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Low physical function as a risk factor for incident diabetes mellitus and insulin resistance

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Abstract

Data from 1790 HIV-infected and uninfected men in the Multicenter AIDS Cohort Study (MACS) were analyzed to evaluate relationships between physical function, incident diabetes mellitus (DM) and insulin resistance among HIV-infected and -uninfected men. DM was defined in two ways, using less stringent and more stringent criteria. The 10-item Physical Functioning Scale from the Short Form-36 Health Survey measured baseline physical function. Cumulative DM incidence was highest among HIV-uninfected and HIV-infected men with low physical function. Physical function was a risk factor for DM in HIV-uninfected men and remained so after controlling for BMI, DM family history and race. Among HIV-infected men, physical function was an independent risk factor for DM using the less stringent diabetes definition. This study supports our previous findings that low physical function is an important risk factor for DM in the MACS cohort.

Keywords

AIDS; diabetes mellitus; HIV; insulin resistance; physical function

Individuals living with HIV infection now have a longer life expectancy than in the past, albeit one faced with comorbidities common in the general population that might occur prematurely owing to infection with HIV [1]. Diabetes mellitus (DM) and insulin resistance

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(IR) are two such conditions. To date, the etiology of DM and IR in HIV infection remains unclear. Traditional risk factors such as advancing age [2,3] and higher BMI [2,3] have consistently been reported, and HIV-specific risk factors such as HAART use [4,5] are thought to play a role.

Physical activity is an accepted intervention for the prevention of DM in the general population [6–14] and low physical activity predicts incidence of new-onset DM [13,15]. However, its role as a contributing factor to the prevention of DM has not been described in most studies of HIV-infected populations [2,16–19].

We previously demonstrated that low physical function was associated with DM and IR in a cohort of HIV-infected and -uninfected men from the Pittsburgh component of the Multicenter AIDS Cohort Study (MACS) [20]. However, men with pre-existing diabetes were not excluded and a temporal relationship could not be established. In addition, we were unable to assess the impact of ART on DM incidence.

Physical activity and physical function are related, yet distinct. Physical activity is defined as any voluntary movement produced by the skeletal muscles that results in increased energy expenditure [21], whereas physical function is defined as one's ability to carry out various activities that require physical capability, ranging from self-care to more vigorous activities that require increasing degrees of mobility, strength or endurance [101].

The current study addresses important limitations of our prior study [20] by using incident diabetes cases from the MACS cohort to assess the independent contribution of physical function to the onset of DM and IR in HIV-infected and -uninfected men. The effect of HAART on this relationship was assessed. Finally, we compared the incidence rates of diabetes among HIV-infected and -uninfected men with low physical function to men with high physical function.

Methods

Study participants

Participants were from the MACS. The MACS is an ongoing NIH-supported (Johns Hopkins University, MD, USA; Northwestern University, IL, USA; University of California, CA, USA; University of Pittsburgh, PA, USA) prospective cohort study of the natural history of HIV infection. It was designed to gather information on the epidemiology, virology, immunology and pathogenesis of HIV. Homosexual and bisexual men aged 18 years without AIDS were recruited from local communities in three recruitment cycles (April 1984–March 1985; April 1987–September 1991; October 2001–August 2003). Briefly, the MACS follows a 6-month visit schedule and involves detailed data collection regarding medical history, physical examination results and specimen collection. HIV seropositivity was determined by a positive ELISA confirmed by western blot. Fasting glucose levels were measured by the combined hexokinase/glucose-6-phosphate dehydrogenase method (coefficient of variation: 1.8%) [22]. Fasting insulin levels were measured using a radioimmunoassay technique (coefficient of variation: 2.6%; Linco Research, St Charles, MO, USA). This cut-off point was based on the published normal range for the insulin assay used. Both assays used serum samples that had been stored at –80°C and were processed at a central laboratory (Heinz Laboratory, PA, USA). These fasting measures of insulin sensitivity are well correlated with the euglycemic hyperinsulinemic clamp [23]. Institutional review boards at each site approved the protocol, and each participant provided informed consent. Further detail can be found elsewhere [24,25].

Our analysis includes data collected after implementation of the MACS Metabolic Study in April 1999 when serum samples (8-h fasting) were added to measure glucose and insulin levels. The first visit at which a participant had such testing was defined as his baseline visit. Of 2800 eligible men, 193 (6.9%) had pre-existing diabetes at baseline and were excluded. Pre-existing diabetes was defined as a fasting glucose concentration of ≥ 126 mg/dl, self-reported DM or use of an anti-diabetic medication at baseline. An additional 817 participants did not have any fasting serum samples and were excluded. Therefore, the final sample includes 1790 men (1023 HIV uninfected and 767 HIV infected) without baseline diabetes.

End point ascertainment: diabetes mellitus & insulin resistance

Diabetes was defined at each biannual visit from 1 April 1999 to 2 April 2008. The date of incident DM was defined as the mid point between the last visit with a fasting glucose of <126 mg/dl and the date of the first visit with a fasting glucose measurement of ≥ 126 mg/dl. Incident DM was defined in two ways. The first definition, consistent with our previous work [26], was a single fasting glucose level of ≥ 126 mg/dl, self-reported DM or use of an antidiabetic medication. The second, more stringent definition is similar to the standard diabetes definition and required two consecutive 6-month visits with a fasting glucose level of ≥ 126 mg/dl, one visit with a glucose level of ≥ 126 mg/dl and self-reported initiation of antidiabetic medication or self-reported DM.

Insulin resistance was estimated using the homeostasis model assessment (HOMA): (fasting insulin [μ -units(U)/ml] $\times$ fasting glucose [mmol/l]/22.5) [27] in men with fasting blood glucose <126 mg/dl. IR was defined by the highest HOMA quintile ($\geq 4.3 \mu$ U/ml $\times$ mmol/l men with pre-existing IR were excluded from incident IR analysis).

Physical function assessment

The 10-item Physical Functioning Scale (PF-10) from the Medical Outcomes Study Short Form-36 (SF-36®) Health Survey served as the physical function measure. The SF-36 is one of the most widely used health-related quality of life instruments and consistently demonstrates high levels of reliability and validity [28–30]. In the MACS cohort, internal consistency estimates ranged from 0.85 to 0.86 depending on the SF-36 scale used [31].

This study includes data from PF-10 questionnaires administered at each biannual visit from 1 April 1999 to 31 March 2005 and then annually on even visit dates. Participants were asked the following question regarding ten physical activities that might be undertaken in a typical day “Does your health now limit you in these activities? If so, how much?” Participants chose between “Yes, limited a lot”, “Yes, limited a little” or “No, not limited at all” for the following activities: vigorous (running, lifting heavy objects, participating in strenuous sports); moderate (moving a table, pushing a vacuum cleaner, bowling, playing golf); lifting or carrying groceries; climbing several flights of stairs; climbing one flight of stairs; bending, kneeling or stooping; walking more than a mile; walking several blocks; walking one block; and bathing or dressing yourself. Each item was scored on a 0–100 scale as follows: 100 = not limited at all; 50 = limited a little; and 0 = limited a lot, based on the Rand Corporation (RAND) scoring method [32]. A mean score of the ten activities was calculated to determine an overall score ranging from 0 to 100, with a score of 100 indicating that a participant’s health did not limit his ability to complete physical activity. A lower score indicated lower physical function. For use in Kaplan–Meier plots, baseline physical function scores were categorized as high physical function (>80) and low physical function (≤ 80). A score of 80 was chosen based on the lowest quintile of physical function in the current study population. The baseline physical function score was used in multivariate models as a continuous variable.

Assessment of exposure to ART

Each visit included questions regarding the use of specific ARTs. The definition of HAART followed the Department of Health and Human Services (DHHS)/Kaiser Panel Guidelines and has been described elsewhere [33,34].

Men were classified into the following three groups: HIV uninfected; HIV infected not using HAART; and HIV infected using HAART. The 'HIV infected not using HAART group' combined men who were antiretroviral free ($n = 254$), men using monotherapy ($n = 3$) and men using combination therapy ($n = 22$) at the baseline visit. Combination therapy that which did not meet the DHHS/Kaiser Panel Guidelines for HAART. This classification was chosen because of the small numbers of men using either monotherapy or combination therapy.

Statistical analysis

Statistical analysis software version 9.2 was used for all statistical analyses. χ^2 test and the Student's t-test were used to test for differences in proportions and distributions between HIV serostatus groups and physical function groups. Statistical significance was determined using two-tailed tests with an α of 0.05.

Person-time for each participant was calculated from the date of the baseline visit to the date of onset of DM/IR or to the date of censoring at the last visit free of DM/IR (either because of loss to follow-up or the study end date of 2 April 2008). Incidence rates per 100 person-years (PY) were calculated by dividing the number of DM/IR end points by PY and multiplying by 100.

The association between baseline physical function and incident DM and IR was examined using unadjusted and adjusted hazard ratios (HRs) from the Cox proportional hazards regression model. Univariate Cox regression for each variable was used to determine the association between the variable of interest and incident DM. Baseline physical function, used as a continuous variable, was forced into all models followed by the addition of each significant variable from the univariate analyses, from the most to least significant. Models were run separately for all men combined, HIV-uninfected men and HIV-infected men. The proportional hazard assumption was met based on visual inspection of Kaplan–Meier survival curves.

Results

The baseline characteristics of the 1790 men, of whom 43% were HIV infected, are displayed in Table 1. The mean age of the study population was 43.1 years, 58.2% were white, 31.1% had a family history of diabetes and 66% had a history of smoking. The mean BMI was 25.9 kg/m² and the mean physical function score was 86.0 (standard deviation [SD]: 22.1).

The HIV-infected men were younger, had a lower mean BMI and had lower CD4 counts. The mean baseline physical function score was significantly lower ($p < 0.001$) in HIV-infected men (mean: 83.0; SD: 23.3) compared with HIV-uninfected men (mean: 88.2; SD: 20.8). A greater proportion of HIV-infected men were nonwhite. Mean glucose levels and family history of DM did not differ between HIV serostatus groups; however, mean insulin ($p = 0.0007$) and HOMA levels ($p = 0.0006$) were significantly higher in HIV-infected men.

Table 2 compares men with high and low physical function, stratified by HIV serostatus. Characteristics tended to differ more in HIV-uninfected men compared with the HIV-infected men. Among the HIV-uninfected men, those with low physical function were older

and had higher insulin and HOMA levels. In addition, a greater proportion of men with low physical function were nonwhite. BMI, fasting glucose concentrations and family history of DM did not differ between the groups. In the HIV-infected men, race, CD4 count and proportion with AIDS differed by physical function level. A greater proportion of men with low physical function were nonwhite. HIV-infected men with low physical function had lower CD4 counts and a higher proportion had AIDS.

Incident DM varied substantially depending on the diabetes definition used. Of the 1790 men, 73 developed diabetes (41 HIV uninfected and 32 HIV infected) using the more stringent definition. When using the less stringent definition, 238 (126 HIV uninfected and 112 HIV infected) incident cases of diabetes were observed. The incidence rate for DM among all men was 0.943 per 100 PY using the more stringent definition and 3.24 per 100 PY using the less stringent definition. Among HIV-uninfected men, the rate was 0.896 per 100 PY using the more stringent definition and 2.89 per 100 PY with the less stringent definition. Finally, among HIV-infected men, use of the more stringent definition yielded a rate of 1.04 per 100 PY compared with 3.75 per 100 PY using the less stringent definition. Similarly, the DM definition used strongly influenced the incidence rates for HIV-infected men based on HAART status. HIV-infected men using HAART had an incidence rate range of 1.0 per 100 PY using the more stringent definition compared with 2.48 per 100 PY using the less stringent definition. The HIV-infected men not using HAART had a rate of 1.1 per 100 PY with the more stringent definition and 3.97 per 100 PY with the less stringent definition.

Figure 1 presents the percentage of men free of DM stratified by HIV status and physical function for both definitions of DM. The cumulative incidence of DM was higher in all four groups when the less stringent definition was used. Regardless of the definition used, the cumulative DM incidence was highest among HIV-uninfected men with low physical function and next highest in HIV-infected men with low physical function.

In the univariate analysis (data not shown), lower physical function score, higher BMI, older age, nonwhite race and family history of DM were found to be individually associated with diabetes using both definitions. Among HIV-uninfected men, lower physical function, BMI and family history of DM were associated with DM when the more stringent definition was used. When using the less stringent definition, age, race and CD4 cell count were also associated with DM. Among HIV-infected men, only age and BMI were significant risk factors. Neither physical function nor HAART use was significantly associated with DM in HIV-infected men using the more stringent definition; however, using the less stringent definition, physical function, race and family history of DM were significantly associated with DM.

Multivariate results are presented in Table 3. When using the more stringent definition, the physical function HR was somewhat diminished after adjustment for BMI, family history of DM and age, but remained a significant risk factor for incident DM (HR: 1.24; 95% CI: 1.04–1.49) in all men. The effect of physical function was no longer significant with the addition of race into the model (HR: 1.14; 95% CI: 0.94–1.38). While the use of the less stringent definition had little effect on the HR for DM when compared with the more stringent definition, physical function remained significant after adjustment for all covariates, including the addition of race to the model (HR: 1.21; 95% CI: 1.08–1.35). The first-order interaction between HIV and physical function was not significant using either definition.

For HIV-uninfected men, adjustment for BMI, family history of DM and race had little effect on the independent effect of physical function on DM incidence (HR: 1.31; 95% CI:

1.02–1.66) using the more stringent definition. After the addition of age, physical function was no longer a significant risk factor; however, the HR was only slightly attenuated (HR: 1.24; 95% CI: 0.96–1.60). Use of the less stringent definition did not change the HR for DM among HIV-uninfected men, yet physical function remained significantly associated with DM in the model with all covariates entered (HR: 1.20; 95% CI: 1.02–1.41).

The choice of DM definition had the greatest impact on HIV-infected men. Using the more stringent definition, physical function was not an independent risk factor for incident DM, and adjustment for BMI, age and race had little effect on the HR. When the less stringent definition was used, the HR increased and physical function was independently associated with DM even after adjustment for BMI and age (HR: 1.23; 95% CI: 1.06–1.44). Although the addition of race to the model slightly decreased the HR, only borderline significance was achieved (HR: 1.16; 95% CI: 1.00–1.38).

Lower physical function, higher BMI, black race and HIV status were significantly associated with incident IR among all men in a univariate analysis. Among HIV-uninfected men, only physical function and BMI were associated with IR. Physical function was not an independent risk factor for IR in HIV-infected men, while older age, higher BMI and HAART use were associated with incident IR.

Adjustment for covariates only minimally decreased the HR for low physical function among all men with incident IR (Table 4). Physical function was associated with IR in univariate analysis (HR: 1.15; 95% CI: 1.04–1.27) but was not significantly associated with IR after adjusting for covariates. Similarly, among HIV-uninfected men, physical function was associated with IR in univariate analysis (HR: 1.20; 95% CI: 1.04–1.38) but the addition of BMI, CD4 count and family history of DM attenuated the physical function HR (HR: 1.01; 95% CI: 0.84–1.22). Finally, physical function was not an independent risk factor for incident IR in HIV-infected men (HR: 1.08; 95% CI: 0.94–1.25).

Discussion

Our finding that lower physical function is a risk factor for incident DM in a large cohort of HIV-uninfected and HIV-infected men is biologically plausible and supports our previous findings [20]. Men with low physical function were more likely to develop diabetes than men with higher physical function, even after adjustment for risk factors such as BMI, family history of DM and age. We observed similar associations between physical function and DM in HIV-uninfected men, but the association was weaker among HIV-infected men, regardless of the DM definition used. Although mean ages differed between groups, these differences could be controlled for through adjustment in the model due to overlapping distributions. The current study expands our previous research [20] by suggesting a temporal relationship between physical function and incident DM, as men with pre-existing DM were excluded. Additionally, we assessed the effect of HAART use on incident DM and utilized a second, more stringent DM definition. Given the strength of previous studies that support the strong correlation of physical function with physical activity [35–40], our results are consistent with the notion that low physical activity is a risk factor for incident DM in HIV-uninfected and -infected men. Although the majority of prior studies did not assess the role of physical function or physical activity as a contributing factor to DM among HIV-infected persons, our results support the Howard *et al.* [41] and Gavrilu *et al.* [42] studies, in which physical inactivity was associated with DM and IR in HIV-infected persons. Our analysis is unique in that we used a prospective design with incident DM cases, in contrast to the cross-sectional designs used in prior studies. We also included HIV-uninfected as well as HIV-infected men, allowing us to assess and control for HIV infection. Finally, we used a

definition of DM consistent with American Diabetes Association criteria [43], while prior studies either used only self-reported DM or did not confirm glucose concentrations.

Our finding that HIV-infected men had lower physical function scores than their HIV-uninfected counterparts supports a recent study of physical frailty in HIV-infected and HIV-uninfected men [44]. However, HIV infection was not found to be a significant risk factor for DM in our study, but was shown to be associated with incident IR in univariate analysis, consistent with our previous study [20]. Similarly, HAART use was not a significant risk factor for DM in our study, but was found to be associated with incident IR. These findings suggest that, early on, pancreatic function may be able to overcome underlying IR caused by HIV or HAART use. This underscores the need for the oral glucose tolerance test or HOMA measurements rather than relying on fasting glucose values in an HIV-infected population with other risk factors. Although the HOMA ($r = -0.820$, $p < 0.0001$) has been found to correlate well with the gold-standard euglycemic clamp technique, it is possible that more sensitive and precise measures of IR might better assess the effect of physical activity on insulin sensitivity in HIV-infected populations [45]. Similarly, the use of fasting plasma glucose rather than the oral glucose tolerance test might have underestimated the incidence of DM, thus limiting our ability to detect associations [46]. HAART use, specifically protease inhibitors [4] as well as cumulative exposure to nucleoside reverse transcriptase inhibitors [47], has been associated with elevated IR markers among HIV-infected individuals. Finally, individual HAART regimens are heterogeneous with respect to effects on glucose metabolism [4]; therefore, using HAART as a drug-exposure class might have reduced the effect of any individual medication or specific medication combinations.

This study emphasizes the impact of diabetes definition on the incidence rates of DM, regardless of HIV infection. The DM incidence rate in our study is lower than that initially published for the MACS [26] when using the more stringent diabetes definition; however, when using the less stringent definition employed in our previous work [26], the incidence rates were similar. We previously reported a rate of 1.4 per 100 PY among HIV-uninfected men compared with our current findings of 0.9–2.9 per 100 PY depending on the definition used. Similarly, for HIV-infected men, the incidence rate of DM using the less stringent definition was comparable to our prior work (1.7 vs 2.5 per 100 PY in HAART-naïve men [26] and 4.7 vs 4.0 per 100 PY in HAART users [26]). The additional requirement of a confirmatory fasting glucose level substantially reduced these incidence rates (1.1 and 1.0 per 100 PY, respectively). Other studies using confirmatory glucose concentrations also report low DM incidence rates [16].

The current study had two main limitations. The number of persons developing DM was smaller than expected because of the stringent case definition that we used. Thus, our power to detect differences might have been reduced, especially in analytic models stratified by HIV status. The secondary analyses using the less stringent definition increased the number of DM events; therefore, our power to detect differences with this more sensitive and less specific definition was increased. We also did not have the power to limit our analysis to men with normoglycemia at baseline; however, mean physical function scores did not significantly differ between men with normoglycemia and men with prediabetes at baseline.

Second, because the MACS never collected physical activity data, we were limited to the use of physical function. Future studies with objective measures of physical activity are required to confirm our results. Numerous studies conducted among HIV-uninfected populations have established that physical activity levels are correlated with physical function performance. Brach *et al.* observed a correlation between pedometer readings and the Functional Status Questionnaire ($r = 0.34$); the Physical Performance Test ($r = 0.41$); and gait speed ($r = 0.52$) [35]. Cross-sectional and prospective studies suggest that low physical

activity is an independent predictor of both measured and self-reported low physical function [35–40]. While similar studies have not yet been conducted in HIV-infected cohorts, Roubenoff and Wilson reported an increase in physical function in HIV-infected patients with wasting who completed a resistance training program [48]. Given these results, it is plausible to suggest that the men in our study with low physical function also had lower physical activity levels compared with men with higher physical function.

Conclusion

To our knowledge, this is the first prospective study to assess the contribution of physical function to incident DM and IR in a cohort that included both HIV-infected and -uninfected men. This study supports our previous findings that self-reported low physical function is an important risk factor for DM in the MACS cohort. These results underscore the clinical relevance of the association between physical function, BMI and DM, particularly as the glucoregulatory benefits (insulin sensitivity) of physical activity in HIV-infected adults have been demonstrated [49,50]. Improved physical function in this population would likely result from an increase in physical activity and a decrease in BMI, two important factors known to reduce the incidence of DM. Although future research using objective physical activity measures is necessary to further elucidate the contribution of low physical activity to DM and IR development in HIV-infected persons, ongoing studies addressing the issues of glucose metabolism in HIV-infected populations should include assessments of physical activity levels.

Future perspective

Over the next decade, clinical trials among HIV-infected populations similar to those completed in HIV-uninfected populations are necessary to establish a casual association between low physical activity and the onset of DM and IR. This will take time. At present, researchers and clinicians are encouraged to consider the potential for a similar benefit in HIV-infected individuals, as demonstrated in the general population. As this relationship becomes more clearly defined, increased physical activity will become an integral part of diabetes prevention and cardiovascular health and management in HIV-infected individuals.

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Executive summary

- Physical activity is an accepted intervention for the prevention of diabetes mellitus (DM) in the general population and low physical activity predicts incidence of new-onset DM.
- We previously demonstrated that low physical function was associated with DM and insulin resistance (IR) in a cohort of HIV-infected and -uninfected men from the Pittsburgh component of the Multicenter AIDS Cohort Study (MACS).
- Data from 1790 HIV-infected and -uninfected men in the MACS were analyzed to evaluate relationships between physical function, incident DM and IR among HIV-infected and -uninfected men.
- Cumulative DM incidence was highest among HIV-uninfected and -infected men with low physical function.
- Physical function was a risk factor for DM in HIV-uninfected men and remained so after controlling for BMI, DM family history and race.
- Among HIV-infected men, physical function was an independent risk factor for DM using the less stringent diabetes definition but not the more stringent diabetes definition.
- Physical function was not an independent risk factor for incident IR in HIV-infected men.
- This study underscores the impact of diabetes definition on the incidence rates of DM, regardless of HIV infection.
- To our knowledge, this is the first prospective study to assess the contribution of physical function to incident DM and IR in a cohort that included both HIV-uninfected and -infected men.
- This study supports our previous findings that self-reported low physical function is an important risk factor DM in the MACS cohort.

Figure 1. Kaplan–Meier survival curve for incident diabetes mellitus among HIV-uninfected and HIV-infected men with high and low physical function at baseline using more stringent (A) and less stringent (B) definitions of diabetes.

Table 1

Characteristics of 1790 men at the index visit in the Multicenter AIDS Cohort Study.

Characteristic	Current study population (n = 1790)	HIV-uninfected (n = 1023)	HIV-infected (n = 767)	p-value
Age in years; mean (range)	43.1 (18.2–82.6)	44.9 (18.2–82.6)	40.6 (19.6–68.9)	<0.001 [†]
White subjects; no. (%)	1042 (58.2)	710 (69.4)	332 (43.3)	<0.001 [†]
BMI [‡]	25.9 (4.4)	26.3 (4.6)	25.4 (4.0)	<0.001 [†]
Glucose level (mg/dl)	89.5 (12.3)	89.3 (11.9)	89.9 (12.7)	0.3
Insulin (μU/ml)	13.5 (10.4)	12.7 (10.5)	14.4 (10.3)	<0.001 [†]
HOMA (μU/ml × mmol/l)	3.1 (2.6)	2.9 (2.5)	3.3 (2.7)	<0.001 [†]
CD4 count (cells/mm ³)	764.1 (362.3)	930.8 (317.1)	540.7 (292.8)	<0.001 [†]
Physical function	86.0 (22.1)	88.2 (20.8)	83.0 (23.3)	<0.001 [†]
Family history of DM; no. (%)	555 (31.1)	300 (29.5)	255 (33.3)	0.2
History of smoking; no. (%)	1163 (66.0)	628 (62.0)	535 (71.4)	<0.0001 [†]

Data are presented as mean (standard deviation) unless otherwise indicated.

[†] p < 0.05 comparing the HIV-uninfected men with the HIV-infected men using the χ^2 test or the Student's t-test, as appropriate.

[‡] Calculated as weight in kilograms divided by the square of the height in meters.

DM: Diabetes mellitus; HOMA: Homeostasis model assessment.

Table 2

Baseline characteristics of men with high (>80) and low (< 80) physical function stratified by HIV serostatus in the Multicenter AIDS Cohort Study.

Characteristic	HIV-uninfected		HIV-infected	
	High physical function (n = 775)	Low physical function (n = 248)	High physical function (n = 461)	Low physical function (n = 286)
Age in years; mean (range)	44.0 (18.2–76.8)	47.7 (20.1–82.6)	40.4 (19.6–68.9)	41.0 (19.6–67.4)
White subjects; no. (%)	570 (73.5)	140 (56.5)	253 (52.6)	79 (27.6)
BMI [‡]	26.2 (4.4)	26.6 (5.0)	25.3 (3.9)	25.4 (4.2)
Glucose level (mg/dl)	89.1 (11.1)	89.9 (14.2)	90.5 (11.8)	88.7 (14.0)
Insulin (μU/ml)	12.1 (10.3)	14.6 (10.8)	14.3 (10.6)	14.7 (9.9)
HOMA (μU/ml × mmol/l)	2.7 (2.4)	3.3 (2.8)	3.3 (2.8)	3.3 (2.5)
CD4 count (cells/mm ³)	913.2 (309.2)	985.6 (335.4)	565.3 (284.0)	499.4 (301.8)
Family history of DM; no. (%)	232 (30.1)	68 (27.6)	158 (32.9)	97 (33.9)
History of smoking; no. (%)	446 (57.6)	182 (76.5)	338 (70.2)	197 (73.5)
AIDS; no. (%)	N/A	N/A	25 (5.2)	43 (15.0)
HAART use; no. (%)	N/A	N/A	406 (84.5)	237 (82.9)

[†] p < 0.05 comparing the HIV-uninfected men with the HIV-infected men using the χ^2 test or the Student's t-test, as appropriate.

[‡] Calculated as weight in kilograms divided by the square of the height in meters.

DM: Diabetes mellitus; HOMA: Homeostasis model assessment; N/A: Not applicable.

Table 3

Cox regression for incident diabetes mellitus in the Multicenter AIDS Cohort Study.

	Stringent diabetes definition[†]		Less stringent diabetes definition[‡]	
	<i>Physical function HR</i>	<i>95% CI</i>	<i>Physical function HR</i>	<i>95% CI</i>
<i>All men</i>				
Model 1 (physical function)	1.34	1.13–1.59	1.34	1.22–1.50
Model 2 (physical function, BMI)	1.24	1.04–1.49	1.30	1.17–1.44
Model 3 (physical function, BMI, DM family history)	1.25	1.04–1.49	1.30	1.17–1.44
Model 4 (physical function, BMI, DM family history, age)	1.24	1.04–1.49	1.30	1.17–1.44
Model 5 (physical function, BMI, DM family history, age, race)	1.14	0.94–1.38	1.21	1.08–1.35
<i>HIV-uninfected men</i>				
Model 1 (physical function)	1.50	1.22–1.83	1.43	1.25–1.63
Model 2 (physical function, BMI)	1.36	1.08–1.73	1.33	1.15–1.56
Model 3 (physical function, BMI, DM family history)	1.36	1.06–1.73	1.33	1.15–1.56
Model 4 (physical function, BMI, DM family history, race)	1.31	1.02–1.66	1.29	1.11–1.50
Model 5 (physical function, BMI, DM family history, race, age)	1.24	0.96–1.60	1.22	1.04–1.44
Model 6 (physical function, BMI, DM family history, race, age, CD4 count)	1.23	0.94–1.63	1.20	1.02–1.41
<i>HIV-infected men</i>				
Model 1 (physical function)	1.12	0.85–1.50	1.23	1.06–1.44
Model 2 (physical function, BMI)	1.08	0.80–1.47	1.22	1.06–1.41
Model 3 (physical function, BMI, age)	1.10	0.82–1.50	1.23	1.06–1.44
Model 4 (physical function, BMI, age, race)	1.02	0.76–1.38	1.16	1.00–1.38

Physical function HR is per 20-point decrease.

[†]DM defined using a confirmatory fasting glucose >126 mg/dl.[‡]DM defined using a single fasting glucose >126 mg/dl.

DM: Diabetes mellitus; HR: Hazard ratio.

Table 4

Cox regression for incident insulin resistance in the Multicenter AIDS Cohort Study.

	Physical function HR	95% CI
All men		
Model 1 (physical function)	1.15	1.04–1.27
Model 2 (physical function, BMI)	1.09	0.96–1.22
Model 3 (physical function, BMI, age)	1.07	1.00–1.20
Model 4 (physical function, BMI, age, DM family history)	1.15	1.02–1.30
Model 5 (physical function, BMI, age, DM family history, HIV)	1.14	1.00–1.30
HIV-uninfected men		
Model 1 (physical function)	1.20	1.04–1.38
Model 2 (physical function, BMI)	1.00	0.84–1.17
Model 3 (physical function, BMI, CD4 count)	1.01	0.84–1.17
Model 4 (physical function, BMI, CD4 count, DM family history)	1.01	0.84–1.22
HIV-infected men		
Model 1 (physical function)	1.08	0.94–1.25
Model 2 (physical function, age)	1.07	0.94–1.25
Model 3 (physical function, age, BMI)	1.11	0.96–1.30
Model 4 (physical function, age, BMI, HAART)	1.10	0.94–1.27

Insulin resistance was defined as the highest homeostasis model assessment quintile in our data ($4.3 \mu\text{U/ml} \times \text{mmol/l}$).

Physical function HR is per 20-point decrease.

DM: Diabetes mellitus; HR: Hazard ratio.