SUMMARY

This section provides an overview of the content of this thesis per chapter.

Chapter 1 introduces the pressing global health issue of comorbid depression in patients with diabetes mellitus type 2 (DM2) and/or coronary heart disease (CHD). The rationale behind the research questions investigated in this thesis is explained in detail. In short, depression, DM2 and CHD are individually leading contributors to the global burden of disease but also often co-occur. Given the public health significance of poorly treatable co-morbid depression among patients with DM2 and CHD, research is necessary to determine whether integrated mental and somatic health care strategies to prevent the development of major depressive disorder (MDD), could reduce its burden of disease. This thesis aims to gather more knowledge about how to prevent MDD in primary care patients with DM2 and/or CHD and subthreshold depression.

In chapter 2, the design of the Step-Dep study, an economic evaluation conducted alongside a pragmatic cluster randomized controlled trial, is described. The objective of the Step-Dep study was to evaluate the effectiveness and cost-effectiveness of a nurse-led stepped-care program as compared to usual primary care to prevent MDD among patients with DM2 and/or CHD and subthreshold depression. The latter was defined as having clinically relevant depressive symptoms, as indicated by a Patient Health Questionnaire 9 (PHQ-9) ≥ 6, but no MDD according to the Mini International Neuropsychiatric Interview (MINI). The stepped-care intervention consisted of four increasingly intensive sequential steps; 1) watchful waiting, 2) guided self-help, 3) problem solving treatment (PST) and 4) referral to the general practitioner. The primary clinical outcome measure was the cumulative incidence of MDD as determined with the MINI. Secondary outcomes included severity of depressive and anxiety symptoms as well as quality of life. Costs were measured from a societal perspective and included health care utilization, medication and lost productivity costs. Measurements were performed at baseline and at 3, 6, 9 and 12 months of follow-up.

Chapter 3 reports the results of the effectiveness evaluation of Step-Dep. A total of 27 primary care centers participated and 236 patients were allocated to the intervention group (n=96) or usual care group (n=140). Of these 236 patients, 210 (89%) completed the MINI at 12 months. The cumulative incidence of MDD was lower than expected in both groups: 9 out of 89 participants (10.1%) in the intervention group and 12 out of 121 participants (9.9%) in the usual care group.
Mixed model analyses were used and conducted according to the intention-to-treat principle. We found no statistically significant overall effect of the intervention (OR=1.21 and 95% CI (0.12; 12.41)) and there were no clinically relevant, statistically significant differences in the course or severity of secondary outcomes (severity of depression and anxiety symptoms, and perceived recovery) between the 2 groups.

In chapter 4, we present a qualitative process evaluation of Step-Dep, exploring the experiences with the intervention from a patient and practice nurse perspective. The main facilitators and barriers of the intervention were identified. The RE-AIM model was used to assess perspectives on five dimensions of the intervention: reach, efficacy, adoption, implementation and maintenance. Data were collected through semi-structured interviews with 24 participants from the Step-Dep intervention (15 purposively sampled patients and all 9 participating practice nurses) and a thematic analysis of the data was performed. The process evaluation showed, despite a negative trial, that Step-Dep was perceived as beneficial for patients’ well-being by both patients and practice nurses. The increased awareness of mental health problems in chronic disease management and improved accessibility and decreased experienced stigma of receiving mental health care were viewed as important facilitators of the pro-active Step-Dep approach. Additionally, regularly filling out the PHQ-9 both functioned as a useful starting point for the conversation on mental health and provided patients with more insight into their mental health. Monitoring mental health was deemed important in chronically ill patients by both patients and practice nurses. A main barrier appeared to be that virtually all patients named the importance of contributing to scientific research as (one of) their main motivator(s) to participate, whereas less than half named the desire to improve their mood as a primary motivation. Furthermore, various practice nurses preferred offering therapy tailored to the individual patient rather than pre-determined interventions in a protocolled sequence. Patients and practice nurses did not widely support the use of the PHQ-9 to monitor depressive symptoms or to base treatment decisions on. Finally, somatic practice nurses expressed a lack of competence to recognize and treat mental health problems.

Chapter 5 offers a qualitative study that aims to explore patients’ and practice nurses’ perceptions of depression in patients with DM2 and/or CHD that were screened for subthreshold depression. Semi-structured interviews were conducted with 15 patients and 9 practice nurses who participated in the Step-Dep intervention. A topic guide that drew upon the Common Sense Self-Regulation Model of Health and Illness was used, with a focus on illness perception (‘identi-
ty'), need for care ('control/cure'), causes of depression and the interplay with DM2 and/or CHD ('cause'). The patients’ and practice nurses’ datasets were inspected for commonalities using a constant comparative method which led to a final thematic framework. Both patients’ and practice nurses’ perceptions of depressive symptom severity at inclusion of Step-Dep varied from ‘not depressed’ to ‘severely depressed’ and were not necessarily congruent with the PHQ-9 scores. Patients generally considered themselves at least mildly depressed; but initially recognizing or naming their mental state as a (subthreshold) depression was difficult for some. Having trouble sleeping was frequently experienced as the most burdensome symptom. Most patients experienced a need for care, and psycho-educational advice and talking therapy were preferred. Practice nurses frequently perceived patients as ‘not depressed’ and with minimal need for specific care, except for attention. In patients, perceived symptom severity corresponded with perceived need for care, but this did not necessarily match their help-seeking behaviour due to experienced barriers. Examples of such barriers were the experienced stigma about depression and a lack of awareness of mental health care possibilities. Though the majority of reported causes for depression were related to negative life events and circumstances, patients and practice nurses also generally perceived indirect causal links with DM2 and/or CHD.

Chapter 6 comprises a study that both evaluated the effectiveness of the Step-Dep intervention in comparison to usual care in reducing the incidence of MDD during 24 months of follow-up among primary care patients with DM2 and/or CHD and subthreshold depression, and investigated which factors predict incident MDD during 24 months of follow-up in this patient group. Data from the 236 Step-Dep patients were used. For the effectiveness analyses, Generalized Estimating Equations (GEE) were used for binary outcome variables and linear mixed models for longitudinal data for continuous outcome variables. Results showed that the cumulative incidence of MDD (as measured with the MINI at 6, 12 and 24 months of follow-up) was about 17% in both groups. There was no clinically relevant, statistically significant overall treatment effect of the intervention over 24 months (OR 1.37 and 95% CI (0.52; 3.55)) nor at any of the time-points, nor in the course or severity of secondary outcomes. The statistically non-significant intervention effects for incident MDD at both 12-months and 24-months of follow-up justified using the Step-Dep population as a cohort. Subsequently, we created a multivariable logistic regression model using the demographic and psychological baseline variables estimating the probability of having at least one MDD (defined as a PHQ-9 ≥10) during the two-year assessment. Data of 192 patients (81%) were available at two-year follow-up. The cumulative incidence of MDD (as measured with the PHQ-9 with measurement at 3, 6, 9, 12 and 24 months) was 97/192
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(51%). Baseline levels of anxiety, depression, the presence of more than three chronic diseases and stressful life-events predicted the incidence of MDD. The final model with these four factors performed well (Hosmer–Lemeshow test p=0.12 and median of pooled Nagelkerke’s $R^2$ explained variance 0.34 interquartile range (IQR) 0.33-0.36) with good discriminative properties (median of the pooled AUC 0.80 IQR 0.79-0.80) and continued to do so after internal validation using bootstrapping techniques.

In chapter 7 we reflect upon the outcomes of the abovementioned chapters and their implications for research and daily practice. The interpretation of the main quantitative and qualitative findings is discussed in a clinical perspective using three overarching questions.

1. **How should a subthreshold depression, as measured with a PHQ-9 ≥ 6, in primary care patients with DM2 and/or CHD be interpreted?**
   A subthreshold depression in these patients posed a lower than expected risk of MDD during two-year follow-up. Because symptoms of depression and DM2 and/or CHD can partly overlap, there is a risk of over-diagnosing subthreshold depression in this population. Additionally, the PHQ-9 might not be sufficiently discriminative to avoid mislabeling ‘neighboring’ constructs such as anxiety or sleeping disorders as subthreshold depression. Nevertheless, as patients generally perceived the subthreshold depression they were screened for as burdensome, it does merit attention in chronic disease care.

2. **Why was the Step-Dep intervention not more effective in preventing MDD compared to usual care?**
   A relatively low rate of care adherence in addition to the lower than expected prior risk of MDD in our population could predominantly explain the lack of effectiveness of the Step-Dep intervention as compared to usual care. Additionally, due to the research setting, usual care might have been ‘enhanced’ in comparison to daily practice. Offering preventive interventions to higher risk patients according to their preferences instead of stepped-care principles might be more effective, although it could also lead to an increase in costs.

3. **How might depression prevention in patients with DM2 and/or CHD be feasible in primary care?**
   Both interviewed patients and practice nurses believed that mental health is currently a severely under-discussed topic in the care for the chronically ill. Paying more attention to depressive
symptoms in all DM2 and/or CHD patients might increase the awareness of these problems in the chronically ill and could improve accessibility and decrease the experienced stigma of receiving mental health care. Subsequently, future effective depression prevention interventions should target those with the highest MDD risk; possibly those with persistently and clinically significantly elevated levels of both anxiety and depression, the presence of more than three chronic diseases and stressful life-events. Furthermore, it should be verified if general practitioners and practice nurses feel sufficiently competent and supportive to deliver the mental health care tasks assigned to them, to make depression prevention in primary care feasible.

Lastly, the following box is presented which provides a summary of recommendations for primary care practice based on this thesis:

- The widespread implementation of the Step-Dep intervention is currently not recommended, as it was not more effective than usual care in preventing MDD during 12 or 24 months of follow-up. Further research is needed to determine to whom and which preventive psychological interventions should be offered to achieve effective depression prevention in patients with DM2 and/or CHD in primary care.
- The PHQ-9 might not be the optimal instrument to screen for or monitor levels of depressive symptoms in patients with DM2 and/or CHD, due to the risk of over-diagnosing depression severity. The use of the PHQ-9 does provide an easy starting point for the conversation on psychological problems and improves patients' insight into their mental state. Better instruments are needed to accurately determine depression severity in DM2 and/or CHD patients, which are also supported in practice.
- Depression currently seems to be a severely under discussed topic in chronic disease care. The conversation on and monitoring of depressive symptoms should be routinely included in chronic disease care, as patients appear to experience these as burdensome. This approach might increase the awareness of mental health problems in the chronically ill, improve accessibility and decrease the experienced stigma of receiving mental health care.
- Given the increasingly leading role of somatic practice nurses in chronic disease care, more education and training to recognize and handle psychological problems in the chronically ill may be needed during their vocational training to enhance their (self perceived) competences and skills. Future depression prevention interventions might best be delivered by psychological practice nurses.
- Prevention of depression in patients with DM2 and/or CHD should be reserved for patients with the highest risk of MDD. A PHQ-9 of six or higher alone does not seem to reflect a high enough risk for effective targeted prevention. Instead, the highest risk patients could be those with persistently and clinically significantly elevated levels of anxiety and depression, who have been diagnosed with more than three chronic diseases and who have recently suffered a stressful life event.
- Care adherence to interventions to prevent depression may improve if these depend on the patients’ need for care and preferences instead of stepped-care principles. Strategies to ameliorate sleep and increase physical exercise were preferred by interviewed Step-Dep patients and potentially benefit both patients’ mental and somatic health status.