quintiles. We assessed incident depression through the self-report of a medical diagnosis during follow-up. This definition had been previously validated[3].

We estimated hazard ratios (HRs) and 95% confidence intervals (95% CIs) of depression across sex-specific quintiles of predicted CVD risk. Models were adjusted for age, adherence to the Mediterranean dietary pattern (low/moderate/high), physical activity (quintiles), total energy intake (quintiles), menopause due to natural causes (yes/no), living alone (yes/no), employment status (employed, unemployed, retired), marital status (married or not), and personality traits (competitiveness, relaxation, dependence).

Over 151,125 person-years of follow-up, we identified 927 incident cases of depression. A higher predicted cardiovascular risk at baseline was significantly associated with higher risk of depression. Young adult participants (<40 years) in the highest quintile of CVD risk (mean risk: 0.30%) presented an adjusted HR of 1.47 (95% CI: 1.08-2.00) compared to those in the lowest quintile (mean risk: 0.05%). The second, third and fourth quintiles presented non-significant HRs of 1.05, 1.21, and 1.16, respectively. This association was even stronger for older participants (≥40 years): 1.65 (1.17-2.34) for the second quintile (mean risk: 0.54%), 1.68 (1.16-2.42) for the third quintile (mean risk: 0.85%), 1.85 (1.24-2.75) for the fourth quintile (mean risk: 1.43%), and 2.17 (1.33-3.54) for the fifth quintile (mean risk: 4.31%), all of them compared to the first quintile (mean risk: 0.31%).

So, a higher predicted CVD risk was strongly associated with a higher future incidence of depression, both in younger and older adults. This finding may support the hypothesis that CVD and depression share common pathophysiological mechanisms[4-6]. As an alternative, depression and CVD may share risk factors but not the mechanisms through which these risk factors act. Actually, there is a growing body of research on the bi-directional relationship between depression and metabolic syndrome[7], obesity[8] or type 2 diabetes[9].

The clinical implications of our findings are of great importance for public health and clinical practice. First, public health agencies may consider sharing efforts for the primary prevention of both depression and CVD, which may be synergic. Both CVD and depression are associated with a set of known and modifiable risk factors that it is worth to target from a public health perspective. Second, general practitioners should consider that both older and younger patients at higher risk of CVD may also be at higher risk of depression. Physicians can calculate the predicted cardiovascular risk using the Framingham risk score or other similar equations which are available in charts and user-friendly versions. Their interventions addressed to obtain improvements in these equations through changes in lifestyle are likely to also be an appropriate approach for the prevention of depression.

Finally, the knowledge that lifestyle factors are not only increasing the risk of CVD but also that of depression, even at younger ages, needs to reach the general public. This take-home message may be useful to achieve greater changes in unhealthy habits throughout the life cycle in the population at large.

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Depressive symptom profiles and glucose tolerance status

Depression is known to be two to three times more prevalent among individuals who have diabetes than among those without it[1]. The conventional hypothesis suggests that the higher prevalence of depression among individuals with diabetes is a consequence of the psychological distress created by the diagnosis, namely its stigmatizing effects and the long-term complications. However, there is contradictory evidence that an association can also be observed between insulin resistance and depression among individuals without diabetes[2]. To address this inconsistency, three recent reviews[3-5], including one published in this journal[5], have called for greater precision in studies, proposing that specific depression profiles (e.g., atypical depression) should be further investigated.

We conducted a population-level investigation on the importance of atypical and non-atypical depressive symptoms in specific pre-diabetic states as well as in previously undiagnosed and diagnosed diabetes mellitus. The 75 g oral glucose tolerance test was used to define each person's glucose tolerance status. Depressive symptom profiles were defined by using the 21-item Beck Depression Inventory (BDI-II). Participants who scored at least 14 points and responded positively (at least one point) to both reversed vegetative symptoms (oversleeping and overeating) were defined as having atypical depressive symptoms[6]. The rest of the participants with at least 14 BDI-II points were defined as having non-atypical depressive symptoms.

In the study sample (N=4838; Northern Finland Birth Cohort

1966 members with written consent who volunteered to participate in clinical examination at the age of 46 years), we found 379 (7.8%) and 74 (1.5%) participants with non-atypical and atypical depressive symptoms, respectively. The prevalence of normal glucose tolerance, defined as having a fasting plasma glucose (FPG) concentration <6.1 mmol/l and a two-hour glucose <7.8 mmol/l, was only 61% among those with atypical depressive symptoms, whereas it was 73% and 79% among those with non-atypical and no depressive symptoms, respectively.

The proportions of all abnormal glucose tolerance states were highest among participants with atypical depressive symptoms. The prevalence of impaired fasting glucose (FPG 6.1-6.9 mmol/l and a two-hour glucose <7.8 mmol/l) among those with atypical, non-atypical and no depressive symptoms was 8%, 7% and 7%, respectively. The corresponding prevalence of impaired glucose tolerance (FPG <7.0 mmol/l and a two-hour glucose of 7.8-11.0 mmol/l) was 15%, 11% and 8%, respectively. The prevalence of previously undiagnosed type 2 diabetes (FPG ≥7.0 mmol/l or a two-hour glucose ≥11.1 mmol/l) was 5%, 3% and 2%, respectively.

Previously diagnosed diabetes was designated if any of the following was observed: self-reported diagnosis of diabetes made by a physician; self-reported medication for diabetes; inpatient or outpatient visit at a hospital due to diabetes (all hospital visits were obtained from the Finnish Care Register for Health Care); or the right to purchase diabetes medication at a subsidized cost (data obtained through national medication registers from the Social Insurance Institution of Finland). The prevalence of previously diagnosed type 2 diabetes was 11%, 6% and 3% among those with atypical, non-atypical and no depressive symptoms, respectively.

Differences in the distribution of glucose tolerance status between depressive symptoms profile groups were statistically significant (Pearson's chi-square test: $F/\chi^2=40.26$, df=10, p=0.00002). Mean body mass index was 30.8 ± 7.5 kg/m^2, 28.0 ± 5.7 kg/m^2 and 26.7 ± 4.7 kg/m^2 among those with atypical depressive symptoms, non-atypical depressive symptoms and no depressive symptoms, respectively (p=0.002, Kruskal-Wallis test, pairwise; atypical vs. non-atypical). The participants self-reported their physical activity, education level, smoking status, alcohol and antidepressant medication use; of these, when tested pairwise, only use of selective serotonin reuptake inhibitors was different among the subtypes (30% for atypical vs. 11% for non-atypical, p=0.0001, Fisher's exact test).

Taken together with previous findings[5,7], our results support the importance of subtyping depression in people with type 2 diabetes, as recently postulated in this journal[5]. The current results also highlight the phenomenon already in pre-diabetic states. We speculate that the results of previous studies on the association between depression and type 2 diabetes might have been different if depression subtypes had been analyzed.

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