

Effect of changes in body mass index on the risk of cardiovascular disease and diabetes mellitus in HIV-positive individuals: results from the D:A:D study

Kathy Petoumenos PhD¹, Locadiah Kuwanda MMed Statistics¹, Lene Ryom MD PhD², Amanda Mocroft PhD³, Peter Reiss MD PhD⁴, Stephane De Wit MD⁵, Christian Pradier MD⁶, Andrew Phillips PhD³, Camilla I Hatleberg MD PhD², Antonella d'Arminio Monforte MD PhD⁷, Rainer Weber MD DMSc MPH⁸, Caroline A Sabin PhD³, Jens Lundgren MD DMSc PHD², Matthew G Law PhD¹ for the D:A:D Study group

¹The Kirby Institute, UNSW Sydney, Sydney NSW Australia

²Rigshospitalet, University of Copenhagen, CHIP, Department of Infectious Diseases, Section 2100, Centre for Cardiac, Vascular, Pulmonary and Infectious Diseases, Copenhagen, Denmark

³Centre for Clinical Research, Epidemiology, Modelling and Evaluation (CREME), Institute for Global Health, University College London, London, United Kingdom

⁴Amsterdam University Medical Centers (location AMC), Dept. of Global Health and Div. of Infectious Diseases, University of Amsterdam, Amsterdam, The Netherlands and HIV Monitoring Foundation, Amsterdam, The Netherlands

⁵Division of Infectious Diseases, Saint Pierre University Hospital, Université Libre de Bruxelles, Brussels, Belgium

⁶Dept. of Public Health, Nice University Hospital, Nice, France

⁷Dipartimento di Scienze della Salute, Clinica di Malattie Infettive e Tropicali, Azienda Ospedaliera-Polo Universitario San Paolo, Milan, Italy

⁸Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland

Corresponding author: A/Professor Kathy Petoumenos, The Kirby Institute, UNSW Sydney, Sydney Australia, NSW 2052, Email: kpetoumenos@kirby.unsw.edu.au

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Abstract:**Background**

Weight gain is common among people with HIV once antiretroviral treatment (ART) is commenced. We assess the effect of changes in body mass index (BMI), from different baseline BMI levels, on the risk of cardiovascular disease (CVD) and diabetes mellitus (DM).

Methods

D:A:D participants receiving ART were followed from their first BMI measurement to the first of either CVD or DM event, or earliest of 1/2/2016 or 6 months after last follow-up. Participants were stratified according to their baseline BMI, and changes from baseline BMI were calculated for each participant. Poisson regression models were used to assess the effects of changes on BMI on CVD or DM events.

Results

There were 2,104 CVD and 1,583 DM events over 365,287 and 354,898 person years (rate: CVD 5.8/1000 (95% CI 5.5–6.0); DM 4.5/1000 (95% CI 4.2 – 4.7)). Participants were largely male (74%), baseline mean age of 40 years and median BMI of 23.0 (IQR: 21.0-25.3). Risk of CVD by change in BMI from baseline, stratified by baseline BMI strata showed little evidence of an increased risk of CVD with an increased BMI in any baseline BMI strata. An increase in BMI was associated with an increased risk of DM across all baseline BMI strata.

Conclusions

While increases in BMI across all levels of baseline BMI were not associated with an increased risk of CVD, such changes were consistently associated with increased risk of DM. There was also some evidence of an increased risk of CVD with a decrease in BMI.

Key words: HIV, Antiretroviral treatment, BMI, cohort

Introduction

Weight gain is common among people with HIV once antiretroviral treatment (ART) is commenced and has become increasingly prevalent among people with HIV receiving more contemporary ART agents. There is growing evidence that some of the excess weight gain recently observed may be attributed to the use of integrase inhibitors (INSTIs), namely dolutegravir (DTG) and bictegravir¹⁻⁴. These effects may be enhanced with the concomitant use of tenofovir alafenamide (TAF), implicating not only the INSTI class but also the nucleoside reverse transcriptase inhibitor (NRTI) drug class⁵. Although the initial weight gained following ART commencement may be attributed to the 'return to health' phenomena, excess weight gain can lead to elevated risk of many different comorbidities^{6,7} and multimorbidity⁸. This may be compounded by poorer lifestyle behaviours including poor diet and insufficient exercise especially within the context of an increasing obesity epidemic globally.

Increases in body mass index [(BMI) (weight (kg)/height (m²))] have been associated with an increased risk for several serious clinical outcomes including diabetes mellitus (DM) and cardiovascular disease (CVD) in the general population^{9,10} and among people with HIV¹¹⁻¹³. At the same time, being underweight or having a low BMI have also been associated with increased mortality in the general population¹⁴, and low BMI has been associated with CVD, cancer and mortality among people with HIV¹³.

Previously shown in the D:A:D cohort, a gain in BMI in the first year post ART initiation was associated with an increased risk of CVD, but only in those with pre-ART BMI in the normal range (18.5-25 kg/m²). In contrast, among people with HIV with BMIs in the lower

and higher categories, a gain in BMI over the first year post ART did not appear to increase the risk of CVD. In a follow-up study from the D:A:D , a non-linear association with latest (time updated) BMI and CVD, cancer and all-cause mortality was reported, with both low (<18.5 / <20 kg/m²) and very-high (>30 kg/m²) BMI being associated with increased risk of these events¹³. In both studies, however, the relationship with BMI and DM was linear, with risk of incident DM increasing linearly with increases in BMI, whether assessed as short-term change in BMI or time updated (recent) BMI^{13,15}. A study by the Veterans Aging cohort study (VACS), have also report a linear association with increasing weight gain and incident DM¹⁶.

In this study we aim to assess the effect of changes in BMI, from different baseline BMI levels, on the incidence of centrally validated CVD and DM events in the D:A:D Study. We hypothesise that decreases in BMI at low baseline BMI and increases in BMI at high baseline BMI are associated with an increased risk of CVD. In contrast, the risk of DM will increase linearly with short term increases in BMI across all baseline BMI strata.

Methods:

The D:A:D study is a prospective, multi-cohort observational collaborative study, including 11 previously established cohorts following more than 40,000 people with HIV from Europe, Argentina, Australia and the US. The primary aim of the study is to investigate the possible association between ART and the risk of CVD as well as other clinical events. The study methodology has been described in detail previously¹⁷. Briefly, people with HIV were under active follow-up at the individual cohorts at the time of enrolment into the D:A:D study, and were included irrespective of whether or how long they were receiving ART. Data were collected as part of their routine clinical care and include demographic and other

prospectively collected data such as age, sex, BMI, CVD, DM, family history of coronary heart disease, cigarette smoking, blood pressure therapy, DM therapy, lipid lowering and antihypertensive therapy and serum lipid levels (total (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol (LDL) and triglycerides (including fasting status) and lipid lowering therapy; as well as HIV-related core clinical data - ART medication received, CD4, viral load and all clinical AIDS diagnoses.

Definitions:

CVD and DM are protocol defined D:A:D endpoints with all prospective cases verified by the completion and central validation of D:A:D specific case report forms (for details see https://chip.dk/Portals/0/files/Study documents/DAD_MOOP_revised2013.pdf). In these analyses, a CVD event was the first event from a composite of myocardial infarction (MI), sudden cardiac death or invasive cardiovascular procedure (coronary artery bypass graft, carotid endarterectomy), or stroke. The first DM event was defined as the first of a documented fasting glucose >7.0 mmol/L on at least two occasions, a single value of national glycohemoglobin standardization program (NGSP) haemoglobin A1c $>6.5\%$, or symptoms of DM with a random glucose >11.1 mmol/L, 2-h oral glucose tolerance test >11.1 mmol/L, or use of antidiabetic drugs.

Statistical methods:

For these analyses we included all D:A:D participants who initiated combination (3+) ART, with at least two BMI measures available and at least one year of further follow-up from baseline (defined as the later of cohort entry, ART initiation, or first BMI measurement). We excluded any participants with pre-existing diagnoses of CVD or DM.

Participants were stratified according to their baseline BMI into the following categories: BMI <20, 20-24.9, 25-29.9, and ≥ 30 kg/m². The lower and upper of these categories broadly correspond with increased risk of CVD seen in our previous analyses¹³. Change in BMI was then calculated from the baseline BMI at each new BMI assessment allowing the inclusion of time-updated BMI in analyses. Participants were then stratified into the following BMI change groups: BMI decrease ≥ 2 kg/m², BMI decrease 1-1.99kg/m², BMI stable ± 1 kg/m²(range from -0.99 to 0.99 kg/m²) BMI increase ≥ 1 -1.99 kg/m² and BMI increase ≥ 2 kg/m². These cut-offs were chosen to reflect reasonably substantial weight changes while retaining sufficient events and follow-up in each category for analyses.

Descriptive analyses were conducted to summarize the baseline characteristics of participants included in the analyses. Person years of follow-up (py), number of CVD and DM events and incidence rate ratios were calculated. Median weight change corresponding to median BMI changes were also determined.

We used Poisson regression to assess BMI change as a predictor of CVD and DM. Follow-up time commenced from baseline (as defined above) to the first event or earliest of the following: 1/2/2016, 6 months after last follow-up visit or death. Models were adjusted for key confounders not thought to be on the causal pathway for each respective endpoint, as previously identified in the D:A:D¹³. The model for CVD was adjusted for the categorized baseline BMI, age, race, mode of transmission, sex, cumulative abacavir use, cumulative protease inhibitor (PI) use, cumulative nucleoside reverse transcriptase inhibitor (NRTI) use, CD4 count, family history of CVD and smoking status. BMI and other time-updated covariates were lagged by one year with last observation carried forward. The model for DM was adjusted for categorized baseline BMI, age, race, mode of transmission, sex, cumulative

stavudine use, triglycerides, CD4 count, smoking status and HDL. A missing variable category was created for all variables to ensure all observations were included in models. The BMI change associations with CVD and DM were based on regression coefficients, significance levels ($P < 0.05$) and visually using forest plots. Interactions between BMI and BMI change were examined using the likelihood ratio test. The main purpose for also assessing DM in these analyses was to act as a control, as the linear association with increasing weight or BMI and DM is well described in the literature both in the general population and among people with HIV. Demonstrating a similar linear association in these analyses would confirm the robustness of the overall study findings.

We undertook the following additional analyses. First, for the CVD endpoint, we additionally adjusted for variables thought to be on the causal pathway between BMI changes and CVD as identified in prior analysis of this cohort¹³. These include fasting and non-fasting lipids (total, HDL and LDL cholesterol), systolic blood pressure (SBP) and incident DM. Second, given the strong evidence for differential weight gain affects among women compared to men, we also stratified our analyses by sex for both the CVD and DM outcomes.

Results:

Baseline characteristics of covariates stratified by baseline BMI category are provided in Table 1. A total of 43,805 (88.1%) participants were included in the analyses for the CVD outcome, of whom 74% were male. Median age was 38.9 years (Interquartile range (IQR): 33.2-45.7), and the median BMI (IQR) overall was 23.1 (21.1-24.4) kg/m^2 . Characteristics by baseline BMI strata were broadly similar overall, although the proportion of males in the lowest ($< 20 \text{ kg/m}^2$) and highest ($\geq 30 \text{ kg/m}^2$) baseline BMI groups (62% and 55%, respectively) was lower than that in the two middle BMI strata (77 and 78%). The lowest and highest BMI categories also reported lower proportions of participants of white race (47%

and 41% compared with 52% and 51%). Similar baseline characteristics were observed among the 5,901 who were excluded from the CVD analyses, apart from smaller proportion with undetectable viral load in the excluded population 28% (data not shown).

For the DM outcome, 42,521 (85.6%) of the cohort were included in these analyses. Baseline characteristics were similar to the population assessed for the CVD outcome, with 74% were male, median age was 38.7 (IQR: 33 – 45.3), 50% were white, and the median BMI was 23.0 (IQR: 21.0-25.4) (Supplementary Table S1, <http://links.lww.com/QAI/B583>).

The median weight change (kg) by baseline BMI grouped by BMI change (kg/m^2) category is illustrated in Figure S1, <http://links.lww.com/QAI/B583>. The greatest absolute change in weight was observed in the BMI change categories with the greatest loss of $2 \text{ kg}/\text{m}^2$ or more (BMI change: decrease ≥ 2), and greatest gain of $2 \text{ kg}/\text{m}^2$ or more (BMI change increase ≥ 2). For the group with loss in BMI $\geq 2 \text{ kg}/\text{m}^2$ or more, the median weight change was notably different between the baseline BMI categories $<20 \text{ kg}/\text{m}^2$ and BMI $30+ \text{ kg}/\text{m}^2$ (-7.0 kg (IQR -9. to -6.5) and -11.0 kg (IQR -16.3 to -8.0), respectively). Within the remaining BMI change categories, even for BMI change $\geq 2 \text{ kg}/\text{m}^2$ or more, the median weight changes were similar across baseline BMI categories.

CVD and DM outcomes:

There were 2,104 CVD events, with a total follow up time of 365,287 person years (py), an overall rate of 5.8/1000 py (95% confidence interval [CI]: 5.5-6). Figure 1a shows the incident rate ratios (IRR) for BMI change groups stratified by baseline BMI category.

Elevated risk of CVD was observed for the baseline BMI categories of $<20 \text{ kg}/\text{m}^2$ and 25-29.9 kg/m^2 . After adjustment for covariates a loss in BMI of $\geq 2 \text{ kg}/\text{m}^2$, resulted in an almost

2-fold increased risk of CVDS (IRR 1.99, 95% CI 1.29-3.06) compared to a stable BMI for baseline BMI <20 kg/m². For baseline BMI 20-24.9 kg/m², a loss of ≥ 2 kg/m² was marginally associated with increased risk compared to stable BMI, while a loss between 1 and 1.9 kg/m² had a significant association with increased risk of CVD (1.24, 95% CI 1.03-1.49), compared to stable BMI. Conversely, within the baseline BMI $\geq 30+$ kg/m² category, a lower risk of CVD was observed for those with a gain between 1-1.9 kg/m² (0.37, 95% CI 0.15-0.93) compared with stable BMI. For all baseline BMI categories however, there was no consistent evidence of increasing risk of CVD as changes in BMI increased.

Additional analyses for CVD adjusting for variables on the causal pathway yielded similarly associations (Table S2). We also assessed for potential interactions between BMI and BMI change, which were not found to be statistically significant (p-value 0.17).

There were 1,583 DM cases with a total follow-up time of 354,898 py, an event rate of 4.5/1000 py (95%CI: 4.2-4.7). Figure 1b illustrates that across all baseline BMI categories risk of DM increases linearly by increases in BMI change. For all baseline BMI categories, a BMI gain of ≥ 2 kg/m² was associated with a significantly higher DM risk compared with stable BMI. Within the baseline BMI category 25-29.9 kg/m², the risk of DM for a BMI gain of 1-1.9 kg/m² (1.33, 95% CI 1.02-1.74) was also statistically significantly increased compared with a stable BMI. As with the CVD outcome, there was no significant interaction between BMI and BMI change (p=0.81).

For both CVD and DM risk, when analyses were stratified by sex, similar trends were observed by gender (Figure 2a and b, Figure 3a and b).

Discussion

Among participants in the D:A:D cohort we have shown that overall increases in BMI across all levels of baseline BMI were not associated with an increased risk of CVD. There was some evidence of an increased risk of CVD with a decrease in BMI especially at low baseline BMI. As hypothesized, however, increases in BMI across all levels of baseline BMI were consistently associated with an increased risk of DM. These findings were consistent for men and women and persisted after further adjustment for factors on the causal pathway (lipids, blood pressure and prior DM) for CVD.

Previously the D:A:D study has reported a non-linear (J-shaped) association between BMI and CVD¹³. A non-linear association of BMI and CVD risk has also been reported in the general population¹⁸. Our current findings suggests the non-linear association between BMI change in CVD risk at lower BMI levels is driven by short-term and larger decreases in BMI at the lowest baseline BMI category, and to some extent this was also observed for the middle BMI categories 20-24.9 and 25-29.9 kg/m². The larger decrease in BMI for the low and middle baseline BMI categories and increased risk of CVD may reflect declining health. In the general population low BMI was associated with high risk of death with one study reporting an 80% increased risk of death among those with BMI less than 18.5 compared to BMI of 22.5-25 kg/m²¹⁴. Others have also found increased risk of non-communicable disease among people with HIV with low BMI (20 kg/m² compared to those with a BMI of 25 kg/m²)¹⁹ as well as increased mortality among people with HIV who experience weight loss after ART initiation²⁰. It is unlikely that declining health is the reason for our findings, the weight measures were lagged by 12 months meaning the measures we have used preceded the events by at least 1 year. However, the possibility of some residual confounding remains, despite having controlled for a number of known confounders such as smoking in our

analyses. As previously suggested, it is also possible that people with low BMI are perceived to be a low risk and therefore get less aggressive disease prevention interventions compared with those with higher BMI¹³

For baseline BMI levels 30 kg/m² or more, there was little to no evidence of increased CVD risk with increases in changes of BMI. In the D:A:D study previously we have shown that at higher BMI the risk of CVD increases, although the risk was attenuated after adjustment for lipids, blood pressure, and incident DM¹³. It is possible that these changes would only be differentiating among individuals with very high BMI over 35 kg/m²; in our analyses, the number of participants in this category is very small and the power of analyses would be limited. In the study by Koethe et al, individuals commencing ART with a BMI 30 kg/m² experienced a lower risk of CVD and other morbidities, compared to those with a BMI 25 kg/m², although this protective effect was attenuated at BMI 35 kg/m²¹⁹.

We explored DM as a secondary outcome in these analyses mostly to act as a control analysis. We show a significantly increase in risk of DM with BMI changes of >2kg/m², equivalent to a median increase of 10kg or more (Supplementary figure 1, <http://links.lww.com/QAI/B583>). While weight gains less than 10kg were not generally associated with DM risk. These findings of increased risk as BMI changes increase is consistent with studies in both the general population and among studies of people with HIV¹⁶. In the VACS, for all baseline BMI levels, 12-month weight change was linearly associated with incident DM¹⁶. Including DM as an outcome demonstrates the robustness of our methodology and is a strength to this study. However, there are some limitations to our analyses. First, we could not assess the impact of INSTIs, as the D:A:D largely predated INSTI use, with follow-up ceasing in 2016. Second, there are no behavioural data collected

including diet and exercise. Third, BMI is not a perfect anthropometric measure for CVD risk, and the use of waist:hip ratio or another similar assessment may improve accuracy, but is not available in the D:A:D study. Further, BMI poorly discriminates between lean body mass and fat body mass, which can be influenced by sex, age, and race/ethnicity²¹. Finally, even in this very large cohort collaboration, we had low event rates in the very low and very high BMI categories, and so limited power to disentangle BMI changes from baseline BMI level. The cut-offs we chose for our analyses were driven largely by sample size and ensuring sufficient event numbers in each group. We were also unable to explore events at very high BMI levels ($>35 \text{ kg/m}^2$), as well as limited to explore the effects in detail among women, and by race where recent data suggest differential impact of ART use and weight gain on women and black race⁴.

In summary, we found that increasing change in BMI was not associated with an increased risk of CVD apart from larger decreases of BMI at lower baseline BMI levels, whilst a consistent linear association with increases in BMI change was shown for DM risk. In the context of increased weight change due to newer ART classes the extent to which these results apply is unclear. For people with low BMI, weight gain may be beneficial for reducing CVD risk, however, for those with normal and high BMI, increase in weight appears not to have any impact on CVD risk. Whilst weight gain at any level of BMI linearly increases the risk of DM. Data from recent clinical trials report increases in weight following commencement of ART among individuals starting on INSTI, in particular DTG, as well as TAF^{1,5}. These increases are more pronounced among women than men, although from our study, the implications of our findings remain the same.. As people with HIV are increasingly exposed to new ART agents, in particular INSTI or TAF, data from large cohort studies are needed.

Tables and figures

Attached – Appendix A

Acknowledgements

D:A:D Participating Cohorts

Aquitaine	CPCRA	NICE Cohort
France	USA	France
ATHENA	EuroSIDA	SHCS
The Netherlands	Europe	Switzerland
AHOD	HIV-BIVUS	St.Pierre Brussels Cohort
Australia	Sweden	Belgium
BASS	The ICONA Foundation	
Spain	Italy	

D:A:D Steering Committee: Names marked with *, Chair with †

Cohort PIs: W El-Sadr* (CPCRA), G Calvo* (BASS), F Bonnet and F Dabis* (Aquitaine), O Kirk* and A Mocroft* (EuroSIDA), M Law* (AHOD), A d'Arminio Monforte* (ICONA), L Morfeldt* (HivBIVUS), C Pradier* (Nice), P Reiss* (ATHENA), R Weber* (SHCS), S De Wit* (Brussels)

Cohort coordinators and data managers: A Lind-Thomsen (coordinator), R Salbøl Brandt, M Hillebrecht, S Zaheri, FWNM Wit (ATHENA), A Scherrer, F Schöni-Affolter, M Rickenbach (SHCS), A Tavelli, I Fanti (ICONA), O Leleux, J Mourali, F Le Marec, E Boerg

(Aquitaine), E Thulin, A Sundström (HIVBIVUS), G Bartsch, G Thompsen (CPCRA), C Necsoi, M Delforge (Brussels), E Fontas, C Caissotti, K Dollet (Nice), S Mateu, F Torres (BASS), K Petoumenos, A Blance, R Huang, R Pühr (AHOD), K Grønberg Laut, D Kristensen (EuroSIDA)

Statisticians: CA Sabin*, AN Phillips*, DA Kamara, CJ Smith, A Mcroft*

D:A:D coordinating office: CI Hatleberg, L Ryom, A Lind-Thomsen, RS Brandt, D Raben, C Matthews, A Bojesen, AL Grevsen, JD Lundgren*[‡]

Member of the D:A:D Oversight Committee: B Powderly*, N Shortman*, C Moecklinghoff*, G Reilly*, X Franquet*

D:A:D working group experts:

Kidney: L Ryom, A Mcroft*, O Kirk *, P Reiss*, C Smit, M Ross, CA Fux, P Morlat, E Fontas, DA Kamara, CJ Smith, JD Lundgren *[‡]

Mortality: CJ Smith, L Ryom, CI Hatleberg, AN Phillips*, R Weber*, P Morlat, C Pradier*, P Reiss*, FWNM Wit, N Friis-Møller, J Kowalska, JD Lundgren*[‡]

Cancer: CA Sabin*, L Ryom, CI Hatleberg, M Law*, A d'Arminio Monforte*, F Dabis*, F Bonnet*, P Reiss*, FWNM Wit, CJ Smith, DA Kamara, J Bohlius, M Bower, G Fätkenheuer, A Grulich, JD Lundgren*[‡]

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The current members of the 11 Cohorts are as follows:

ATHENA (AIDS Therapy Evaluation Project Netherlands):

Central coordination: P. Reiss*, S. Zaheri, M Hillebregt, F.W.N.M. Wit;

CLINICAL CENTRES ([□] denotes site coordinating physician) **Academic Medical Centre of the University of Amsterdam:** J.M. Prins[□], T.W. Kuijpers, H.J. Scherpbier, J.T.M. van

der Meer, F.W.N.M. Wit, M.H. Godfried, P. Reiss, T. van der Poll, F.J.B. Nellen, S.E.

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C.J. Schinkel, X.V. Thomas. **Admiraal De Ruyter Ziekenhuis, Goes:** M. van den Berge, A.

Stegeman, S. Baas, L. Hage de Looff, D. Versteeg. **Catharina Ziekenhuis, Eindhoven:**

M.J.H. Pronk[□], H.S.M. Ammerlaan, E.S. de Munnik, A.R. Jansz, J. Tjhie, M.C.A. Wegdam,

B. Deiman, V. Scharnhorst. **Emma Kinderziekenhuis:** A. van der Plas, A.M. Weijzenfeld.

Erasmus MC, Rotterdam: M.E. van der Ende[□], T.E.M.S. de Vries-Sluijs, E.C.M. van Gorp,

C.A.M. Schurink, J.L. Nouwen, A. Verbon, B.J.A. Rijnders, H.I. Bax, M. van der Feltz. N.

Bassant, J.E.A. van Beek, M. Vriesde, L.M. van Zonneveld. A. de Oude-Lubbers, H.J. van

den Berg-Cameron, F.B. Bruinsma-Broekman, J. de Groot, M. de Zeeuw- de Man, C.A.B.

Boucher, M.P.G Koopmans, J.J.A van Kampen, S.D. Pas. **Erasmus MC–Sophia,**

Rotterdam: G.J.A. Driessen, A.M.C. van Rossum, L.C. van der Knaap, E. Visser.

Flevoziekenhuis, Almere: J. Branger[□], A. Rijkeboer-Mes, C.J.H.M. Duijf-van de Ven.

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Geilings. G. van der Hut. P.F.H. Franck. **HIV Focus Centrum (DC Klinieken):** A. van

Eeden[□]. W. Brokking, M. Groot, L.J.M. Elsenburg, M. Damen, I.S. Kwa. **Isala, Zwolle:**

P.H.P. Groeneveld[□], J.W. Bouwhuis, J.F. van den Berg, A.G.W. van Hulzen, G.L. van der

Bliek, P.C.J. Bor, P. Bloembergen, M.J.H.M. Wolfhagen, G.J.H.M. Ruijs. **Leids**

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Virology: H. Fleury, Me. Lafon, P. Trimoulet, P. Bellecave, C. Tumiotto

Pharmacology: S. Bouchet, D. Breilh, F. Haramburu, G. Miremeont-Salamé

Data collection, Project Management and Statistical Analyses: MJ. Blaizeau, M. Decoin,

C. Hannapier, E. Lénard et A. Pougetoux; S. Delveaux, C. D'Ivernois, F. Diarra B.

Uwamaliya-Nziyumvira, O. Leleux; F. Le Marec, Eloïse Boerg, S. Lawson-Ayayi;

IT department and eCRF development: G. Palmer, V. Conte, V. Sapparrart

AHOD (Australian HIV Observational Database, Australia):

Central coordination: M. Law *, K. Petoumenos, R Pühr, R Huang (Sydney, New South

Wales). **Participating physicians (city, state):** R. Moore, S. Edwards, J. Hoy, K. Watson, N.

Roth, H Lau (Melbourne, Victoria); M Bloch, D. Baker, A. Carr, D. Cooper, (Sydney, New

South Wales); M O'Sullivan (Gold Coast, Queensland), D. Nolan, G Guelfi (Perth, Western

Australia).

BASS (Spain):

Central coordination: G. Calvo, F. Torres, S. Mateu (Barcelona);

Participating physicians (city): P. Domingo, M.A. Sambeat, J. Gatell, E. Del Cacho, J.

Cadafalch, M. Fuster (Barcelona); C. Codina, G. Sirera, A. Vaqué (Badalona).

The Brussels St Pierre Cohort (Belgium):

Coordination: S. De Wit*, N. Clumeck, M. Delforge, C. Necsoi.

Participating physicians: N. Clumeck, S. De Wit*, AF Gennotte, M. Gerard, K. Kabeya, D.

Konopnicki, A. Libois, C. Martin, M.C. Payen, P. Semaille, Y. Van Laethem.

CPCRA (USA):

Central coordination: J. Neaton, G. Bartsch, W.M. El-Sadr*, E. Krum, G. Thompson, D.

Wentworth;

Participating physicians (city, state): R. Luskin-Hawk (Chicago, Illinois); E. Telzak (Bronx,

New York); W.M. El-Sadr (Harlem, New York); D.I. Abrams (San Francisco, California); D.

Cohn (Denver, Colorado); N. Markowitz (Detroit, Michigan); R. Arduino (Houston, Texas);

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(Newark, New Jersey); E. Tedaldi (Philadelphia, Pennsylvania); E. Fisher (Richmond,

Virginia); F. Gordin (Washington, DC); L.R. Crane (Detroit, Michigan); J. Sampson

(Portland, Oregon); J. Baxter (Camden, New Jersey).

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Chair: J Rockstroh

Study Co-leads: A Mocroft, O Kirk

Coordinating Centre Staff: O Kirk, L Peters, C Matthews, AH Fischer, A Bojesen, D Raben, D Kristensen, K Grønberg Laut, JF Larsen, D Podlekareva

Statistical Staff: A Mocroft, A Phillips, A Cozzi-Lepri, L Shepherd, A Schultze, S Amele

The multi-centre study group, EuroSIDA (national coordinators in parenthesis).

Argentina: (M Losso), M Kundro, Hospital JM Ramos Mejia, Buenos Aires.

Austria: (B Schmied), Pulmologisches Zentrum der Stadt Wien, Vienna; R Zangerle, Medical University Innsbruck, Innsbruck.

Belarus: (I Karpov), A Vassilenko, Belarus State Medical University, Minsk, VM Mitsura, Gomel State Medical University, Gomel; D Paduto, Regional AIDS Centre, Svetlogorsk.

Belgium: (N Clumeck), S De Wit, M Delforge, Saint-Pierre Hospital, Brussels; E Florence, Institute of Tropical Medicine, Antwerp; L Vandekerckhove, University Ziekenhuis Gent, Gent.

Bosnia-Herzegovina: (V Hadziosmanovic), Klinicki Centar Univerziteta Sarajevo, Sarajevo.

Croatia: (J Begovac), University Hospital of Infectious Diseases, Zagreb.

Czech Republic: (L Machala), D Jilich, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen.

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Georgia: (N Chkhartishvili) Infectious Diseases, AIDS & Clinical Immunology Research Center, Tbilisi

Greece: (P Gargalianos), G Xylomenos, K Armenis, Athens General Hospital "G Gennimatas"; H Sambatakou, Ippokration General Hospital, Athens.

Hungary: (J Szlávik), Szent László Hospital, Budapest.

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Ireland: (F Mulcahy), St. James's Hospital, Dublin.

Israel: (I Yust), D Turner, M Burke, Ichilov Hospital, Tel Aviv; E Shahar, G Hassoun, Rambam Medical Center, Haifa; H Elinav, M Haouzi, Hadassah University Hospital, Jerusalem; D Elbirt, ZM StHoeger, AIDS Center (Neve Or), Jerusalem.

Italy: (A D'Arminio Monforte), Istituto Di Clinica Malattie Infettive e Tropicale, Milan; R Esposito, I Mazeu, C Mussini, Università Modena, Modena; F Mazzotta, A Gabbuti, Ospedale S Maria Annunziata, Firenze; V Vullo, M Lichtner, University di Roma la Sapienza, Rome; M Zaccarelli, A Antinori, R Acinapura, M Plazzi, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, A Castagna, N Gianotti, Ospedale San Raffaele, Milan; M Galli, A Ridolfo, Osp. L. Sacco, Milan.

Latvia: (B Rozentale), Infectology Centre of Latvia, Riga.

Lithuania: (V Uzdaviniene) Vilnius University Hospital Santariskiu Klinikos, Vilnius; R Matulionyte, Center of Infectious Diseases, Vilnius University Hospital Santariskiu Klinikos, Vilnius.

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Slovenia: (J Tomazic), University Clinical Centre Ljubljana, Ljubljana.

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Ukraine: A Kuznetsova, Kharkov State Medical University, Kharkov; G Kyselyova, Crimean Republican AIDS centre, Simferopol; M Sluzhynska, Lviv Regional HIV/AIDS Prevention and Control CTR, Lviv.

United Kingdom: (B Gazzard), St. Stephen's Clinic, Chelsea and Westminster Hospital, London; AM Johnson, E Simons, S Edwards, Mortimer Market Centre, London; A Phillips, MA Johnson, A Mocroft, Royal Free and University College Medical School, London (Royal Free Campus); C Orkin, Royal London Hospital, London; J Weber, G Scullard, Imperial College School of Medicine at St. Mary's, London; A Clarke, Royal Sussex County Hospital, Brighton; C Leen, Western General Hospital, Edinburgh.

The following centers have previously contributed data to EuroSIDA:

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Hôpital de la Pitié-Salpêtrière, Paris, France

Unité INSERM, Bordeaux, France

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Bernhard Nocht Institut für Tropenmedizin, Hamburg, Germany

1st I.K.A Hospital of Athens, Athens, Greece

Ospedale Riuniti, Divisione Malattie Infettive, Bergamo, Italy

Ospedale di Bolzano, Divisione Malattie Infettive, Bolzano, Italy

Ospedale Cotugno, III Divisione Malattie Infettive, Napoli, Italy

Dérer Hospital, Bratislava, Slovakia

Hospital Carlos III, Departamento de Enfermedades Infecciosas, Madrid, Spain

Kiev Centre for AIDS, Kiev, Ukraine

Luhansk State Medical University, Luhansk, Ukraine

Odessa Region AIDS Center, Odessa, Ukraine

HivBivus (Sweden):

Central coordination: L. Morfeldt, G. Thulin, A. Sundström.

Participating physicians (city): B. Åkerlund (Huddinge); K. Koppel, A. Karlsson (Stockholm); L. Flamholz, C. Håkangård (Malmö).

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Nice HIV Cohort (France):

Central coordination: C. Pradier*, E. Fontas, K. Dollet, C. Caissotti.

Participating physicians: P. Dellamonica, E. Bernard, J. Courjon, E. Cua, F. De Salvador-Guillouet, J. Durant, C. Etienne, S. Ferrando, V. Mondain-Miton, A. Naqvi, I. Perbost, S. Pillet, B. Prouvost-Keller, P. Pugliese, V. Rio, K. Risso, P.M. Roger.

SHCS (Swiss HIV Cohort Study, Switzerland):

The data are gathered by the Five Swiss University Hospitals, two Cantonal Hospitals, 15 affiliated hospitals and 36 private physicians (listed in <http://www.shcs.ch/180-health-care-providers>).

Members of the Swiss HIV Cohort Study :

Aubert V, Battegay M, Bernasconi E, Böni J, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Günthard HF (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nicca D, Pantaleo G, Paioni P, Rauch A (Chairman of the Scientific Board), Rudin C (Chairman of the Mother & Child Substudy), Scherrer AU (Head of Data Centre), Schmid P, Speck R, Stöckle M, Tarr P, Trkola A, Vernazza P, Wandeler G, Weber R*, Yerly S.

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Figure 1a and 1b. Effect of changes in BMI (kg/m^2) on the risk of CVD and DM stratified by baseline BMI (kg/m^2) category

Figure 2a and b – Effect of changes in BMI (kg/m^2) on the risk of CVD by sex: male (a) and female (b)

Figure 3a and b – Effect of changes in BMI (kg/m^2) on the risk of DM by sex: male (a) and female (b)

Table 1. Patient characteristics at baseline (for CVD outcome analysis) by BMI kg/m²

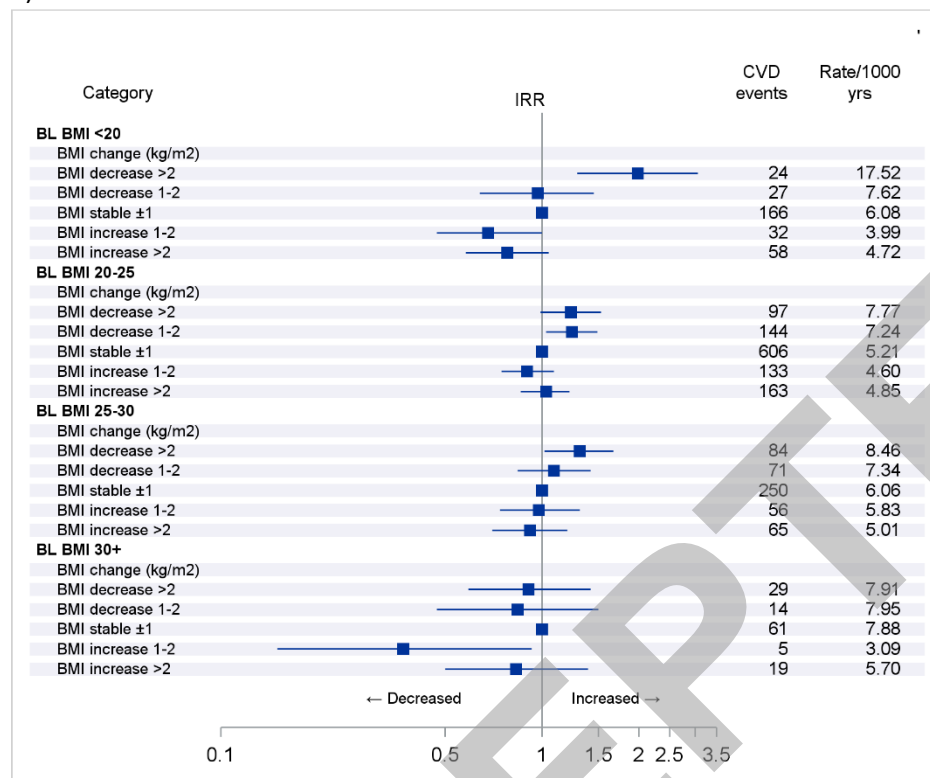
	Overall	BMI <20	BMI 20-25	BMI 25-30	BMI 30+
N	43,805	6,304	24,850	10,191	2,460
Sex - male (%)	73.9	62.0	77.1	78.4	56.4
Age in years (median, IQR)	38.9 (33.2, 45.7)	37.0 (31.4, 43.2)	38.6 (33.1, 45.1)	40 (34.5, 48.1)	40.1 (33.8, 47.4)
Infected with HIV through sex between men (%)	45.2	36.6	49.2	45	27.7
Infected with HIV through drug use (%)	14.5	20.4	14.8	11.2	9.5
Race (%)					
white	50.5	46.9	52.4	50.5	41.3
black	9.3	7.8	7.6	11.7	21.5
other	2.8	3.4	2.7	2.7	3.2
unknown	37.3	41.9	37.4	35.1	33.9
Current smoker (%)	39.4	48.4	41.8	31.7	24.3
Family history of CVD (%)	6.8	6.2	6.7	7.2	7
BMI (median, IQR)	23.1 (21.1, 25.4)	18.9 (18.1, 19.5)	22.5 (21.4, 23.7)	26.6 (25.7, 27.8)	32.2 (30.9, 34.6)
CD4 count/mm ³ (median, IQR)	400 (254, 574)	351 (185, 538)	400 (260, 577)	412 (279, 590)	429 (280, 602)
Log ₁₀ HIV RNA (copies/mL) (median, IQR)	2.9 (1.7, 4.5)	3.1 (1.7, 4.7)	2.8 (1.7, 4.5)	2.7 (1.7, 4.4)	3.3 (1.7, 4.4)
Undetectable (%) (RNA<200)	39.9	37.0	40.4	41.9	34.8
ART naïve (%)	38.4	37.1	37.5	38.9	49.6
Hep C coinfection (%)	19.1	25.7	19.8	15.0	11.9
Hep B coinfection (%)	19.8	20.8	20.2	18.6	16.5
Total cholesterol mmol/L (median, IQR)	4.8 (4.0, 5.7)	4.5 (3.8, 5.4)	4.7 (4.0, 5.6)	4.9 (4.1, 5.9)	4.9 (4.1, 5.9)
HDL mmol/L (median, IQR)	1.1 (0.9, 1.4)	1.2 (0.9, 1.5)	1.1 (0.9, 1.4)	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)
Systolic BP (median, IQR)	120 (110, 130)	117 (110, 123)	120 (110, 130)	126 (120, 137)	130 (120, 140)

Note: BP= blood pressure, CVD= cardiovascular disease, HDL= high-density lipoprotein.

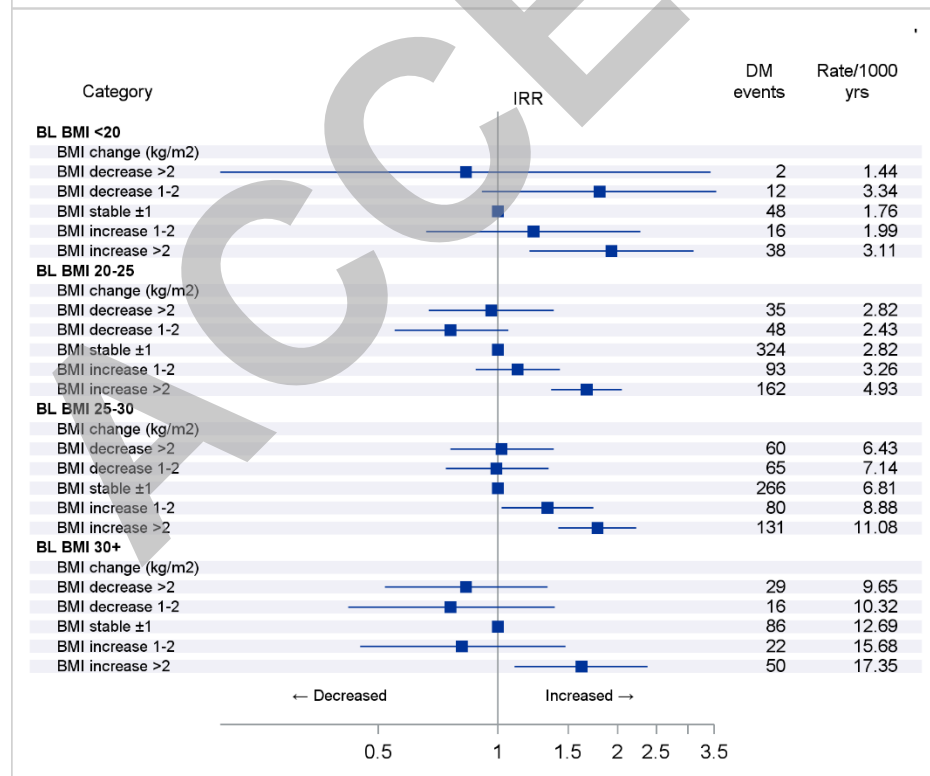
At baseline (defined as the later of cohort entry, ART initiation, or first BMI measurement), smoking status was unknown in 16%; Hepatitis B and C status was unknown in 12% and 16% respectively; total cholesterol was missing in 15%, HDL cholesterol was missing in 444%, SBP was missing in 30%

Figure 1a and 1b. Effect of changes in BMI (kg/m²) on the risk of CVD and DM stratified by baseline BMI (kg/m²) category

a)



b)



CVD adjusted for key covariates: age, race, mode of HIV transmission, sex, abacavir use, protease inhibitor use, nucleoside reverse transcriptase inhibitor (NRTI) use, CD4 count, family history of CVD, smoking status

DM adjusted for key covariates: age, race, mode of HIV transmission, sex, stavudine use, triglycerides, CD4 count, smoking status and high-density lipoprotein (HDL)

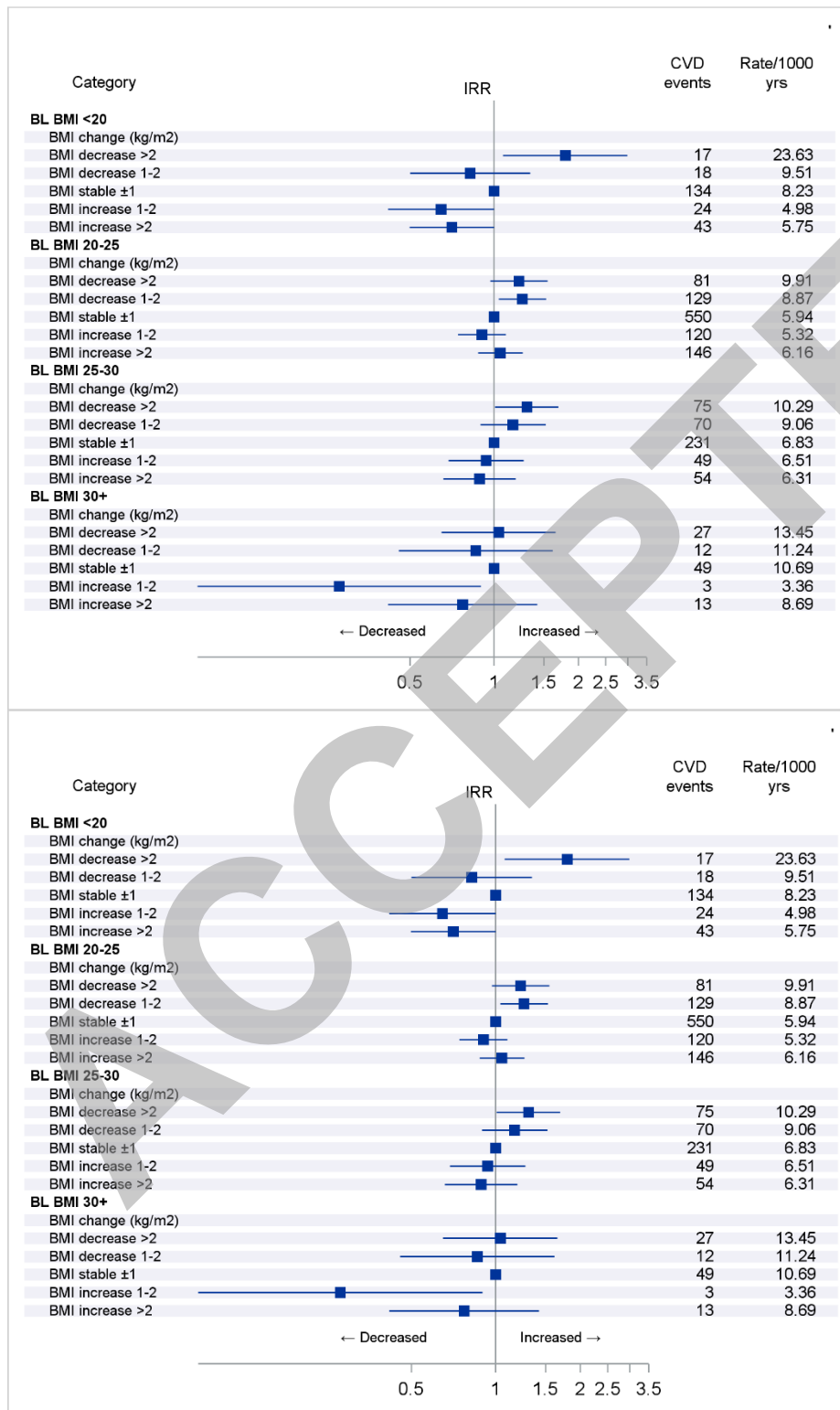
Note: BL=baseline; BMI= body mass index; CVD= cardiovascular disease; DM= diabetes mellitus

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Figure 2a and b – Effect of changes in BMI (kg/m²) on the risk of CVD by sex: male (a) and female (b)

a)

b)



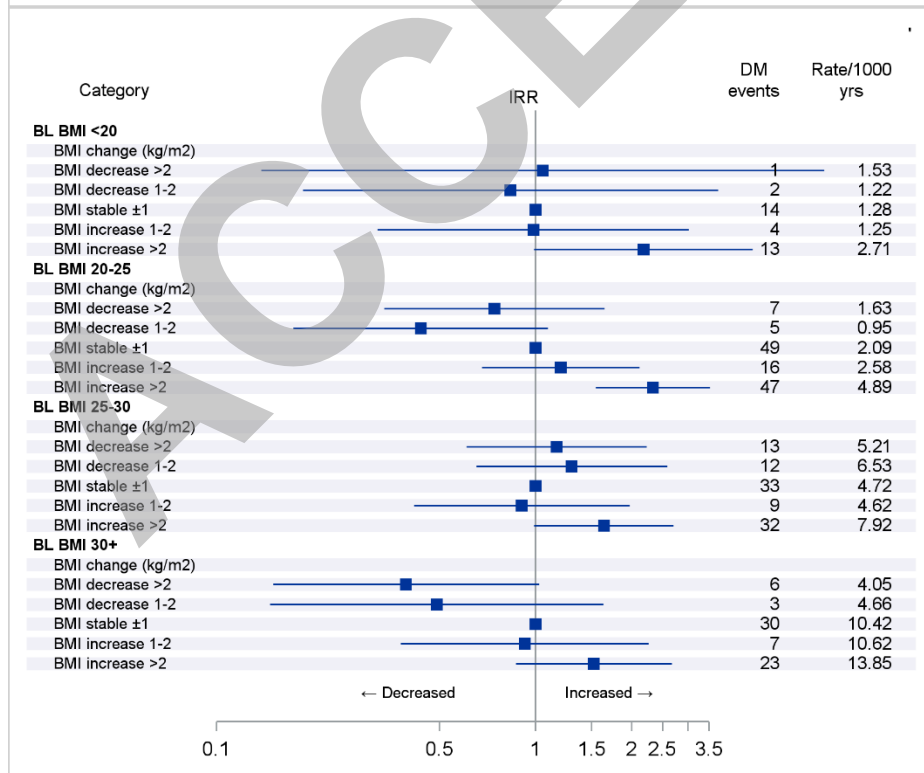
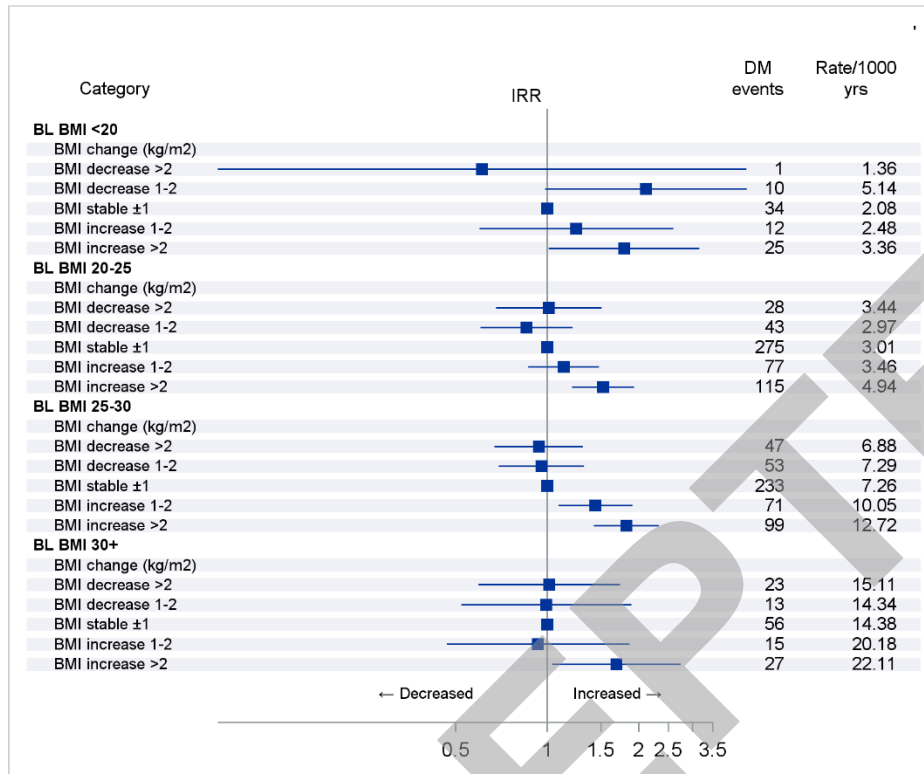
Note: BL = baseline, BMI= body mass index

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Figure 3a and b – Effect of changes in BMI (kg/m²) on the risk of DM by sex: male (a) and female (b)

a)

b)



Note: BL = baseline, BMI= body mass index