Qual Life Res (2014) 23:2515–2520
DOI 10.1007/s11136-014-0689-5

BRIEF COMMUNICATION

# Longitudinal changes in health-related quality of life in normal glucose tolerance, prediabetes and type 2 diabetes: results from the KORA S4/F4 cohort study

**Matthias Hunger · Rolf Holle · Christa Meisinger · Wolfgang Rathmann · Annette Peters · Michaela Schunk**

Accepted: 6 April 2014 / Published online: 13 April 2014


**Abstract**
*Purpose* The aim of this study was to examine how transition between normal glucose tolerance, prediabetes and diabetes over a 7 year period is associated with change in health-related quality of life (HRQL) in an elder German population-based cohort.
*Methods* We used data from 1,046 participants of the KORA S4/F4 cohort study aged 55–74 years at baseline. Based on an oral glucose tolerance test, prediabetes was defined as impaired fasting glucose and/or impaired glucose tolerance. HRQL was assessed with the SF-12 questionnaire. Using linear regression, we estimated mean change in HRQL over time, depending on glucose status at baseline and follow-up, adjusted by demographic and lifestyle variables.
*Results* Individuals progressing to prediabetes or diabetes experienced a greater loss in the physical component score than patients with persistent normal glucose tolerance (−2.31 and −7.44 vs. −1.08), but the difference was only significant for subjects converting to diabetes. Subjects with prediabetes at baseline and diabetes at follow-up had a significant loss in mental health compared to subjects with persistent prediabetes.
*Conclusions* There is first evidence that worsening of glucose metabolism over time is associated with deteriorating HRQL, however, further and larger longitudinal studies are needed to confirm these findings.

**Keywords** Prediabetes · Quality of life · Impaired glucose tolerance · Diabetes · Health status · Longitudinal studies · Health services research

M. Hunger (✉) · R. Holle · M. Schunk
Institute of Health Economics and Health Care Management, Helmholtz Zentrum München - German Research Center for Environmental Health (GmbH), Ingolstädter Landstr. 1, 85764 Neuherberg, Germany
e-mail: matthias.hunger@helmholtz-muenchen.de

M. Hunger · R. Holle · C. Meisinger · W. Rathmann · A. Peters · M. Schunk
German Center for Diabetes Research (DZD), München, Germany

C. Meisinger · A. Peters
Institute of Epidemiology II, Helmholtz Zentrum München - German Research Center for Environmental Health (GmbH), Ingolstädter Landstr. 1, 85764 Neuherberg, Germany

W. Rathmann
Institute of Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Düsseldorf, Germany

## Introduction

Several studies have shown that individuals with type 2 diabetes (T2DM) report significantly reduced health-related quality of life (HRQL) compared to the general population [1, 2]. However, very little is known about whether HRQL is already impaired during the prediabetic phase, defined as impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT).

There are only few cross-sectional studies on HRQL in prediabetes and these reported inconsistent results, ranging from no effect to associations for specific health domains or subgroups only [3–6].

A large Australian study observed that individuals progressing from normal glucose tolerance (NGT) to IFG or IGT within 5 years had lower baseline scores in some domains of the SF-36 [7], however no study has ever examined longitudinal changes in HRQL with respect to glucose metabolism status.

The aim of this study was to examine how changes between NGT, prediabetes and diabetes over a 7 year period are associated with change in HRQL in an elder German general population cohort.

## Methods

### Study population

Data come from the population-based German KORA (Cooperative Health Research in the region of Augsburg) S4/F4 cohort study which was conducted in the city of Augsburg and its two surrounding counties in Southern Germany. For the baseline examination (S4) in 1999–2001, a random sample of individuals aged 25 to 74 years were selected from population registries (response rate 67 %). The current study was restricted to subjects aged 55 years or older at baseline because in S4, oral glucose tolerance tests (OGTT) were performed in this subgroup only. In the random population sample, the number of subjects in this age group was 2,656, of which 1,653 participated. Seven years later (2006–2008), all participants of the S4 survey were invited to a follow-up examination (called F4) that also included an OGTT. At both time points, OGTTs were not performed in individuals with previously known diabetes. A detailed description of study design, data collection, and response rate can be found elsewhere [8, 9]. Our study sample included all subjects with clearly defined glucose metabolism status at both time points, i.e., either previously known diabetes or complete OGTT data. We excluded subjects with type 1 diabetes. This led to a final sample size of 1,046 participants, as shown in Fig. 1.

All study participants gave written informed consent and the study was approved by the Ethics Committee of the Bavarian Medical Association.

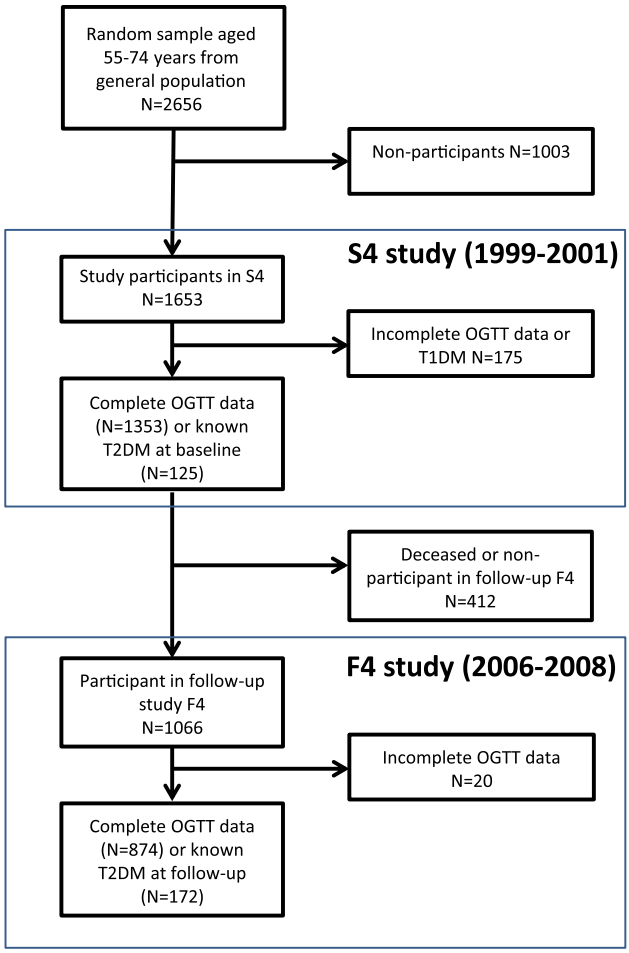


**Fig. 1** Flow chart of participants

### Glucose metabolism status

Prediabetes was defined as IFG and/or IGT. IFG and IGT were defined according to the 2003 ADA diagnostic criteria (IFG: fasting glucose 5.6–6.9 mmol/l, IGT: 2-h glucose 7.8–11.0 mmol/l) [10]. Previously unknown diabetes was defined as fasting glucose $\geq$7.0 mmol/l or 2-h glucose $\geq$11.1 mmol/l. Previously known diabetes was determined by the self-reported use of antidiabetic agents and by asking participants if they had ever been told by a physician that they had diabetes.

### HRQL

HRQL was assessed with the SF-12 Health Survey Version 1 through a face-to-face interview at baseline and through a self-administered questionnaire at follow-up. The SF-12 consists of 12 items covering 8 empirically distinct health domains and provides a physical (PCS) and a mental (MCS) component score. Both scores are standardized with a mean of 50 and a standard deviation of 10 points with higher scores indicating better health.

### Statistical analysis

First, in a cross-sectional analysis, we examined whether there were significant differences in HRQL at baseline between individuals with NGT, prediabetes, previously unknown and previously known T2DM. Therefore we estimated mean PCS and MCS scores, adjusted by age, sex and body mass index (BMI) in categories, and tested differences using a linear regression model.

Second, in a longitudinal analysis, we examined how change in glucose status was associated with change in HRQL over time. Therefore, we created a variable that divides participants into mutually exclusive change categories, defined by the possible combinations between NGT,

prediabetes, or diabetes at baseline and follow-up, respectively. To avoid unreliable results caused by small cell sizes, the longitudinal analysis no longer distinguished between previously known and previously unknown diabetes. Also, we excluded 14 participants who had glucose levels indicating diabetes in S4 but values indicating prediabetes or NGT in F4. Then, we regressed PCS and MCS change scores on this categorical change variable, adjusting by sex and education, as well as by age, BMI and physical activity at baseline. Education, BMI and physical activity were included in the model because, apart from age, these variables were associated with participation in the follow-up study. From the estimated regression coefficients of this linear model, we finally derived adjusted mean change scores together with their 95 % confidence intervals for each glucose status change category.

In additional analyses, we stratified all analyses by sex and also included BMI change between baseline and follow-up in the longitudinal analyses.

## Results

Baseline characteristics of the sample, stratified by glucose status at baseline, are shown in Table 1. Missing values in the SF-12 at baseline reduced the final sample size for the cross-sectional analysis to 1,037 and in the longitudinal analyses to 963. Further adjustment for covariates additionally reduced the sample size of cross-sectional and longitudinal analysis by 5 and 8, respectively.

At baseline, there were no significant differences in mean PCS scores ($p = 0.21$) or mean MCS scores ($p = 0.19$) between individuals with NGT (PCS: 45.3, MCS: 52.1), prediabetes (PCS: 46.0, MCS: 52.9), previously unknown diabetes (PCS: 45.3, MCS: 52.5) or previously known diabetes (PCS: 43.7, MCS: 50.6). Women had on average 2.3 points lower PCS scores ($p < 0.0001$) and 3.7 points lower MCS scores ($p < 0.0001$) than men, but differences in PCS and MCS score between glucose status groups remained insignificant if analyses were stratified by sex.

**Table 1** Characteristics of participants by glucose metabolism status at baseline

| Variable | NGT ($N = 453$) | Prediabetes ($N = 442$) | Previously unknown diabetes ($N = 80$) | Previously known diabetes ($N = 71$) | $p$ value[a] |
|---|---|---|---|---|---|
| Mean age [years, (SD)] | 62.7 (5.5) | 63.7 (5.3) | 63.9 (4.9) | 64.3 (5.2) | 0.009 |
| Male sex [n (%)] | 195 (43.0 %) | 258 (58.4 %) | 50 (62.5 %) | 41 (57.8 %) | <0.0001 |
| Education [n (%)] | | | | | 0.17 |
| Primary | 300 (66.4 %) | 286 (64.7 %) | 61 (76.3 %) | 55 (77.5 %) | |
| Secondary | 91 (20.1 %) | 90 (20.4 %) | 10 (12.5 %) | 7 (9.9 %) | |
| Tertiary | 61 (13.5 %) | 66 (14.9 %) | 9 (11.3 %) | 9 (12.7 %) | |
| Physical activity [n (%)] | | | | | 0.003 |
| >2 h/week, Regularly | 89 (19.7 %) | 83 (18.8 %) | 11 (13.8 %) | 7 (10.0 %) | |
| 1 h/week, Regularly | 133 (29.4 %) | 115 (26.1 %) | 15 (18.8 %) | 12 (17.1 %) | |
| 1 h/week, Irregularly | 73 (16.1 %) | 75 (17.0 %) | 10 (12.5 %) | 10 (14.3 %) | |
| No physical activity | 157 (34.7 %) | 168 (38.1 %) | 44 (55.0 %) | 41 (58.6 %) | |
| Mean BMI [kg/m2, (SD)] | 27.3 (3.9) | 29.0 (3.9) | 29.9 (4.2) | 31.8 (4.9) | <0.0001 |
| Mean HbA1c [%, (SD)] | 5.5 (0.3) | 5.7 (0.3) | 6.3 (1.2) | 7.1 (1.4) | <0.0001 |
| History of myocardial infarction [n (%)] | 19 (4.2 %) | 14 (3.2 %) | 4 (5.0 %) | 5 (7.0 %) | 0.36 |
| Angina [n (%)] | 35 (7.8 %) | 40 (9.1 %) | 10 (12.5 %) | 7 (10.0 %) | 0.55 |
| History of stroke [n (%)] | 9 (2.0 %) | 9 (2.0 %) | 1 (1.3 %) | 3 (4.2 %) | 0.58 |
| Physician diagnosed hypertension | | | | | <0.0001 |
| Yes | 177 (39.2 %) | 241 (54.7 %) | 55 (68.8 %) | 54 (76.1 %) | |
| No | 269 (59.5 %) | 196 (44.4 %) | 25 (31.3 %) | 15 (21.1 %) | |
| NA | 6 (1.3 %) | 4 (0.9 %) | 0 (0.0 %) | 2 (2.8 %) | |
| Glucose status at follow-up [n (%)] | | | | | <0.0001 |
| NGT | 307 (67.8 %) | 89 (20.1 %) | 2 (2.5 %) | 0 (0.0 %) | |
| Prediabetes | 134 (29.6 %) | 265 (60.0 %) | 12 (15.0 %) | 0 (0.0 %) | |
| Diabetes | 12 (2.7 %) | 88 (19.9 %) | 66 (82.5 %) | 71 (100.0 %) | |

*NGT* normal glucose tolerance, *SD* standard deviation, *BMI* body mass index, *HbA1c* hemoglobin A1c

[a] $p$ values are based on $t$ test for continuous and Chi square test for categorical variables. An exception is myocardial infarction where Fisher's exact test was used

**Table 2** Adjusted mean change in SF-12 summary scale scores depending on glucose metabolism status at baseline and follow-up

| Glucose metabolism at follow-up (→) at baseline (↓) | SF-12 physical component scale | | | SF-12 mental component scale | | |
|---|---|---|---|---|---|---|
| | NGT | Prediabetes | T2DM | NGT | Prediabetes | T2DM |
| *Men and women (N = 963)* | | | | | | |
| NGT[a] | −1.08 (−2.24 to 0.09) | −2.31 (−3.99 to -0.63) | −7.44* (−13.09 to −1.79) | −0.02 (−1.36 to 1.32) | −1.25 (−3.18 to 0.68) | −2.23 (−8.72 to 4.26) |
| Prediabetes[b] | −1.89 (−4.01 to 0.21) | −1.44 (−2.62 to -0.25) | −1.85 (−3.91 to 0.20) | 0.60 (−1.82 to 3.02) | 0.55 (−0.80 to 1.91) | −2.89* (−5.26 to −0.53) |
| T2DM | | | −1.83 (−3.58 to −0.09) | | | −2.03 (−4.04 to −0.03) |
| *Men (N = 506)* | | | | | | |
| NGT[a] | −1.79 (−3.54 to −0.05) | −1.05 (−3.59 to 1.48) | −17.24* (−26.57 to −7.90) | −0.59 (−2.40 to 1.22) | −2.64 (−5.28 to −0.01) | −4.73 (−14.44 to 4.98) |
| Prediabetes[b] | −0.64 (−3.89 to 2.61) | −1.23 (−2.73 to 0.27) | −1.74 (−4.24 to 0.77) | 2.64 (−0.74 to 6.02) | 0.43 (−1.13 to 2.00) | −3.13* (−5.74 to −0.53) |
| T2DM | | | −1.09 (−3.21 to 1.03) | | | −2.48 (−4.68 to −0.27) |
| *Women (N = 457)* | | | | | | |
| NGT[a] | −0.39 (−1.94 to 1.15) | −3.39* (−5.62 to −1.15) | −2.72 (−9.82 to 4.38) | 0.38 (−1.60 to 2.36) | −0.14 (−2.99 to 2.71) | −0.64 (−9.70 to 8.42) |
| Prediabetes[b] | −2.82 (−5.58 to −0.07) | −2.05 (−3.93 to −0.16) | −1.50 (−5.06 to 2.05) | −0.45 (−3.97 to 3.07) | 0.50 (−1.89 to 2.91) | −2.44 (−6.98 to 2.10) |
| T2DM | | | −3.07 (−6.12 to −0.03) | | | −1.18 (−5.07 to 2.70) |

*NGT* normal glucose tolerance, *T2DM* type 2 diabetes mellitus, *PCS* physical component summary scale, *MCS* mental component summary scale

* $p < 0.05$

[a] $p$ values refer to comparison with persisting NGT

[b] $p$ values refer to comparison with persisting prediabetes

Results for the longitudinal analyses are shown in Table 2. Individuals with NGT at baseline who progressed to prediabetes (−2.31) or diabetes (−7.44) experienced a greater loss in mean PCS scores than patients with persistent NGT (−1.08), but the difference was only significant for subjects converting from NGT to diabetes. Subjects with prediabetes at baseline and diabetes at follow-up (−2.89) had a significant loss in mental health compared to subjects with persistent prediabetes (+0.55).

Sex-specific analyses showed that results for men were similar to those from the whole sample. Women with NGT at baseline and prediabetes at follow-up had a significant loss in PCS scores compared to women with persistent NGT, however, all other group comparisons in the female sample were not significant. The additional inclusion of BMI change as a covariate did not alter the observed associations.

## Discussion

This study examined the association between change in glucose metabolism and HRQL over time in a population-based German cohort. We observed a general trend that progression from NGT to prediabetes or T2DM or progression from prediabetes to T2DM was associated with a higher decline of physical and mental health, but results were only significant for progression to T2DM.

Prediabetes has no specific symptoms, but the potential loss of physical health may be caused by an already elevated risk for diabetic complications. Studies have shown modest increases in risks for cardiovascular disease, microalbuminuria and retinopathy and individuals with prediabetes can already show various forms of diabetic neuropathy [11–14]. Nevertheless, due to the high overlap in the prevalence of prediabetes and the metabolic syndrome, it is also possible that the higher risk for complications is mediated through other components of the metabolic syndrome such as abdominal obesity, hypertension or dyslipidemia [12]. Also, if some individuals start taking medications against hypertension between baseline and follow-up, this might affect the estimated change in HRQL: Studies have shown that blood pressure control with well-tolerated medication regimes can improve HRQL, but that on the other hand, impairments in health status can occur if antihypertensive drugs have side effects [15]. However, in a recent longitudinal study in German patients with type 2 diabetes, there was no link between treatment of hypertension and SF-12 scores [16]. For subjects with newly diagnosed or known diabetes, change in HRQL is likely to be even more related to comorbidities, especially cardiovascular disease, than for individuals with prediabetes [17, 18].

With respect to mental health, numerous studies have observed a negative association between mental health and T2DM [2, 19]. This may be caused by the effects of the diabetes diagnosis itself, the psychological stress associated with diabetes management or by the burden of diabetic complications [20]. For prediabetes, associations are less consistent. Adriaanse et al. [21] observed that depressive symptoms are more common in women with prediabetes. However, a recent meta-analysis concluded that there are no differences between patients with NGT, IGT and undiagnosed diabetes [22]. Also, the relationship between mental health and impaired glucose metabolism is likely to be bidirectional in that depressive symptoms or psychological distress may also lead to a higher risk of prediabetes [23]. Finally, some studies even found that prediabetes was inversely associated with incident depressive symptoms, which might be explained by the effect of specific antidepressant medication suspected to decrease inflammatory markers and increase insulin sensitivity [20, 24]. While we know of no other longitudinal study on HRQL and glucose tolerance, another longitudinal population-based German study has examined the link between glycemic status measured by glycated hemoglobin (HbA1c) and the SF-12 in subjects with type 2 diabetes, but found no significant association for PCS or MCS scores [18].

Our study had several limitations. First, our longitudinal analyses are restricted to individuals aged 55 to 74 at baseline because OGT tests in S4 were not administered in all participants. This also led to small cell sizes for specific combinations of change in glucose status which may reduce the power to detect potentially relevant associations. Second, around 20 % of the S4 participants refused to participate in the follow-up study and this may limit the validity of our longitudinal analyses. Finally, the different administration modes of the SF-12 at baseline and follow-up could have influenced the estimation of change. Strengths include the longitudinal design and that we used the OGTT as the gold standard to determine glucose metabolism status.

In conclusion, there is first evidence that worsening of glucose metabolism over time is associated with deteriorating HRQL, however, further and larger longitudinal studies are needed to validate these findings and clarify potential causal pathways.

**Acknowledgments** The KORA research platform (KORA, Cooperative Research in the Region of Augsburg) was initiated and financed by the Helmholtz Zentrum München-German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research and by the State of Bavaria.

## References

1. Janssen, M. F., Lubetkin, E. I., Sekhobo, J. P., & Pickard, A. S. (2011). The use of the EQ-5D preference-based health status measure in adults with Type 2 diabetes mellitus. *Diabetic Medicine, 28*(4), 395–413. doi:10.1111/j.1464-5491.2010.03136.x.

2. Schunk, M., Reitmeir, P., Schipf, S., Volzke, H., Meisinger, C., Thorand, B., et al. (2012). Health-related quality of life in subjects with and without type 2 diabetes: pooled analysis of five population-based surveys in Germany. *Diabetic Medicine, 29*(5), 646–653. doi:10.1111/j.1464-5491.2011.03465.x.
3. Chittleborough, C. R., Baldock, K. L., Taylor, A. W., Phillips, P. J., & North West Adelaide Health Study, T. (2006). Health status assessed by the SF-36 along the diabetes continuum in an Australian population. *Quality of Life Research, 15*(4), 687–694. doi:10.1007/s11136-005-3570-8.
4. Marcuello, C., Calle-Pascual, A. L., Fuentes, M., Runkle, I., Soriguer, F., Goday, A., et al. (2012). Evaluation of health-related quality of life according to carbohydrate metabolism status: a Spanish population-based study (Di@bet.es Study). *International Journal of Endocrinology, 2012*, 872305. doi:10.1155/2012/872305.
5. Seppala, T., Saxen, U., Kautiainen, H., Jarvenpaa, S., & Korhonen, P. E. (2013). Impaired glucose metabolism and health related quality of life. *Prim Care Diabetes,*. doi:10.1016/j.pcd.2013.03.001.
6. Tapp, R. J., Dunstan, D. W., Phillips, P., Tonkin, A., Zimmet, P. Z., Shaw, J. E., et al. (2006). Association between impaired glucose metabolism and quality of life: Results from the Australian diabetes obesity and lifestyle study. *Diabetes Research and Clinical Practice, 74*(2), 154–161. doi:10.1016/j.diabres.2006.03.012.
7. Tapp, R. J., O'Neil, A., Shaw, J. E., Zimmet, P. Z., Oldenburg, B. F., & AusDiab Study, G. (2010). Is there a link between components of health-related functioning and incident impaired glucose metabolism and type 2 diabetes? The Australian diabetes obesity and lifestyle (AusDiab) study. *Diabetes Care, 33*(4), 757–762. doi:10.2337/dc09-1107.
8. Kowall, B., Rathmann, W., Heier, M., Holle, R., Peters, A., Thorand, B., et al. (2012). Impact of weight and weight change on normalization of prediabetes and on persistence of normal glucose tolerance in an older population: the KORA S4/F4 study. *International Journal of Obesity (Lond), 36*(6), 826–833. doi:10.1038/ijo.2011.161.
9. Rathmann, W., Haastert, B., Icks, A., Lowel, H., Meisinger, C., Holle, R., et al. (2003). High prevalence of undiagnosed diabetes mellitus in Southern Germany: target populations for efficient screening. The KORA survey 2000. *Diabetologia, 46*(2), 182–189. doi:10.1007/s00125-002-1025-0.
10. Genuth, S., Alberti, K. G., Bennett, P., Buse, J., Defronzo, R., Kahn, R., et al. (2003). Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care, 26*(11), 3160–3167.
11. Ford, E. S., Zhao, G., & Li, C. (2010). Pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. *Journal of the American College of Cardiology, 55*(13), 1310–1317. doi:10.1016/j.jacc.2009.10.060.
12. Grundy, S. M. (2012). Pre-diabetes, metabolic syndrome and cardiovascular risk. *Journal of the American College of Cardiology, 59*(7), 635–643. doi:10.1016/j.jacc.2011.08.080.
13. Rajabally, Y. A. (2011). Neuropathy and impaired glucose tolerance: an updated review of the evidence. *Acta Neurologica Scandinavica, 124*(1), 1–8. doi:10.1111/j.1600-0404.2010.01425.x.
14. Ziegler, D., Rathmann, W., Dickhaus, T., Meisinger, C., Mielck, A., & Group, K. S. (2008). Prevalence of polyneuropathy in pre-diabetes and diabetes is associated with abdominal obesity and macroangiopathy: the MONICA/KORA Augsburg Surveys S2 and S3. *Diabetes Care, 31*(3), 464–469. doi:10.2337/dc07-1796.
15. Handler, J. (2005). Quality of life and antihypertensive drug therapy. *The Journal of Clinical Hypertension (Greenwich), 7*(5), 274–285.
16. Maatouk, I., Wild, B., Herzog, W., Wesche, D., Schellberg, D., Schottker, B., et al. (2012). Longitudinal predictors of health-related quality of life in middle-aged and older adults with hypertension: results of a population-based study. *Journal of Hypertension, 30*(7), 1364–1372. doi:10.1097/HJH.0b013e328353d81b.
17. Hunger, M., Thorand, B., Schunk, M., Doring, A., Menn, P., Peters, A., et al. (2011). Multimorbidity and health-related quality of life in the older population: results from the German KORA-age study. *Health Qual Life Outcomes, 9*, 53. doi:10.1186/1477-7525-9-53.
18. Maatouk, I., Wild, B., Wesche, D., Herzog, W., Raum, E., Muller, H., et al. (2012). Temporal predictors of health-related quality of life in elderly people with diabetes: results of a German cohort study. *PLoS ONE, 7*(1), e31088. doi:10.1371/journal.pone.0031088.
19. Ali, S., Stone, M. A., Peters, J. L., Davies, M. J., & Khunti, K. (2006). The prevalence of co-morbid depression in adults with type 2 diabetes: a systematic review and meta-analysis. *Diabetic Medicine, 23*(11), 1165–1173. doi:10.1111/j.1464-5491.2006.01943.x.
20. Golden, S. H., Lazo, M., Carnethon, M., Bertoni, A. G., Schreiner, P. J., Diez Roux, A. V., et al. (2008). Examining a bidirectional association between depressive symptoms and diabetes. *JAMA, 299*(23), 2751–2759. doi:10.1001/jama.299.23.2751.
21. Adriaanse, M. C., Dekker, J. M., Heine, R. J., Snoek, F. J., Beekman, A. J., Stehouwer, C. D., et al. (2008). Symptoms of depression in people with impaired glucose metabolism or type 2 diabetes mellitus: The Hoorn Study. *Diabetic Medicine, 25*(7), 843–849. doi:10.1111/j.1464-5491.2008.02464.x.
22. Nouwen, A., Nefs, G., Caramlau, I., Connock, M., Winkley, K., Lloyd, C. E., et al. (2011). Prevalence of depression in individuals with impaired glucose metabolism or undiagnosed diabetes: a systematic review and meta-analysis of the European Depression in Diabetes (EDID) Research Consortium. *Diabetes Care, 34*(3), 752–762. doi:10.2337/dc10-1414.
23. Eriksson, A. K., Ekbom, A., Granath, F., Hilding, A., Efendic, S., & Ostenson, C. G. (2008). Psychological distress and risk of pre-diabetes and type 2 diabetes in a prospective study of Swedish middle-aged men and women. *Diabetic Medicine, 25*(7), 834–842. doi:10.1111/j.1464-5491.2008.02463.x.
24. Silva, N., Atlantis, E., & Ismail, K. (2012). A review of the association between depression and insulin resistance: pitfalls of secondary analyses or a promising new approach to prevention of type 2 diabetes? *Current psychiatry reports, 14*(1), 8–14. doi:10.1007/s11920-011-0245-8.