**Age-dependent association of NT-proBNP with obesity, insulin resistance, and inflammation in type 2 diabetes: a cross-sectional study in the DD2 cohort**

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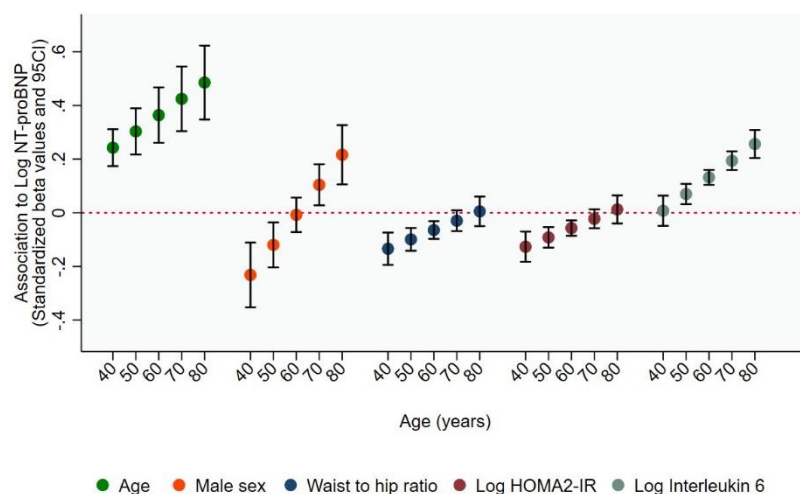
**Background and aims:** Natriuretic peptides play an important role in cardiorenal and cardiometabolic protection, with their secretion increasing in response to cardiac strain. Individuals with obesity have lower levels of these hormones than lean individuals, leading to the concept of "natriuretic deficiency". This deficiency has been associated with insulin resistance and inflammation. However, the effect of age on natriuretic deficiency is poorly understood. Therefore, this study aims to investigate the relationship between circulating N-terminal pro-brain natriuretic peptide (NT-proBNP) levels and obesity, insulin resistance, and inflammation in patients with type 2 diabetes, and to determine if age modifies this relationship.

**Materials and methods:** A total of 4,162 patients (1,755 females) from the Danish Center for Strategic Research in Type 2 Diabetes (DD2) cohort were included in this cross-sectional study. Multiple linear regression was used with log-transformed NT-proBNP as the dependent variable and age, sex, waist-to-hip ratio (WHR), and log-transformed values of IL-6 and HOMA2-IR as independent variables. Modification by age was evaluated for all associations. Beta values are reported as standardized coefficients and 95% CI.

**Results:** Age was positively associated with log NT-proBNP ($\beta$=0.43 [0.40-0.46], P<0.001), and the association was further accentuated with increasing age ($P_{age^2}$<0.001). Age significantly modified the sex differences in NT-proBNP levels ($P_{interaction}$<0.001). In participants younger than 50 years, male sex was associated with lower log NT-proBNP ($\beta$=-0.21 [-0.36, -0.06], P=0.007), while in those older than 75 years, male sex was positively associated with log NT-proBNP ($\beta$=0.30 [0.08-0.52], P=0.007). The inverse associations between WHR and log NT-proBNP ($\beta$=-0.06 [-0.09, -0.03], P<0.001) and between Log HOMA2-IR and log NT-proBNP ($\beta$=-0.05 [-0.08, -0.02], P<0.001) were both weakened by age ($P_{interaction}$=0.004 and $P_{interaction}$=0.049, respectively). Finally, log IL-6 and log NT-proBNP were positively associated ($\beta$=0.14 [0.11-0.17], P<0.001), and the association was strengthened by age ($P_{interaction}$<0.001).

**Conclusion:** The association between obesity, insulin resistance, inflammation and NT-proBNP levels varies with age. In younger patients, obesity and insulin resistance may impair natriuretic peptide production or increase degradation, leading to natriuretic deficiency. Conversely, age strengthens the association between inflammation and BNP levels

Multiple linear regression model

*Disclosure:* **T. Olesen:** None.