D:A:D

Triglycerides and the risk of myocardial infarction in the D:A:D study

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On behalf of the D:A:D study group

Background

- Elevated triglyceride (TG) levels are a common complication of antiretroviral therapy (ART)

Eron JJ, Jr, et al. Lancet. 2006;368
Shafran SD, et al. HIV Med. 2005;6:4
van Leth F, et al. PLoS Med. 2004
Fontas E, et al. JID 2004; 189

Background

- Elevated triglyceride (TG) levels are a common complication of antiretroviral therapy (ART)
- HIV infection, insulin resistance, obesity and fatty liver disease can cause elevated TG levels as well

Grunfeld C el at. J Clin Endocrinol Metab. 1992; 74(5)
Fabbrini E et al. Hepatology. 2010;51(2)
Capaeu J Diabetes Metab. 2008 ;34(6 Pt 2)

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- It is unclear whether TG levels provide additional prognostic information regarding myocardial infarction (MI) risk once total cholesterol (TC) and HDL-cholesterol (HDL) are taken into account
  - There is no evidence that reduction of elevated TG levels will translate into a reduction in MI risk in HIV-positive persons

Purpose

- Explore the relationship between TG levels and the risk of MI after adjustment for TC and HDL

Methods

- Follow-up counted from D:A:D enrolment until the first MI event, 1st February 2008 or 6 months after the patient's last clinic visit (whichever occurred first)
- Covariates were time-updated at the start of each month
- The incidence of the first MI during prospective D:A:D follow-up was calculated according to the latest (time-updated) TG level

Methods

- TG levels were stratified into sixtiles

mmol/L :	mg/dl :
‹0.90	‹80
0.90–1.25	80-110
1.25-1.70	110-150
1.70-2.30	150-200
2.30-3.45	200-300
›3.45	›300

- Multivariable Poisson regression models were used to describe the independent association between the latest TG level and MI risk
- TG assessed fasting and non-fasting*, continuous measurement, per doubling

** 27% fasting, 13% non-fasting, 60% unknown*

Methods
adjustments in multivariable models

- Two sets of adjustments were made to explore the potential independent association between TG levels and risk of MI :

  i) non-lipid cardiovascular disease (CVD) risk factors

  (sex, age, race, body mass index, smoking, family history of CVD, previous CVD event, diabetes mellitus, receipt of lipid lowering drugs, hepatitis C status), calendar year, the latest HIV-RNA level and CD_4 count and exposure to ART

  ii) as above, **plus** the latest TC and HDL level

Baseline characteristics of patients with at least one TG measurement over follow-up

Patients with at least one TG measurement	30 703 (92.2)*
Age, Median value	39
Male sex %	74.1
Race %	
White	53.6
Black	9.0
Other	2.7
Unknown	33.7
Smoking Status %	
Current smoker	37.0
Ex-smoker	19.2
Family history of CVD %	7.4
Previous CVD %	1.7
Diabetes Mellitus %	2.9

* Out of total 33,308 patients

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Mode of infection %	
Homosexual/bisexual	43.2
IDU	18.2
Heterosexual	31.5
Other/unknown	7.6
BMI › 30 kg/ m^2	4.1
Median value (IQR)	
HDL cholesterol**	1.1 (0.9 - 1.4)
Total cholesterol**	4.9 (4.1 - 5.9)
CD4 counts (cells/mm^3)	407 (249 - 600)
HIV RNA, % suppressed	33
Any exposure to ART %	
PIs	60.3
NNRTIs	34.3
NRTIs	75.3

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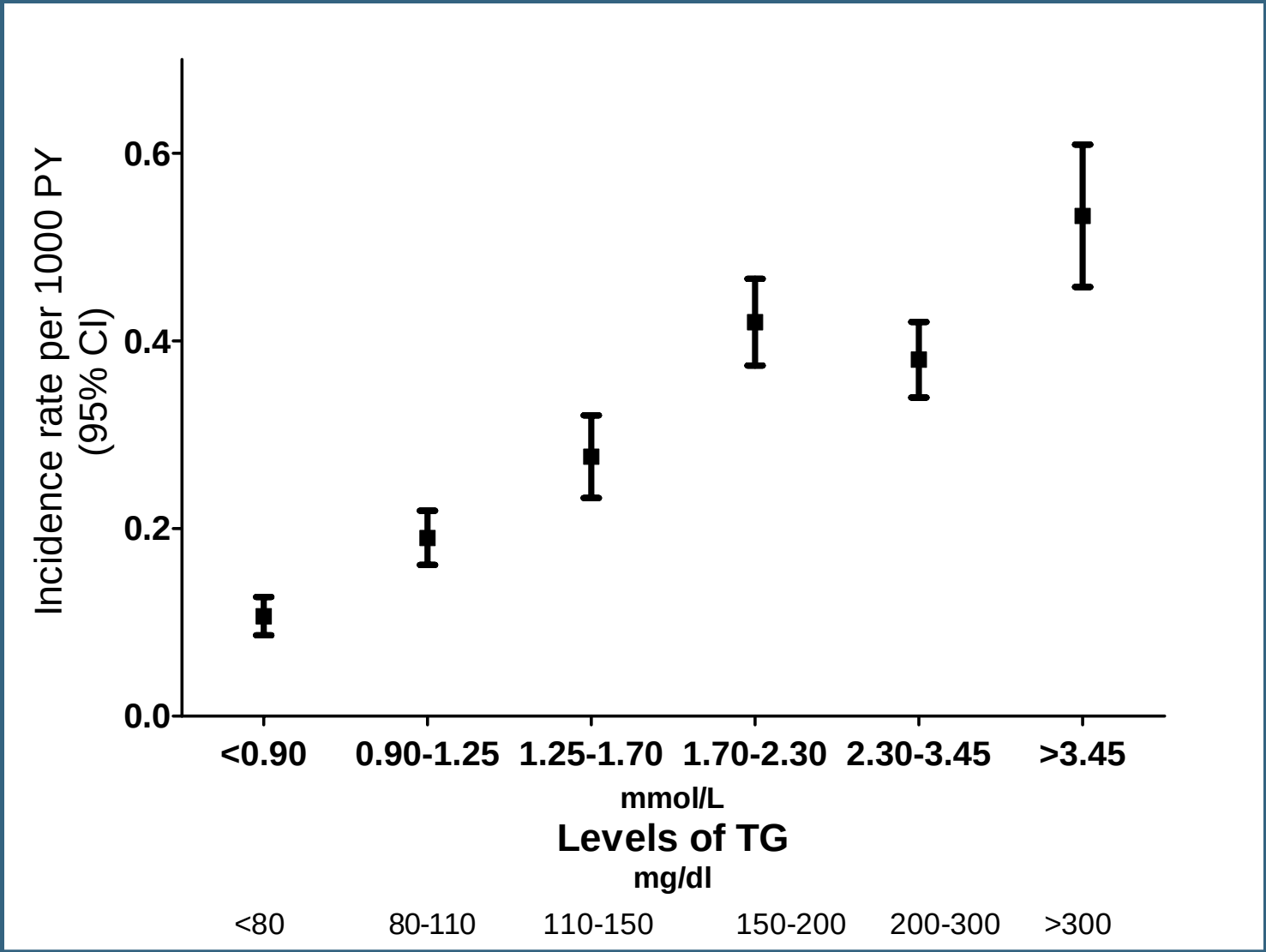
** mmol/L

D:A:D

Results

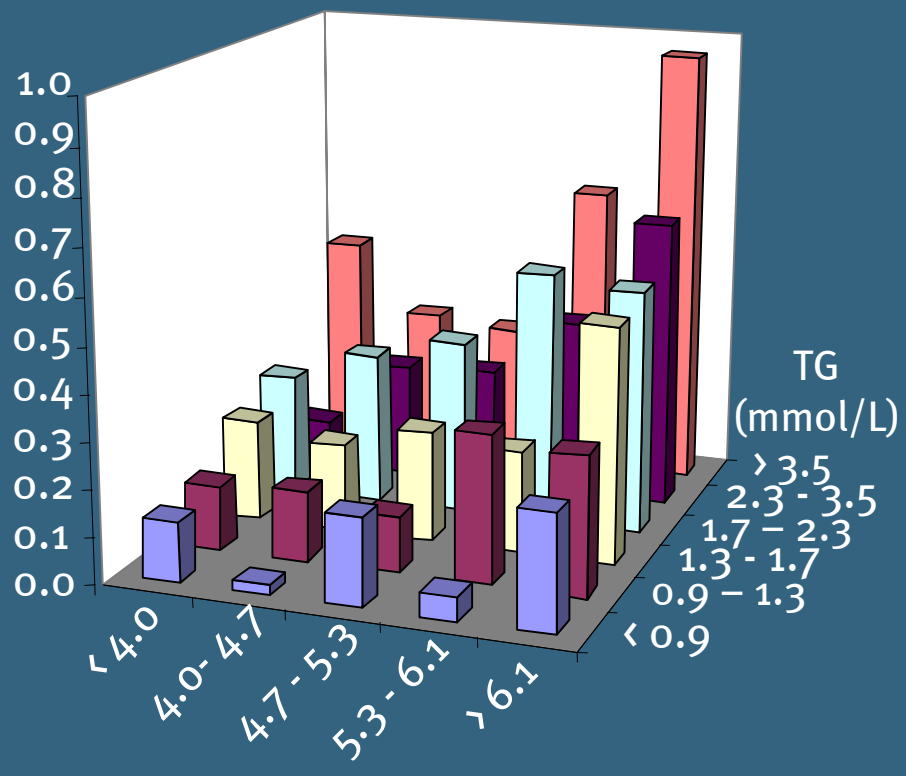
- 580 MIs over 178,835 person-years
- 405,756 TG measurements
- Regardless of fasting status, overall TG levels were
  - higher in men
  - increased with older age
  - higher in those with BMI › 30kg/m^2
  - lower in patients with CD4 of ‹ 300 cells/ m^3 compared to patients with ›600 cells/ m^3
  - higher in patients with viral load less than 500 copies/ml
  - higher in patients currently on ART compared to patient not on ART

Incidence of MI according to TG group

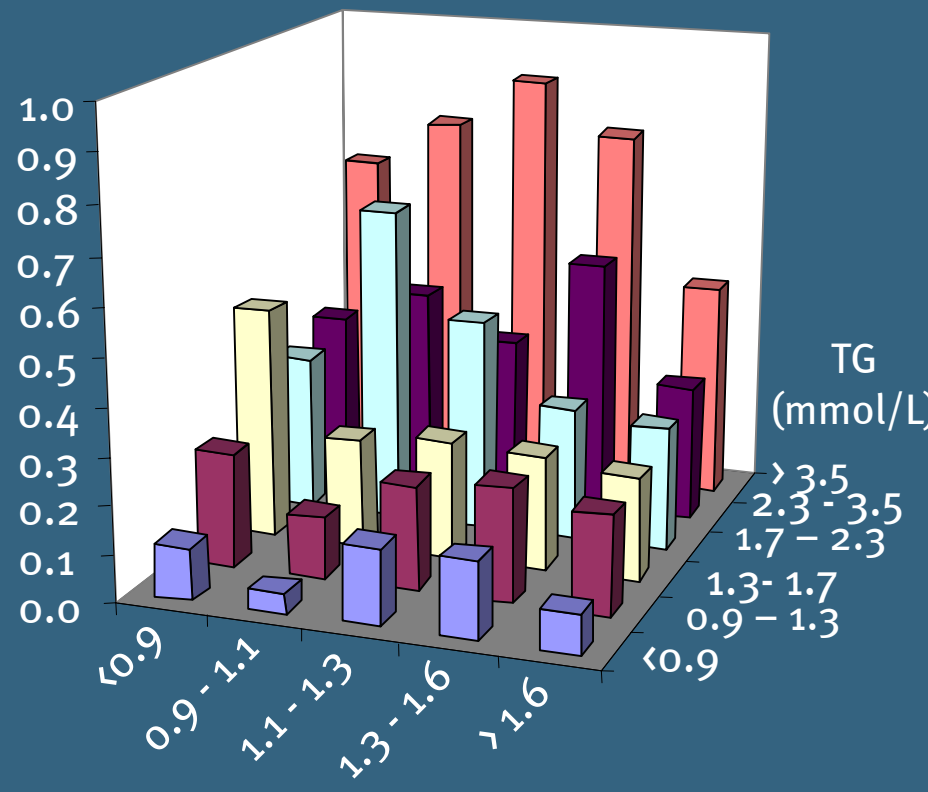


Incidence rates of MI per 100 PYRS

TG and TC



TG and HDL



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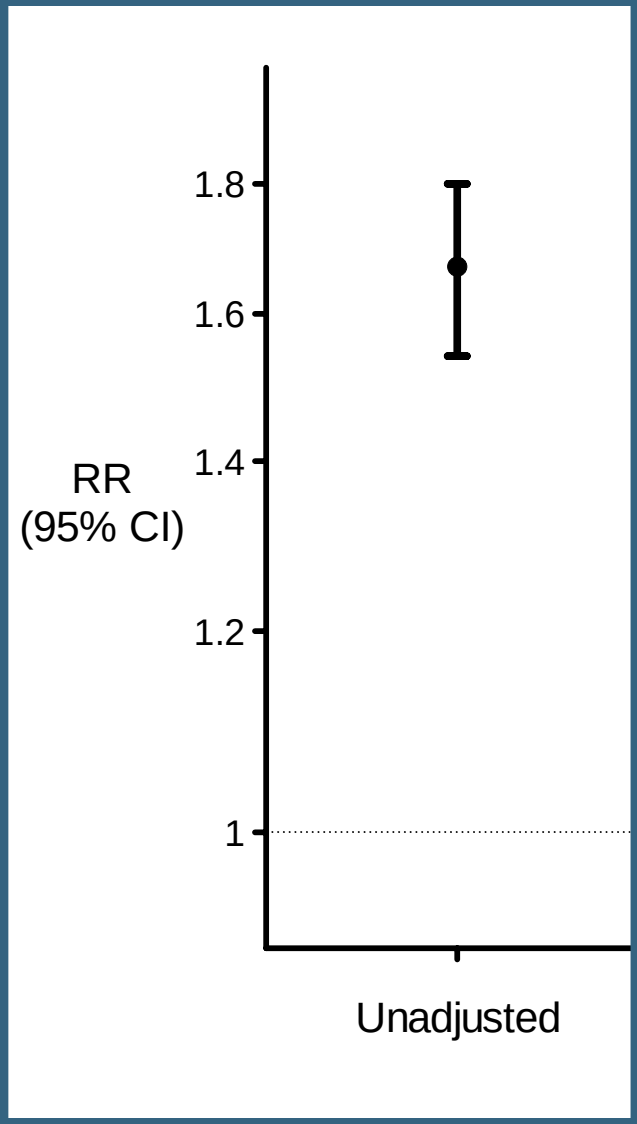
Relative rate of MI per doubling of TG levels



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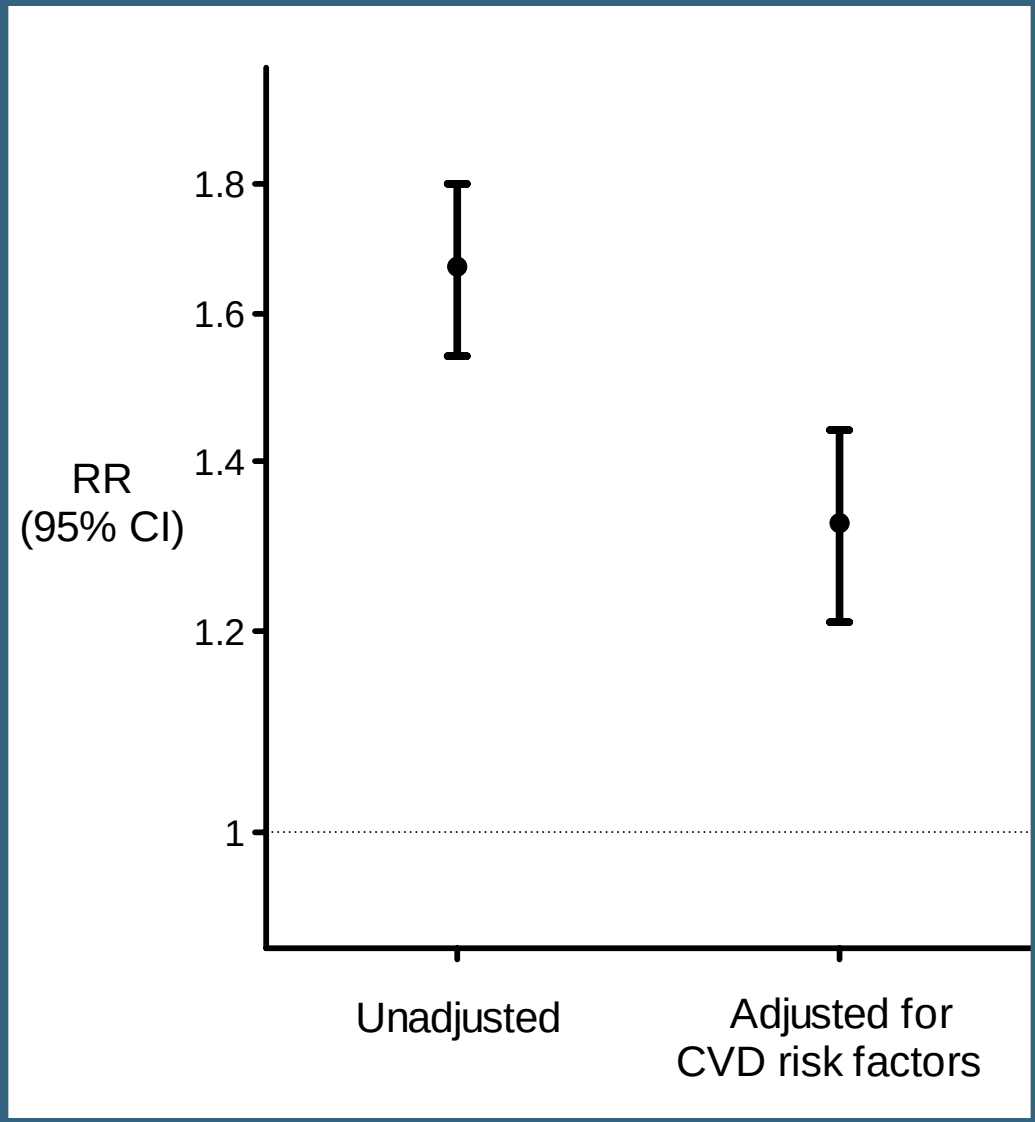

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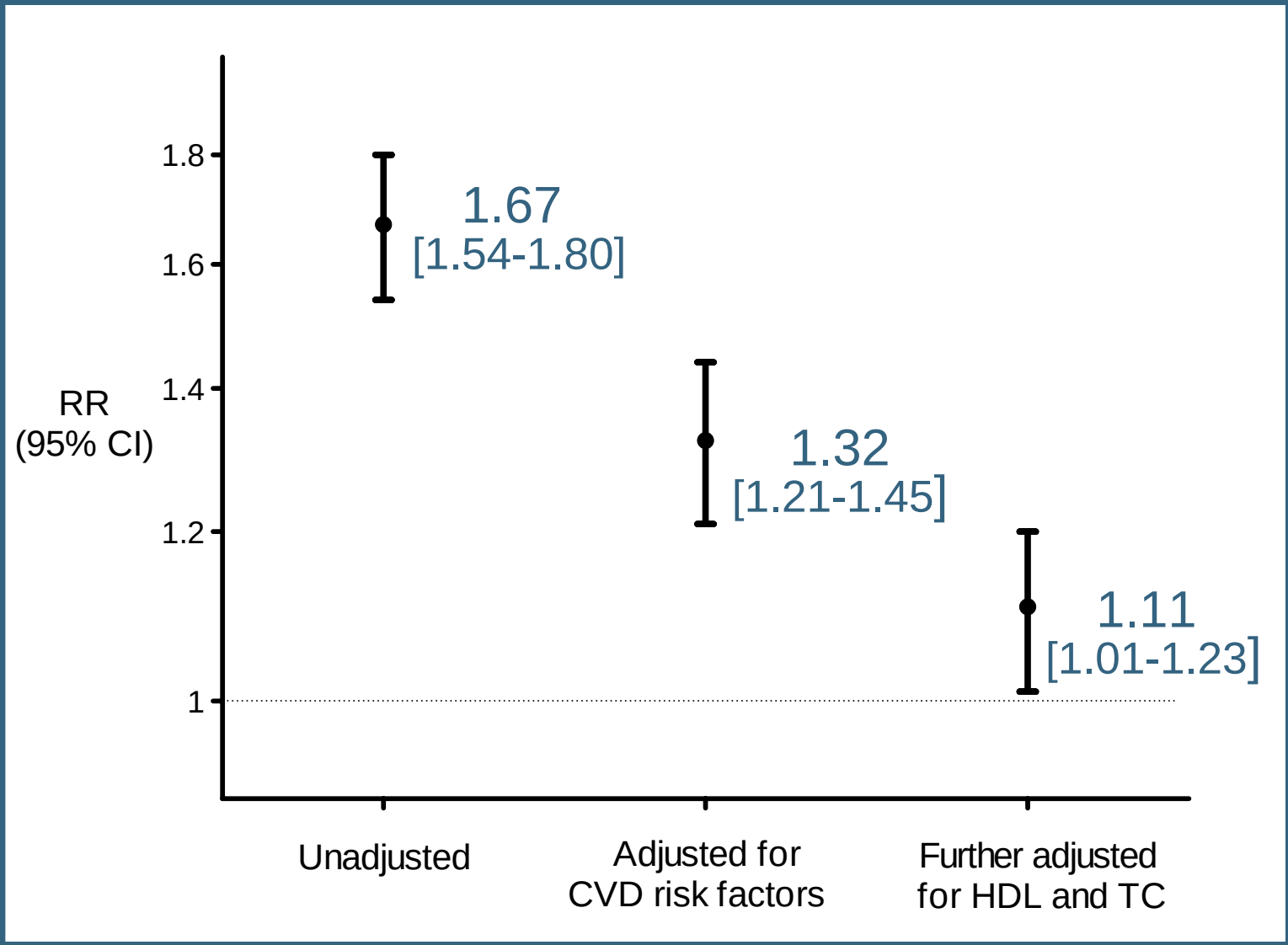

Limitations

- Lack of repeated sampling, variability of TG levels could lead to regression dilution bias
  - -› also underestimate the effects of TC and HDL and hence the extent to which they attenuate the effect of TG
- Sensitivity analysis using fasting, non-fasting and unknown fasting status reached similar conclusions
- Although adjustments for ART was done, drug induced triglyceride elevations could not be compared to TG elevations due to other factors
- Causal link between triglyceride level and MI cannot be established due to the observational nature of study

Conclusions

- Higher TG levels were independently associated with an increased risk of MI in HIV-positive persons

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Conclusions

- Higher TG levels were independently associated with an increased risk of MI in HIV-positive persons
  - However, the residual effect of TG levels after adjustment for non-lipid *and* lipid risk factors of 11% is very small compared with the original unadjusted effect of 67%
- Thus, use of drugs that lower TG levels (e.g. fibrates, nicontinic acid) are unlikely to have major impact on the incidence of MI*

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- **D:A:D coordinating office:** SW Worm, N Friis-Møller, R Brandt, JD Lundgren*¢
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