with a history of communicable HD (particularly an active case) and with low levels of

HDLC may be indicated. The alternative is an increasing burden of non-communicable forms of HD in urban African communities that is supplemented (in origin and confluence) by historical cases of communicable disease that have adversely affected protective HDLC levels (particularly in women).

Acknowledgements

We thank all the doctors, nurses, and patients who participated in the registry; and Elisabeth Tshele, Bridget Phooko, Maureen Kubheka and Phutuma Mathusi who contributed to the meticulous collection and management of clinical data.

Competing interests

All authors declare: all authors had financial support from independent funding bodies, including University of the Witwatersrand and unconditional research grants from Adcock-Ingram, the Medtronic Foundation USA, Servier, Bayer-Schering and BHP Billiton, for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Funding

The 'Heart of Soweto Study' registry was supported by the University of the Witwatersrand and unconditional research grants from Adcock-Ingram, the Medtronic Foundation USA, Servier, Bayer-Schering and BHP Billiton. SS, MJC and JGL are supported by the National Health & Medical Research Council of Australia [Program Grants 320860 and 631947 and Postgraduate scholarship 586739]. JGL is supported by the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand. Baker IDI is supported by the Victorian Government's Operational Infrastructure Support Program. KS and SL are supported by the MRC South Africa and the University of Cape Town.

Author's contributions:

KS, MJC and SS participated in the original design of the study and supervised the collection of data. JGL prepared the first draft of the manuscript, with edits and revisions provided by all authors. FR and FT revised manuscript critically for important intellectual content. All authors

had full access to all the data and read and approved the final version of the manuscript. All authors had final responsibility for the decision to submit the manuscript for publication.

Data sharing statement

Study data will be available on request from the corresponding author.

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FIGURE 1 Sex specific lipid profiles according to heart disease aetiology

Figure legend:

Lipid values are shown as mean ± standard error. P values indicate between-sex comparisons per aetiology group (T-test), ** = P<0.01; * = P<0.05. NCD = non-communicable heart disease; CD = communicable heart disease; TC= total cholesterol; HDL= high-density lipoprotein cholesterol; LDL= low-density lipoprotein. Y-axis dotted lines show thresholds for high TC and LDL or low HDL (sex specific values).

FIGURE 2 Prevalence of low high-density lipoprotein cholesterol according to heart disease aetiology

Figure legend:

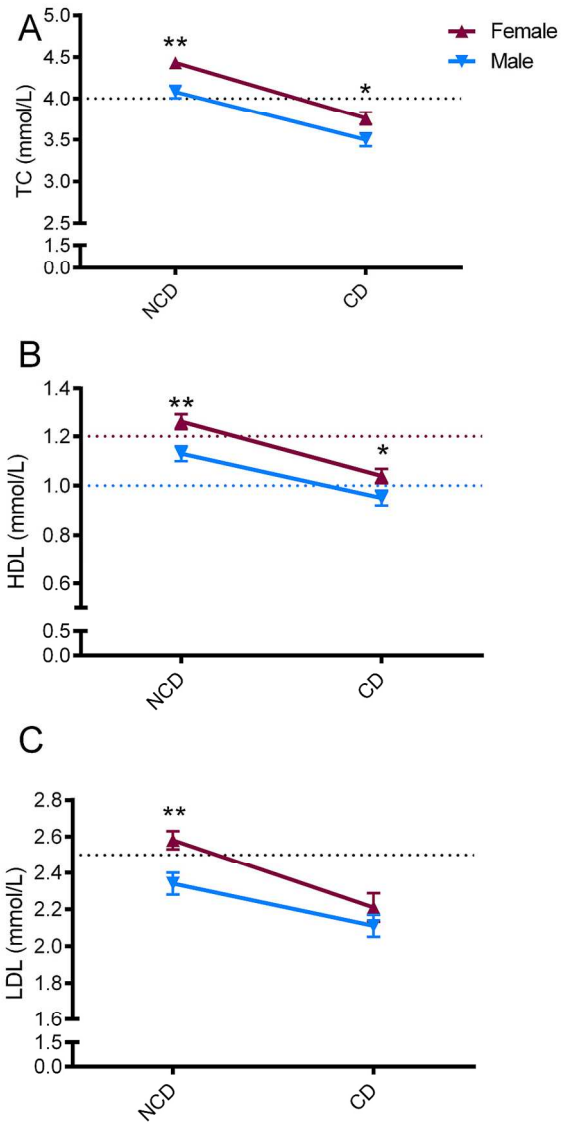
NCD = non-communicable heart disease; CD = communicable heart disease.

High total cholesterol (TC) > 4.5 mmol/L; Low high-density lipoprotein cholesterol (HDLC) (<1.0 mmol/L in ~~males~~men, <1.2 mmol/L in ~~females~~women). High low density lipoprotein cholesterol (LDLC) >2.5 mmol/L; High triglycerides (TGs) >1.7 mmol/L

FIGURE 3 Risk of low high-density lipoprotein cholesterol according to C-reactive protein risk group, relative to low-risk C-reactive protein group (n=367)

Figure legend:

Age-adjusted analysis. CRP = C-reactive protein. ** = P<0.01; * = P<0.05 relative to low CRP group. For confidence intervals, please refer to Results section.



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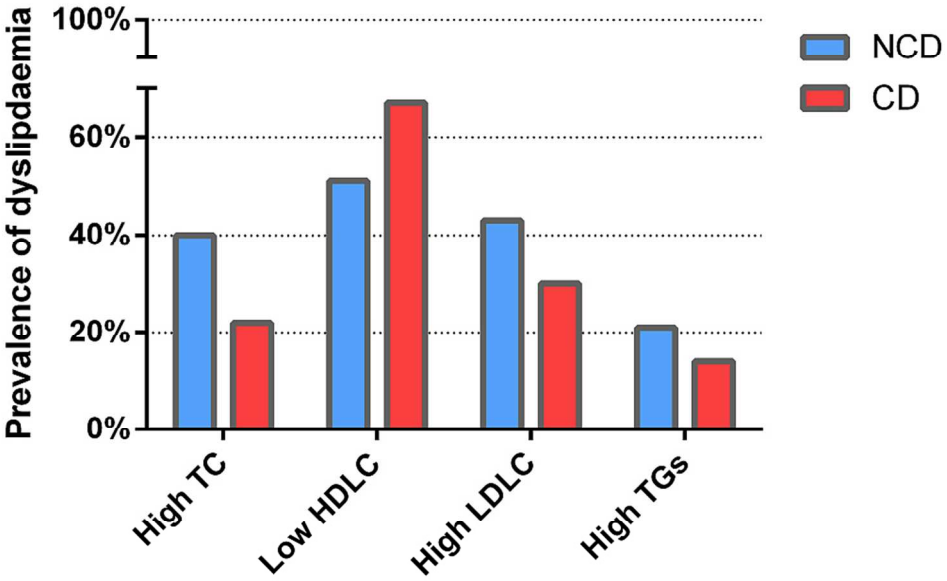

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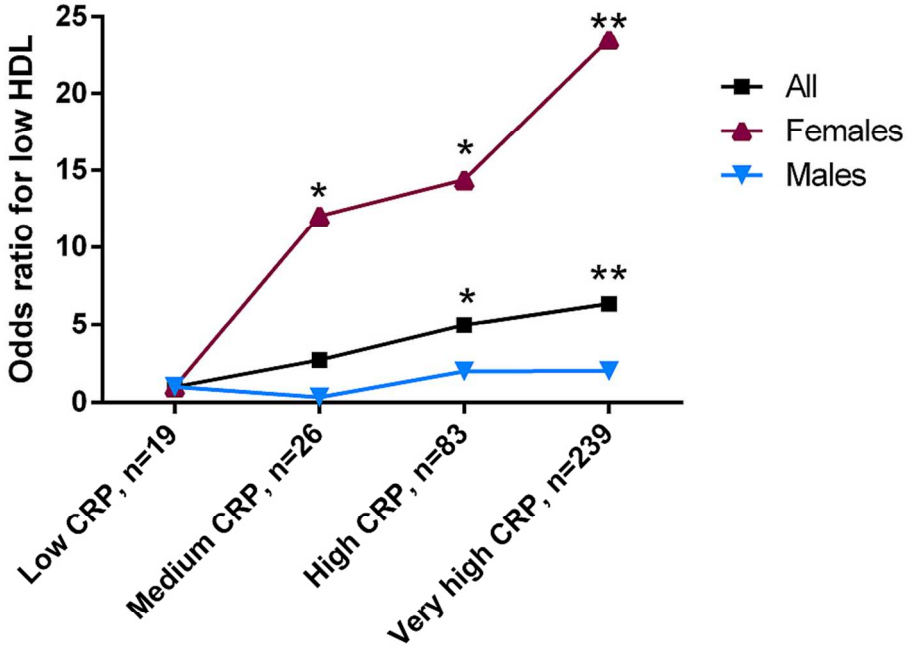

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

Completed for the article: ***Lower Levels of High-density Lipoprotein Cholesterol in Urban Africans Presenting with Communicable Versus Non-communicable Forms of Heart Disease: The 'Heart of Soweto' hospital registry study***
Date: 22 June 2014

	Item No	Recommendation	Complete
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	

		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for exposed and unexposed groups.