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Strong impact of smoking on multimorbidity and cardiovascular risk among HIV infected individuals in comparison to the general population

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Key points: AIDS-associated morbidity has diminished due to excellent viral control. Multimorbidity are more prevalent and incident in Swiss HIV-positive persons compared to HIV-negative controls. However, smoking, but not HIV status, had a strong impact on cardiovascular risk and multimorbidity.

ABSTRACT

Background: While AIDS-associated morbidity has diminished due to excellent viral control, multimorbidity may be increasing among HIV-infected persons compared to the general population.

Methods: We assessed the prevalence of comorbidities and multimorbidity in participants of the Swiss HIV Cohort Study (SHCS) compared to the population-based CoLaus study and the primary care-based FIRE records. The incidence of the respective endpoints were assessed among SHCS and CoLaus participants. Poisson regression models were adjusted for age, sex, BMI and smoking.

Results: Overall, 74,291 participants contributed data to prevalence analyses (3,230 HIV-infected; 71,061 controls). In CoLaus, FIRE and SHCS, multimorbidity was present among 26%, 13% and 27%. Compared to non-smoking individuals from CoLaus the incidence of cardiovascular disease was elevated among smoking individuals but independent of HIV status (HIV-negative smoking: 1.7 [1.2-2.5]; HIV-positive smoking; 1.7 [1.1-2.6]; HIV-positive non-smoking: 0.79 [0.44-1.4]). Compared to non-smoking HIV-negative persons, multivariable Poisson regression identified associations of HIV-infection with hypertension (non-smoking: incidence rate ratio (IRR) 1.9 [95% CI:1.5-2.4]; smoking; 2.0 [1.6-2.4]), kidney (non-smoking: 2.7 [1.9-3.8]; smoking; 2.6 [1.9 to 3.6]) and liver disease (non-smoking: 1.8 [1.4-2.4]; smoking; 1.7 [1.4-2.2]). No evidence was found for an association of HIV-infection or smoking with diabetes mellitus.

Conclusions: Multimorbidity is more prevalent and incident in HIV-positive compared to HIV-negative individuals. Smoking, but not HIV status, has a strong impact on cardiovascular risk and multimorbidity.

INTRODUCTION

Combination antiretroviral treatment has significantly improved life expectancy of HIV-positive individuals [1]. With close to normal life expectancy, HIV-positive persons may face sequential or concurrent comorbidities leading to increased mortality and multimorbidity [2, 3]. Multimorbidity, often defined as co-occurrence of more than two conditions [4], is known to negatively affect health outcomes including a decline in functional status, increased disability and lower quality of life. Another consequence of multimorbidity is an increased number of medications (polypharmacy) [5].

An important focus of current clinical HIV research is to identify whether HIV-positive individuals with suppressed viral replication develop earlier or different comorbidities compared to HIV-negative persons. Previous comparisons have shown conflicting results regarding cardiovascular disease (CVD), stroke, hypertension, diabetes mellitus, psychiatric disorders, and diseases of bone, lung, kidney and liver [6-21]. Possible reasons for the discrepancies are differences in the selection of the HIV-negative controls, either nested within a population with comparable life styles [7-10, 12, 13, 15, 17, 18, 22] or based on administrative data from the same geographic area or hospital [11, 14, 16, 19-21]. Other reasons include the limitations of adjusting for important confounders such as smoking or body mass index (BMI) [8, 9, 11, 13, 14, 16, 20].

The aim of the present study is to compare the prevalence and incidence of different comorbidities and multimorbidity in participants of the Swiss HIV Cohort Study (SHCS) with two HIV-negative populations in Switzerland.

METHODS

Data sources included in the study

The **SHCS** [23] was established in 1988 and is an open cohort study with continued enrolment of cumulatively around 18’000 HIV-infected persons, aged ≥16 years. Demographic, psychosocial, clinical, laboratory and treatment information is systematically collected every six months. Information on cardiovascular endpoints, diabetes mellitus, renal and liver disease is

ascertained and centrally adjudicated within the Data collection on Adverse events of Anti-HIV Drugs Study (D:A:D) [24].

Cohorte Lausannoise (CoLaus) [25] is a population-based study that investigates the clinical, biological and genetic determinants of cardiovascular disease. CoLaus performs endpoint adjudication of cardiovascular events, diabetes and psychiatric disorders and moreover they have access to the electronic patient records of the hospitals and are linked to the death registry. Participants aged 35-75-year old were recruited in 2003 among 19,830 randomly selected inhabitants of Lausanne, Switzerland. The baseline characterization of 6,182 participants was performed during 2003-2006 and a first follow-up visit on more than 5000 of these individuals was done during 2009-2013.

Family Medicine ICPC-Research using Electronic Medical Records FIRE [26] is a Swiss primary care project which has enrolled approx. 150,000 patients from 75 general practitioners since 2009 and uses medical data retrieved from electronic patient records. Laboratory results, demographical and clinical information are collected at routine visits. Morbidity is classified according to the International Classification of Primary Care (ICPC-2) codes [27] and information on the type of prescribed medications is based on the ATC-classification [28]. FIRE analyzed prevalence estimates of chronic conditions in a recent study and found an age- and gender specific distribution comparable to other primary care data sources in Switzerland [29]. Information on smoking and alcohol use has not yet been collected in FIRE and there is only limited information on liver disease and weight available. There is a inherent selection bias in BMI measurements in FIRE as the weight was more likely assessed in case of overweight or obese participants. FIRE data could not be used for incidence analysis due to limited accumulated follow-up time.

Study participants

Individuals from SHCS and CoLaus were eligible if they were Caucasian, non injecting drug-users (non-IDU), ≥35 years at a study visit 2003-2006 (baseline), and if they had at least one follow-up visit 5-6 years later. FIRE patients were eligible if they were Caucasian, non-IDU, >40 years old, and if they had >1 visit between January 1, 2009 and December 31, 2011. Thus, all

participants were at least 40 years old in 2009-2011 and contributed to prevalence analyses. For the conceptual design refer to **Supplementary Figure 1**. All cohorts were approved by the local Ethics Committees.

Definitions

Clinical events were validated according to the standards of each cohort. We collected informations on the following clinical events: cardiovascular diseases (myocardial infarction, coronary heart disease with/ without angina, heart failure and coronary heart disease, coronary artery bypass graft and coronary angioplasty/stenting); stroke; diabetes mellitus (diabetes mellitus insulin dependent/ insulin resistant and use of oral anti-diabetics or insulin (ATCA10*; PCG: A10)); hypertension (measured diastolic or a systolic blood pressure >90/>160 mm Hg, or use of antihypertensive medications (ATC C0*; PCG: C02, C03A, C03EA01 C07, C08,C09A, C09B)); Kidney insufficiency (GFR < 60 ml/min, MDRD Formula) [30] ; Liver event (ALT > 50 U/l for males/ 35 U/l for females). We used the term “comorbidities” throughout the manuscript. Multimorbidity was termed as the co-occurrence of at least two of the above mentioned conditions (i.e. ≥2 comorbidities). By definition, HIV-infection was not considered as a comorbid condition. In CoLaus and SHCS comedications were recorded according to the Anatomical Therapeutic Chemical classification System (ATC) [28], FIRE applied a Pharmaceutical Cost Group (PCG) model [27]. We recorded the use of antihypertensives and antidiabetics. An table indicating the definitions of each clinical event is available in the appendix (**Supplementary table 1**).

BMI (kg/m^2) was stratified into <18.5 (underweight), 18.5-24.9 (normal), 25-29.9 (overweight) and ≥30 (obese), [31]. We distinguished two smoking categories (ever/current smokers and non-smokers). Age was stratified into <50, 50-65 and 65+ years. Information on HIV-infection included years since first HIV diagnosis and cumulative exposure to drug classes (protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitor (NNRTI) based ART combinations).

Statistical analysis

Differences between cohorts were analyzed by chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables.

We calculated the cumulative prevalence of endpoints for CoLaus, FIRE and SHCS until end of 2011. Logistic regression analyses were adjusted for age-groups and sex among all cohorts and in SHCS and CoLaus models were further adjusted for smoking and BMI.

We calculated incidence rates of endpoints as the number of new endpoints since the first visit in 2003-2006 divided by the number of person-years of follow-up. The time at risk for patients without an event was calculated as time between the baseline visit and the follow-up visit. In case of an event we used the time from baseline until the date of the event. Since precise dates of diabetes mellitus, hypertension, kidney disease and liver disease were not available in CoLaus, we used the midpoint between the baseline and follow-up visit for these events. To check whether this approximation was valid, we compared CoLaus estimates for cardiovascular events and stroke using the available dates with the estimates using the midpoint of baseline and follow-up visit. The findings were unchanged (data not shown). Comparisons of incidence across CoLaus and SHCS were done with Poisson regression adjusted for sex, age groups, BMI groups and smoking as an interaction term. To rule out important effect attenuation by using stratified age and BMI values we performed sensitivity analyses using continuous age and BMI measurements. We excluded IDU and therefore we assumed HCV would not contribute to the endpoint liver disease. To check this, we performed a sensitivity analysis and excluded HCV-infected individuals in other HIV transmission groups than IDU.

We used Stata/SE (Version 13.1, StataCorp, College Station, Texas, USA) for analyses.

RESULTS

Patients characteristics

Characteristics of the participants are shown in **Table 1**. Compared to the SHCS, participants from FIRE and CoLaus were older, more frequently female and had a higher BMI; previous or current smoking was more prevalent in the SHCS than in CoLaus.

The median duration of HIV-infection in the SHCS was 14 years (IQR, 9.5-19). Median exposure times to PI or NNRTI based ART regimens were 4.5 years (0.99-8.8) and 2.6 years (0.0-6.6), respectively. Nadir CD4 cell count was 172 (70-259), latest CD4 count was 572 (420-754) cells/μL and 880 (27%) of SHCS participants had a prior AIDS-defining event. The percentage of SHCS participants on ART with an event was between 96.4 and 100% depending on the respective endpoint. Median CD4 cells among those with or without CVD; stroke, liver or kidney disease, diabetes and hypertension were: CVD: 459.5 (IQR 340-602) and 508 (IQR 370-699) cells/L; Stroke: 443 (IQR 270-590) and 522.5 (IQR 386-798) cells/L; liver disease: 570 (IQR 430-763) and 571 (IQR 424.5-751) cells/L; kidney disease: 511 (IQR 397-695) and 572 (IQR 430-758) cells/L; diabetes: 560 (IQR 384-850) and 510 (IQR 373-701) cells/L and hypertension: 544 (IQR 392-731)) and (549 (IQR 404-735) cells/L, respectively.

Prevalence analyses

4,569 CoLaus participants, 66,492 FIRE participants and 3,230 SHCS participants contributed to the prevalence analyses of different comorbidities. Multimorbidity was present in 26%, 13% and 27% for CoLaus, FIRE and SHCS, respectively.

In unadjusted logistic regression analysis, most comorbidities were less prevalent in FIRE participants compared to CoLaus and SHCS. When comparing the SHCS with CoLaus, the unadjusted prevalence of cardiovascular disease (CVD) (odds ratio (OR) 1.5 [95% Confidence Interval (CI) 1.2-1.9]) and liver disease (1.2 [1.1-1.4]) was increased, and diabetes mellitus (0.60 [0.51-0.71]) and kidney disease (0.76 [0.65-0.88]) were less prevalent among HIV-infected individuals. Adjusted models (only SHCS and CoLaus) showed associations of HIV with all comorbidities (CVD: 2.1 [1.6-2.7]; stroke: 2.3 [1.4-3.6]; hypertension: 1.4 [0.62-0.77]; kidney disease: 1.6 [1.5-2.2]; liver disease: 1.3 [1.5-2.0]) except for diabetes mellitus resulting in an adjusted OR of 1.7 [1.5-2.0] for multimorbidity. **Table 2** shows unadjusted and adjusted results of logistic regression with smoking as an interaction term. We found evidence of an increased prevalence of CVD among smoking individuals irrespective of HIV status. Hypertension, kidney disease and liver disease were associated with HIV-infection but not with smoking. For stroke,

HIV and smoking had an additive effect. Diabetes mellitus was associated with HIV-negative, smoking individuals(**Figure 1** and **Supplementary Table 2**).

Incidence analyses

The 3,230 SHCS and 4,569 CoLaus participants contributed 43,313 person-years of follow-up and an average follow-up of 5.5 years per person. Compared to CoLaus, we observed higher adjusted incidences of hypertension (Incidence rate ratio [IRR] 1.8 [95% CI 1.6-2.1], kidney disease (IRR 1.8 [1.6-2.1]) and liver disease (IRR 1.8 [1.6-2.1]) and a lower rate of diabetes mellitus (IRR 0.72 [0.56-0.93]) among SHCS participants. **Table 3** and **Supplementary Table 3** show the incidence rates and unadjusted and adjusted incidence rate ratios of different comorbidities with smoking as an interaction term. Adjusted analyses showed a different effect of smoking status for the respective comorbidities. As shown in **Figure 2** incident CVD and - to a lesser extent- stroke were not increased among HIV-positive patients when stratified by smoking. Hypertension, kidney and liver disease appeared more frequent among HIV-positive individuals irrespective of smoking. Incidences of all comorbidities except liver disease increased with age in each cohort. Results from sensitivity analyses using continuous age and BMI values instead of stratified variables were similar. The association of HIV with the liver disease remained unchanged after excluding HCV-infected individuals in the SHCS.

Incident multimorbidity was found in 1,147/ 7799 (15%) subjects. Compared to non-smoking CoLaus participants, incident multimorbidity was increased among non-smoking and smoking SHCS participants with IRR of 1.7 [1.4-2.1] and 1.9 [1.5-237], respectively. 80% of multimorbid SHCS participants had two, 19% had three and 1.3% had four or more comorbidities. Among SHCS participants, the most frequent combinations were: hypertension plus liver disease (29%), hypertension plus diabetes (23%) or hypertension plus kidney disease (14%). The most frequent combinations among CoLaus participants were: hypertension plus diabetes mellius (41%), hypertension plus liver disease (14%) and hypertension plus kidney disease (12%).

DISCUSSION

In this comparative analysis of an HIV cohort (SHCS) with a population-based (CoLaus) and a primary care based study (FIRE) in Switzerland, we found evidence for an increased prevalence and incidence of co- and multimorbidity among Swiss HIV-positive persons. The prevalence and incidence of CVD was similar among HIV-positive and -negative patients when stratified by smoking status. There was an excess prevalence and incidence among HIV-positive individuals for hypertension, kidney and liver disease that was independent of smoking. For incident stroke, HIV and smoking appeared to have an additive effect. We did not find evidence for an increased prevalence or incidence of diabetes mellitus associated with HIV-infection or smoking.

The effect of HIV on CVD and stroke disappears after adjustment for BMI and smoking. The comparison of our findings with published literature is difficult because either combined cardiovascular endpoints, acute myocardial infarction only, or separated individual components of CVD were reported. Most importantly, adjustment for smoking and BMI is lacking in many studies [8, 9, 14, 16, 20]. However, our results are in line with recent studies. Rasmussen et al [21] investigated HIV-infected individuals with incident mycocardial infarction from the Danish HIV Cohort Study and compared them to population controls matched on age and gender. They found higher rates of mycocardial infarction in smoking individuals irrespective of HIV status (HIV+non smoking: IRR, 1.01 [95% CI 0.41–2.54]; HIV+ previous and current smokers: IRR, 1.78; [95% CI, .75–4.24] and aIRR, 2.83; 95% CI, [1.71–4.70]). The Veterans aging Cohort primarily investigated the age at, and the risk of incident diagnosis of myocardial infarction, kidney disease and non-AIDS defining cancer. Althoff et al did not find a difference in the age at diagnosis of these age-associated diseases compared with HIV-negative individuals again challenging the concept of premature aging among HIV patients [22]. Our results of increased risks of kidney and liver disease but not of diabetes mellitus among HIV-positive individuals are congruent with published studies [9, 12, 15-18, 20]. Findings regarding an association of hypertension with HIV have been inconsistent: while the AGE$_h$IV study in the Netherlands [17] and our study found strong associations of HIV with hypertension, other studies reported no [15, 20] or even negative associations of HIV [9] with hypertension.

Finding adequate HIV-negative control groups to identify the independent effect of HIV on age-related comorbidities is challenging. The approaches differ from study to study and may contribute to the heterogeneity of observed results. Some studies have included HIV-negative persons from the same healthcare plan [9, 12, 13], same clinics [8, 17], focused on specific risk groups [15], used individual administrative data from the region [11, 16, 18, 20, 21] or used published data from the general population [14]. In our study, CoLaus, a well-documented prospective HIV-negative cohort with validated endpoints contributed to prevalence and incidence analyses and FIRE, a large patient registry from private physicians contributed to prevalence analyses. Because participants in CoLaus likely are a selection of motivated health-seeking persons the absence of an increased CV risk in our study, when comparing SHCS and CoLaus participants is noteworthy. FIRE participants, on the other hand, are followed by general practicioners, and thus may be expected to be healthier, which may explain the lower prevalence of multimorbidity in FIRE.

Several limitations should be noted: we were unable to include some important conditions such as cancer, osteoporosis and pulmonary disease. There might be important lifestyle and socioeconomic demographics differences among comparator groups. Hence we excluded injecting drug users because of significant imbalances between the cohorts and the resulting confounding. Underreporting of a history of IDU in SHCS participants with other known risk factors for HIV is possible. ALT elevations may be transient in nature, and hence it might not be appropriate to take ALT elevations as a proxy for “liver disease”. However, recent literature indicates that high ALT levels are associated with a higher risk of liver-related mortality and diabetes [32]. As a condition for incidence analyses, we required that participants must have survived at least six years. There is no formal record linkage with other hospitals and hence we cannot exclude that information on comorbidities is not complete. 300/3998 (7.5%) SHCS participants and 184/6122 (3%) CoLaus participants died in 2003-2011. Among the 300 SHCS participants who died, 20 (6%) died from a cardiovascular event. SHCS participants had a median of 9 follow-up visits , whereas CoLaus participants had only one follow-up visit. Therefore

we can't exclude a differential recall bias. Finally, the multivariable analyses were adjusted for a small number of shared variables only and therefore residual confounding cannot be excluded.

In our study we have identified associations of HIV with increased risks of hypertension, kidney and liver disease unlike CVD, where the risk is associated with smoking. It remains to be shown whether these associations with HIV are due to direct viral or immunological mechanisms, co-infections (e.g. viral hepatitis, cytomegalovirus), or antiretroviral treatment [33]. In this respect, cohort studies play an important role in pointing basic research to relevant areas and provide phenotypes and biological samples. It is obvious, however, that multimorbidity is a very heterogeneous composite endpoint with varying causes which require different approaches for prevention. In conclusion, from a clinical perspective, our results suggest that emphasis should be given to smoking cessation and lifestyle interventions. Further, blood pressure and kidney as well as liver function should be carefully monitored among HIV-patients keeping in mind the increasing risk of drug-drug interactions with increasing polypharmacy.

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BH has received travel grants from Gilead Sciences.

PET's institution has received advisory fees from MSD and honoraria from ViiV.

PMV: no conflict of interest

GW received an unrestricted grant from GlaxoSmithKline to build the CoLaus study.

MP: no conflicts of interest

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AUTHORS' CONTRIBUTIONS STATEMENT

Barbara Hasse had full access to all the data of the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. Barbara Hasse and Bruno Ledergerber designed the study; Barbara Hasse wrote the first draft; and Barbara Hasse, Philip Tarr and Bruno Ledergerber wrote the final version of the manuscript. Bruno Ledergerber, Pedro Marques Vidal and Fabio Valeri analysed the data. All investigators contributed to data collection and interpretation of the data, reviewed drafts of the manuscript, and approved the final manuscript.

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FIGURE LEGENDS

Figure 1 Prevalence of comorbidities derived from logistic regression analyses adjusted for age, sex, BMI and smoking as an interaction term among 3,230 SHCS and 4,569 CoLaus participants. Non-smoking participants of CoLaus formed the reference group.

Abbreviations: SHCS; Swiss HIV Cohort Study, CoLaus; Cohorte Lausannoise

Figure 2 Incidence rate ratios of comorbidities derived from poisson regression analyses adjusted for age, sex, BMI and smoking as an interaction term among 3,230 SHCS and 4,569 CoLaus participants.

Non-smoking participants of CoLaus formed the reference group.

Abbreviations: SHCS; Swiss HIV Cohort Study, CoLaus; Cohorte Lausannoise

Table 1 Characteristics of 74,291 participants, stratified by cohort

Variables	Cohorts						
	CoLaus 2009-2011		FIRE[1] 2009-2011		SHCS 2009-2011		*P* value[2]
Participants, n (%)	4,569	(6)	66,492	(90)	3,230	(4)	-
Female, n (%)	2,450	(54)	34,968	(53)	607	(19)	< 0.001
Age, median years (IQR)	57	(49-67)	59	(49-72)	50	(45-58)	< 0.001
Smoking, ever, n (%)	2,725	(60)	-		2,166	(68)	< 0.001
Smoking, current, n (%)	989	(22)	-		1,179	(37)	< 0.001
BMI, kg/m^2, median (IQR)	26	(23-29)	27	(24-30)	24	(22-26)	< 0.001
BMI groups, n (%)							< 0.001
underweight	71	(2)	168	(0)	153	(5)	
normal	1,929	(42)	3,853	(6)	1,879	(58)	
overweight	1,778	(39)	4,945	(7)	969	(30)	
obese	791	(17)	3,384	(5)	2249	(7)	
missing	0	(0)	54,142	(81)	0	(0)	

[1]FIRE: Information on smoking is missing and BMI is available only for 12,350 FIRE participants.

[2] *P*-values from 2x3 chi-square tests (categorical variables) and Kruskal Wallis tests (continuous variables)

Abbreviations: vs, versus; BMI, body mass index; IQR, interquartile range; OR, Odds ratio; CI, confidence interval; SHCS, Swiss HIV Cohort Study; CoLaus, Cohorte Lausannoise; FIRE project, Family Medicine ICPC-Research using Electronic Medical Records.

Table 2 Numbers of prevalent comorbidities, stratified by cohort. Unadjusted and adjusted results of logistic regression analyses with smoking as an interaction term

Cohort	All events	Hypertension	Liver disease	Diabetes mellitus	Kidney disease	Cardiovasc. disease	Stroke	Multimorbidity
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
CoLaus non-smoking	1,844 (100)	842 (46)	298 (16)	167 (9)	207 (11)	38 (2)	17 (1)	373 (20)
CoLaus smoking	2,725 (100)	1,296 (48)	451 (17)	358 (13)	273 (10)	114 (4)	34 (1)	647 (24)
FIRE	66,492 (100)	22,206 (33)	- [1]	4500 (7)	509 (1)	2407 (4)	699 (1)	5661 (9) [1]
SHCS non-smoking	1,064 (100)	515 (48)	212 (20)	89 (8)	102 (10)	33 (3)	14 (1)	233 (22)
SHCS smoking	2,166 (100)	941 (43)	405 (19)	146 (7)	161 (7)	126 (6)	37 (2)	448 (21)
Unadjusted logistic regression		**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
CoLaus non-smoking		1	1	1	1	1	1	1
CoLaus smoking		1.1 (0.96-1.2)	1.0 (0.88-1.2)	1.5 (1.2-1.8)	0.88 (0.73-1.1)	2.1 (1.4-3.0)	1.4 (0.76-2.4)	1.2 (1.1-1.4)
FIRE		0.60 (0.54-0.65)	-	0.73 (0.62-0.86)	0.06 (0.05-0.07)	1.8 (1.3-2.5)	1.1 (0.70-1.9)	0.59 (0.51-0.67) [1]
SHCS non-smoking		1.1 (0.96-1.3)	1.3 (1.1-1.6)	0.92 (0.70-1.2)	0.84 (0.65-1.1)	1.5 (0.95-2.4)	1.4 (0.70-2.9)	1.1 (0.92-1.3)
SHCS smoking		0.91 (0.81-1.0)	1.2 (1.0-1.4)	0.73 (0.58-0.91)	0.64 (0.51-0.79)	2.9 (2.0-4.2)	1.9 (1.0-3.3)	1.0 (0.88-1.2)
Adjusted logistic regression [2]		**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
CoLaus non-smoking		1	1	1	1	1	1	1
CoLaus smoking		1.0 (0.89-1.1)	0.97 (0.82-1.1)	1.3 (1.1-1.6)	0.96 (0.79-1.2)	1.8 (1.2-2.7)	1.3 (0.73-2.4)	1.1 (0.98-1.3)
FIRE [2]		-	-	-	-	-	-	-
SHCS non-smoking		1.4 (1.2-1.7)	1.3 (1.0-1.6)	1.0 (0.78-1.4)	1.6 (1.2-2.2)	1.7 (1.0-2.8)	1.9 (0.91-4.1)	1.5 (1.2-1.8)
SHCS smoking		1.4 (1.2-1.6)	1.2 (1.0-1.5)	1.0 (0.79-1.3)	1.5 (1.1-1.9)	4.1 (2.7-6.2)	3.2 (1.7-6.2)	1.7 (1.4-2.0)

Female sex	0.69	(0.62-0.77)	0.85	(0.74-0.97)	0.42	(0.35-0.51)	1.8	(1.5-2.2)	0.45	(0.33-0.60)	0.75	(0.47-1.2)	0.69	(0.61-0.79)
Agegroup 50 65y[3]	2.1	(1.9-2.3)	1.0	(0.90-1.2)	2.6	(2.0-3.2)	2.9	(2.2-3.7)	4.6	(3.0-7.3)	3.5	(1.6-7.3)	3.4	(2.7-4.2)
Agegroup +65y[3]	5.2	(4.5-5.9)	0.61	(0.51-0.73)	5.5	(4.3-7.0)	9.0	(7.0-12)	15	(1.2-1.9)	16	(7.9-34)	12	(10-16)
Normal weight[4]	1.4	(1.0-1.9)	0.83	(0.56-1.2)	1.2	(0.57-2.7)	0.60	(0.39-0.91)	0.94	(0.46-1.9)	1.7	(0.40-7.1)	0.84	(0.53-1.3)
Overweight[4]	2.7	(2.0-3.7)	1.5	(1.0-2.2)	2.9	(1.3-6.2)	0.78	(0.51-1.2)	1.1	(0.53-2.2)	1.5	(0.34-6.3)	1.5	(0.94-2.4)
Obese[4]	6.2	(4.4-8.6)	2.9	(1.9-4.3)	8.3	(3.8-18)	0.85	(0.54-1.3)	1.6	(0.74-3.3)	1.8	(0.39-8.0)	3.8	(2.4-6.0)

Adjusted logistic regression models were adjusted for all variables listed.

[1] There is only limited information on liver endpoints available in FIRE. Therefore we do not provide the liver endpoint for FIRE and the multimorbidity endpoint for FIRE includes no liver disease.

[2] Reference group: non-smoking participants from CoLaus. FIRE was omitted in multivariable models due to missing information on smoking and limited avilability of BMI values

[3] Reference group: 35-49 year old participants

[4] Reference group: underweight participants

Abbreviations: cardiovasc, cardiovascular; vs, versus; y; year old; OR, Odds ratio; CI, confidence interval; SHCS, Swiss HIV Cohort Study; CoLaus, Cohorte Lausannoise; FIRE project, Family Medicine ICPC-Research using Electronic Medical Records.

Table 3 Numbers of incident comorbidities, stratified by cohort. Unadjusted and adjusted results of poisson regression analyses with smoking as an interaction term

Comorbidities among cohort participants	**Hypertension IR (95% CI)**	**Liver disease IR (95% CI)**	**Diabetes mellitus IR (95% CI)**	**Kidney disease IR (95% CI)**	**Cardiovasc. disease IR (95% CI)**	**Stroke IR (95% CI)**	**Multimorbidity IR (95% CI)**
CoLaus non-smoking	26 (22-30)	15 (13-18)	8.5 (6.8-11)	8.2 (6.6-10)	3.5 (2.6-4.9)	1.4 (0.81-2.3)	23 (20-26)
CoLaus smoking	31 (28-35)	13 (11-15)	13 (11-15)	9.0 (7.5-11)	7.0 (5.7-8.4)	1.9 (1.4-2.8)	32 (29-35)
SHCS non-smoking	49 (42-56)	29 (25-34)	6.0 (4.3-8.3)	13 (10-16)	2.6 (1.6-4.3)	1.1 (0.54-2.4)	30 (26-35)
SHCS smoking	47 (41-52)	26 (23-30)	5.6 (4.3-7.1)	11 (8.8-13)	5.2 (4.0-6.7)	2.0 (1.3-3.0)	38 (25-31)
Unadjusted poisson regression	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**
CoLaus non-smoking	1	1	1	1	1	1	1
CoLaus smoking	1.2 (0.98-1.4)	0.84 (0.67-1.1)	1.5 (1.2-2.0)	1.1 (0.82-1.4)	2.0 (1.1-2.9)	1.4 (0.75-2.7)	1.4 (1.2-1.6)
SHCS non-smoking	1.9 (1.5-2.3)	1.9 (1.5-2.4)	0.71 (0.47-1.0)	1.5 (1.1-2.1)	0.74 (0.41-1.3)	0.82 (0.33-2.0)	1.3 (1.1-1.6)
SHCS smoking	1.8 (1.5-2.2)	1.7 (1.4-2.1)	0.66 (0.47-0.91)	1.3 (0.96-1.7)	1.5 (0.96-2.2)	1.4 (0.74-2.8)	1.2 (1.0-1.4)
Adjusted poisson regression [1]	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**
CoLaus non-smoking [2]	1	1	1	1	1	1	1
CoLaus smoking	1.1 (0.92-1.4)	0.84 (0.67-1.1)	1.4 (1.0-1.8)	1.2 (0.89-1.6)	1.7 (1.2-2.5)	1.3 (0.71-2.6)	1.3 (1.1-1.6)
SHCS non-smoking	1.9 (1.5-2.4)	1.9 (1.5-2.4)	0.81 (0.54-1.2)	2.8 (2.0-4.0)	0.83 (0.45-1.5)	1.1 (0.44-3.0)	1.7 (1.1-2.1)
SHCS smoking	2.0 (1.6-2.4)	1.7 (1.4-2.2)	0.93 (0.65-1.3)	2.6 (1.9-3.5)	2.0 (1.2-3.1)	2.3 (1.1-4.9)	1.9 (1.5-2.3)
Female sex	0.65 (0.56-0.76)	1.1 (0.91-1.3)	0.52 (0.41-0.67)	1.5 (1.2-1.9)	0.44 (0.31-0.61)	0.72 (0.42-1.2)	0.70 (0.55-0.88)
Agegroup 50 65y [3]	1.7 (1.5-1.9)	0.82 (0.69-0.97)	2.1 (1.6-2.6)	3.0 (2.3-3.8)	4.61 (2.8-5.9)	5.0 (2.5-9.7)	1.8 (1.43-2.2)
Agegroup +65y [3]	2.4 (2.0-3.0)	0.32 (0.22-0.47)	2.4 (1.8-3.3)	6.7 (5.0-8.9)	10 (6.9-16)	14 (6.6-28)	2.6 (1.9-3.5)
Normal weight [4]	1.1 (0.75-1.7)	1.1 (0.68-1.9)	3.4 (0.47-25)	0.68 (0.39-1.2)	1.4 (0.44-4.4)	0.56 (0.17-1.8)	1.6 (0.69-3.5)
Overweight [4]	1.8 (1.1-2.7)	1.6 (0.93-2.6)	10 (1.4-74)	0.82 (0.47-1.4)	1.4 (0.43-4.4)	0.58 (0.17-2.0)	2.2 (0.97-5.0)

Obese [4]	2.5	(1.6-4.0)	2.1	(1.2-3.6)	25	(3.4-178)	1.0	(0.55-1.8)	2.2	(0.68-7.3)	0.73	(0.20-2.7)	3.4	(1.5-7.9)

[1] Poisson regression models were adjusted for all variables listed.

[2] Reference group: non-smoking participants from CoLaus.

[3] Reference group: 35-49 year old participants

[4] Reference group: underweight participants

Abbreviations: IR, Incidence rate per 1000 person years of follow-up; IRR, Incidence rate ratio; CI, confidence interval; y; year old; SHCS, Swiss HIV Cohort Study; CoLaus, Cohorte Lausannoise

Figure 1

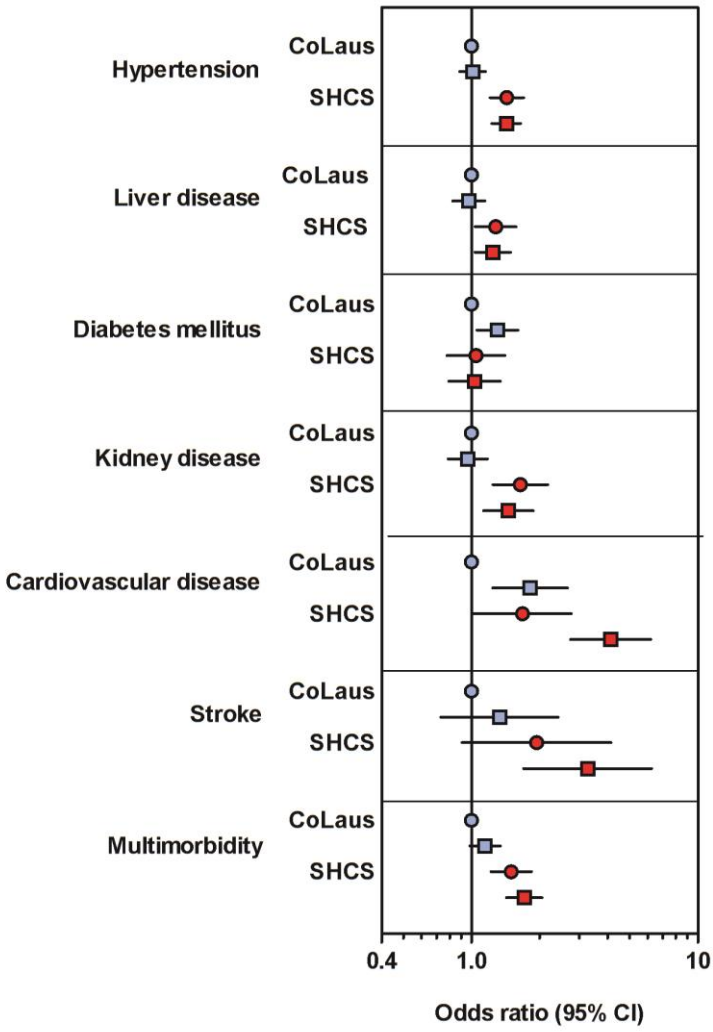

Figure 2