Statistical methods in the Metabolic syndrome and Cancer project (Me-Can)

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In the Me-Can project data from seven cohorts in Norway, Sweden, and Austria were pooled to a total of 578,700 participants (study period from 1972 till 2006). The cohort health examination included measurements of height, weight and blood pressure, and circulating levels of glucose, total cholesterol and triglycerides. The cohorts were linked to their respective national register for the assessment of cancer incidence (ICD-7), migration, vital status, and cause of death. Basically, the research aim focused on associations of the metabolic syndrome (MetS) factors and cancer (death) risk.

Generally, modelling was done by Cox PH regression with attained age as time-scale, stratified by cohort (to account for differences in measurement procedures) and adjusted for birth year, baseline age and smoking status (when appropriate also for sex and body mass index). In most instances the analyses were performed for males and females separately.

Quintile analysis
Quintile cut-points were determined separately within each of the seven cohorts, in both sex groups, and for glucose, cholesterol, and triglycerides also in categories of fasting time. After putting together the data, hazard ratios were estimated with the lowest quintile as the reference.

Analysis of z-scores
To allow the determinants to be compared on the same scale, the exposure variables were transformed to standardised z-scores with a mean of 0 and a standard deviation of 1 (glucose and triglycerides ln-transformed). Also, a combined MetS score was constructed from the standardised sum of the separate z-scores. We calculated extra models with further adjustments for the other MetS variables.

Measurement error
Based on repeated readings, correction for random error and within-person variability of the exposure measurements was performed, to counteract regression dilution bias of risk associations. The regression dilution ratio and the regression calibration method were applied (both based on linear mixed effect models).

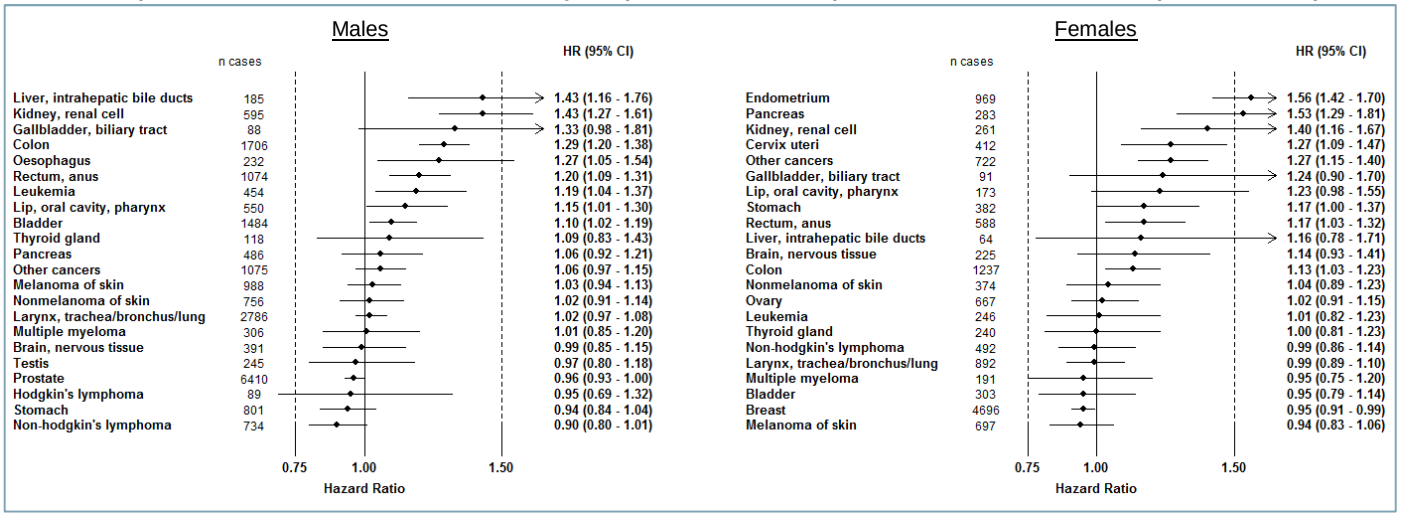
$$y_{ijr} = a + a_i + (b + b_i + c_1|t_{ijr}|)\, y_{ij\,0} + c_2 t_{ijr} + \sum_{k=1}^{p} \alpha_k x_{ij\,0,k} + \sum_{l=1}^{q} \beta_l z_{ij\,0,l} + \varepsilon_{ijr}$$

Regression dilution ratio = $(b+b_i+c_1|t_{ijr}|)$

Lag-time analysis
In the regression models the follow-up starting point was set at one year after the baseline examination in order to reduce the possibility of reverse causation. In some studies we did additional checks with a time lag of 5 years.

Splines
Investigation of the shape of the association of z-score factors with risk was analysed in certain studies by using restricted cubic spline regression with knots placed at the 5th, 35th, 65th and 95th percentiles and linear models, compared with likelihood ratio tests.

Sex-specific risk estimates of incident cancer by site per unit MetS score (standardised sum of the five separate z-scores)



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References

Fibrinogen Studies Collaboration. Correcting for multivariate measurement error by regression calibration in meta-analyses of epidemiological studies. *Stat Med* 2009;28:1067-1092.
Franks PW, Olsson T. Metabolic syndrome and early death: getting to the heart of the problem. *Hypertension* 2007;49:10-12.
Hutcheon JA, Chiolero A, Hanley JA. Random measurement error and regression dilution bias. *Brit Med J* 2010;340:c2289.
Jonsson H. Regression dilution ratio (RDR) and regression calibration for Me-Can studies. Internal paper, 2009.
Stocks T, Bjørge T Ulmer H, et al. Metabolic syndrome score and cancer incidence and mortality: a pooled analysis of seven cohorts. [submitted]
Stocks T, Borena W, Strohmaier S, et al. Cohort Profile: the metabolic syndrome and cancer project (Me-Can). Int J Epidemiol 2010;39:660-667.
Ulmer H, Kelleher C, Diem G, et al. Long-term tracking of cardiovascular risk factors among men and women in a large population-based health system: the Vorarlberg Health Monitoring & Promotion Programme. *Eur Heart* J 2003;24:1004-1013.