Health locus of control, depressive symptoms, and insulin resistance

Implications for treatment and prevention in general population and primary care

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ABSTRACT

The disease burden of type 2 diabetes and depression is large and challenging for healthcare systems. Preventive interventions require resources and better knowledge concerning early stages in the development of these diseases. The aims of this thesis were to explore psychological distress (PD), internal health locus of control (IHLC) and insulin resistance in the population and to investigate the effectiveness of internet-based cognitive behavioural therapy (ICBT) for depression in primary care. Moreover, we aimed to investigate the validity of the question used for IHLC. The association between PD, IHLC and insulin resistance was analyzed in a random population sample (n=2816) in southwest Sweden, the Vara-Skövde Cohort (participation rate: 76%). Papers II and III evaluate ICBT for depression compared with treatment as usual (TAU) in primary care, at post-treatment (II), and after one year (III) in an randomized controlled trial called PRIM-NET (n=90). A validation of IHLC against the Multidimensional Health Locus of Control and the General Self-Efficacy Scale was carried out in Paper IV (n=519). Individuals with low IHLC had higher insulin resistance compared with those with high IHLC, and individuals with PD had higher insulin resistance compared with those without PD. However, the statistically significant differences disappeared in the full models. Individuals with both low IHLC and PD had higher levels of logHOMA-ir also in the final model adjusting for age, sex, education, smoking, alcohol consumption, BMI, and physical activity (Mean difference: 0.11, 95% CI:0.00-0.09, p=0.033). ICBT for depression was equally effective as TAU in primary care. There were no differences between ICBT and TAU in depressive symptoms, psychological distress, quality of life or sick leave. Weak, but positive support was found for using the global scale IHLC to measure IHLC.

In conclusion, ICBT can be delivered as a routine treatment alternative in primary care and may improve preventive interventions in primary care on a larger scale. Individuals with PD and low IHLC seem to be at higher risk of developing insulin resistance, and preventive interventions in this group may prevent or delay development of type 2 diabetes.

Keywords: depression, locus of control, psychological distress, insulin resistance, ICBT, prevention, primary care

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SAMMANFATTNING PÅ SVENSKA

Depression och typ 2-diabetes är vanliga tillstånd som ofta har hög samsjuklighet och medför en stor sjukdomsbörda. Levnadsvanor har stor betydelse för behandling och prevention i båda tillstånden. Effektiva preventiva insatser kan försena debut och minska förekomst av typ 2-diabetes. Syftet med avhandlingsarbetet var att utforska psykiskt illabefinnande, internt hälsorelaterat kontroll-locus (internal health locus of control, IHLC) och insulinresistens i befolkningen samt att undersöka förutsättningarna för att implementera internetbaserad kognitiv beteendeterapi (iKBT) för depression i en randomiserad kontrollerad studie i primärvården.

Delarbete I baseras på Vara-Skövde-kohorten i Skaraborgsprojektet med 2816 kvinnor och män (76% deltagande), med analyser av sambanden mellan psykiskt välbefinnande, IHLC, och insulin-resistens. Delarbete II och III baseras på projektet PRIM-NET, som jämförde internetförmedlad behandlarstödd KBT med sedvanlig depressionsbehandling vid vårdcentral. Delarbete IV är ett metodarbete, där en fråga som kan användas för screening av IHLC jämfördes mot etablerade frågeformulär.

Individer med lågt IHLC hade högre insulinresistens jämfört med de med högt IHLC och individer med psykiskt illabefinnande hade högre insulinresistens jämfört med de som inte hade psykiskt illabefinnande, men den statistiska signifikansen försvann när sambanden kontrollerades för fysisk aktivitet respektive BMI. Individer med både låg IHLC och psykiskt illabefinnande hade högre insulinresistens även vid justering för samtliga kontrollvariabler. IKBT vid depression var lika effektiv som sedvanlig behandling i primärvård, både efter behandling och vid ett årsuppföljning. Det var inga skillnader varken för depressiva symtom, psykiskt illabefinnande, livskvalitet eller sjukskrivning. Screeningfrågan hade ett svagt men positivt statistiskt stöd för att användas för att mäta IHLC.

Sammanfattningsvis är iKBT ett tillämpbart sätt att behandla depressiva symtom i primärvård, och skulle kunna ge ökade möjligheter för preventiva insatser. Avhandlingen visar på vikten av psykologisk orientering i sjukvården och att preventiva insatser för patienter med psykiskt illabefinnande och lågt internt hälsorelaterat kontroll-locus skulle kunna förebygga eller fördröja debut av typ 2 diabetes.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Eriksson MCM, Lundgren, J, Hellgren, M, Björkelund, C, Lindblad, U, Daka, B. Association between low Internal Health Locus of Control, Psychological Distress and Insulin Resistance, a cross-sectional study. Manuscript.

II. Kivi, M, Eriksson, M, Hange, D, Petersson, E-L, Vernmark, K, Johansson, B, Björkelund, C. Internet-based Therapy for Mild to Moderate Depression in Swedish Primary Care: Short Term Results from the PRIM-NET Randomized Controlled Trial. Cognitive Behaviour Therapy 2014; 43; 289-298.

III. Eriksson, M, Kivi, M, Hange, D, Petersson, E-L, Ariai, N, Häggblad, P, Ågren, H, Spak, F, Lindblad, U, Johansson, J, Björkelund, C. Long-term effects of internet-delivered cognitive behavioral therapy for depression in primary care: The PRIM-NET controlled trial. Scandinavian Journal of primary health care 2017; 35:126–136.

IV. Eriksson, MCM, Lindblad U, Daka B, Lundgren, J. Validation of a single question to measure Internal Health Locus of Control in Swedish primary care. Submitted.

CONTENT

ABBREVIATIONS

BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory II
BMI	Body Mass Index
CBT	Cognitive Behavioural Therapy
EQ5D	EuroQol (Quality of life)
GHQ-12	General Health Questionnaire, 12 items
ICBT	Internet-based Cognitie Behavioural Therapy
HOMA-ir	Homeostasis model assessment of insulin resistance
HPA-axis	Hypothalamic-pituitary-adrenal axis
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IHLC	Internal health locus of control
LTPA	Leisure time physical activity
MINI	Mini International Neuropsychiatric Interview
MADRS-S	Montgomery-Åsberg Depression Rating Scale – self-rating
PD	Psychological distress
VSC	Vara-Skövde Cohort

PREFACE

Health is defined by the WHO as “a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity” (1). We are given different preconditions, but we know that it is good to exercise, eat vegetables, and connect with friends and family. We know that cigarettes are not healthy. We know that we thrive with challenges, and that we need recreation and relaxation, and that we should try to make the best of what we have. Yet, we might, in stressful situations, tell ourselves that fat and sugar are the best choices of intake while either fleeing of playing dead. Our mind will sometimes tell us that we can rest depressive thoughts away, and that another cup of coffee will help us when we are stressed out. Things happen, assignments expand, children and parents need us, things sometimes become difficult, and sometimes it is simply impossible to fall asleep. Some call it life.

Non-communicable diseases dominate the disease panorama in most parts of the world, and health behaviours like regular physical activity, healthy diet, smoking cessation, and reduced alcohol consumption are important factors to prevent and treat these diseases. Healthcare systems are increasingly adopting a biopsychosocial approach with consciousness about the spectacles through which the complexity of life and behaviour is understood. This thesis is an attempt to contribute to better understanding of the development of public health illnesses related to lifestyle, and the role of psychology in it. What is needed, what can we do, when, how, and for whom?

1 INTRODUCTION

1.1 PRIMARY CARE

Primary healthcare is defined by the WHO Europe as: “health care received in the community, usually from family doctors, community nurses, staff in local clinics or other health professionals. It should be universally accessible to individuals and families by means acceptable to them, with their full participation and at a cost that the community and country can afford” (2). The Swedish Health and Social Services Act defines primary care as outpatient care without limitations in terms of illness, age, or patient groups. Primary care is responsible for basic medical treatment, nursing, prevention, and rehabilitation that do not require the medical or technical resources of hospitals or other specialized skills (3).

Sweden has a universal healthcare system that is decentralized, and both public and private. The healthcare system is primarily tax-funded and managed on three levels: national, regional, and local. The regional level is divided in 21 county councils. The county councils regulate the rules and establishment for their primary care centres. In Sweden, according to The Swedish Health and Social Services Act, Swedish regions and municipalities are responsible for providing qualitative healthcare services for common healthcare needs in primary care. This includes easy access and preventative interventions, provided both from a population perspective as well as for the individual patient. Primary care also coordinates healthcare services for patients when primary care is most appropriate for the task and enables participation in research. The healthcare provided must be of good quality with high hygienic standards. It must provide security, continuity, and safety for the patient. Priority is given according to healthcare needs.

The National Board of Health and Welfare issue licences for regulated healthcare professions in Sweden. Most of the primary care centres in Sweden are team-based, with nurses, district nurses, general practitioners, physicians, physiotherapists, psychologists/psychotherapists, and occupational therapists. There are several other professions in primary care. Midwives and gynaecologists are usually organized in separate clinics. In some of the counties, physiotherapists and occupational therapists are organized separately in rehabilitation clinics, and in some they are included in the primary care centres. Home care for the elderly and disabled is primarily managed by municipal primary care.

1.1.1 PATIENTS IN PRIMARY CARE

On average, 1.8 visits to physicians and 3.5 visits to other professions were made in primary care by the inhabitants in the county of Stockholm in 2018 (4). Psychosocial visits accounted for about 0.25 of the 3.5 visits to other professions. A study based on the Swedish VAL database (including primary care and specialized care in region Stockholm) (n=2 323,667) has shown that 21.6 per cent of the patients had 2 or more chronic conditions and that the proportion of comorbidity increased with age (5). At aged 30, almost one third of the population had at least one chronic condition. From the age of 50, there was an increase in chronic conditions, and at aged 70, more than half of the population had 2 or more chronic conditions. Diabetes was the second most common comorbidity and had a prevalence of 4.5 per cent. There were associations between depression and anxiety disorders and all common chronic conditions. The prevalence rate of registered diagnosis of depression was 3.1 per cent, and for anxiety disorder 5.6 per cent, interpreted as possible underreporting of depression and anxiety disorder (5). Underreporting can be due to both under-registration and under-diagnosing, as well as undetected diagnosis. A Swedish study from 2010 found that 20 per cent of the patients seeking care at a primary care centre showed signs of depression (6). These patients were invited to participate in a structured diagnostic interview. Among the patients who agreed to participate in the assessment, 7.7 per cent had a major depressive disorder and 5.0 per cent had a mixed depression and anxiety condition (6). Furthermore, a previous international review on unrecognized depression concluded that less than half of the depressed patients were recognized as such (7).

1.2 PSYCHOLOGICAL HEALTH AND IMPAIRED GLUCOSE METABOLISM

The presence of both depression and diabetes has been called a “prototypical example of mental/physical comorbidity” (8). Depression is rated by the World Health Organization (9) as a major contributor to the global burden of disease, and diabetes as a major cause of blindness, kidney failure, heart attacks and strokes and the ninth leading cause of death. In a comparison of chronic diseases, WHO found that compared with other diseases (angina, arthritis, asthma, and diabetes), depression had the largest negative effect on health scores. Among comorbidities of two diseases, the presence of depression resulted in the lowest health scores, and among comorbidities with depression, comorbid depression and diabetes had the lowest health scores (10). Furthermore, there is high comorbidity between type 2 diabetes and depression (11, 12). There seems to be a bidirectional relationship between depression and type 2 diabetes (13, 14), and also indication of a link between psychological

distress and prediabetes (15). Different mechanisms have been suggested to influence these associations. Firstly, the hypothalamic-pituitary-adrenal axis (HPA-axis) is one of the suggested mechanisms in the link between psychological health and impaired glucose metabolism (16). The HPA-axis is a neuroendocrine system involved in stress reactions, the immune system, the metabolism and more. Secondly, lifestyle is another suggested mechanism, where risk factors for type 2 diabetes, like low level of physical activity, obesity and smoking are more common in individuals with depression (17).

1.2.1 INSULIN RESISTANCE

Insulin resistance refers to the impaired ability of cells to respond to insulin. The condition is associated with an impaired effect of insulin on the glucose metabolism. The most common cause of insulin resistance is obesity and especially abdominal obesity (18). Other situations with increased insulin resistance include pregnancy (19), hormonal disorders (like Cushing's syndrome), and medication with steroids (like cortisone) (20). Physical inactivity (21), smoking (22), and unhealthy diet (23) are also associated with increased insulin resistance. The increase in insulin resistance can be viewed as a continuum on which healthy individuals have low values, and increasing values describe a development of conditions with impaired glucose metabolism, i. e. impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) and finally manifest type 2 diabetes (24). Increased insulin resistance is not only associated with higher risk to develop diabetes, but also increases the risk for cardiovascular complications regardless of the development of diabetes (25).

Weight reduction reduces insulin resistance in overweight individuals. Prevention programmes for prediabetes focusing on weight management, diet and physical activity have had positive results, especially short term (26-28). Physical activity also improves insulin sensitivity independently of weight. An hour of physical workout increases insulin sensitivity and decreases the demand for insulin up to two days, and regular exercise can maintain a higher insulin sensitivity over time.

There are several methods to estimate insulin resistance. Homeostasis model assessment of insulin resistance (HOMA-ir) calculates the resistance based on levels of fasting glucose and fasting insulin (29). Although there is some method bias due to difficulties concerning measurements of insulin that has a pulsatile secretion, this method is largely used in population studies due to its high feasibility.

1.2.2 PSYCHOLOGICAL DISTRESS

The term psychological distress (PD) relates to mental illness and symptoms of depression, anxiety, and stress, including subclinical symptoms. Goldberg's 60-item General Health Questionnaire was developed for the identification of non-psychotic psychiatric illness (Goldberg 1972). Anderson, Huppert and Rose have investigated PD measured with the 30-item General Health Questionnare in a population sample and found strong correlation between the number of cases above threshold in sub-groups and the population mean for those sub-groups. This indicates a relationship between the number of individuals with psychiatric illness and the distribution in the population (30).

PD has been found to increase the risk of developing manifest type 2 diabetes in individuals with IGT/IFG and a high risk score of the Framingham Offspring Type 2 Diabetes risk Score (31). In a Swedish study, PD predicted prediabetes and type 2 diabetes 10 years later in men, while in women higher PD predicted prediabetes 10 years later (15). Related constructs like emotional stress and mental stress have also been found to be associated with increased risk for the development of type 2 diabetes (32). There are also several other constructs related to stress (for example work stress) which are not discussed in this thesis.

PD has been measured in different ways. The Swedish research group mentioned above for example used five questions concerning depression, anxiety, insomnia, fatigue, and apathy(15). The 12-item version of the General Health Questionnaire (GHQ-12) (33) has been widely used to measure psychological distress. A Swedish validation study of the GHQ-12 was recently carried out (34).

1.3 HEALTH LOCUS OF CONTROL

Health locus of control is a construct that describes individual beliefs about the location of control over health outcomes and is often described as a measurement of outcome expectancy. The construct is a further development of the construct Locus of control by Rotter in 1966 (35), where Health locus of control, by Wallston (36), describes outcome expectancies concerning health. Locus of control and Health locus of control are both divided into internal and external, where individuals perceive outcomes to result from their behaviour or personal characteristics (internal), or that the outcomes are a function of chance, luck, or controlled by others (external) (37). External locus is in turn divided into chance or powerful others (controlled by others).

Locus of control correlates with age, socioeconomic status, ethnicity, sex, and health and well-being. It is relatively stable over time (38), but also has both

stable and changeable components, and in terms of social learning theory, is continuously learnt through control attempts with failures and successes (39). In general, the internal locus of control increases in early adulthood, and declines in older ages. Low income, lower educational level and female sex are associated with lower sense of control. However, persons with lower socioeconomic status who have a high sense of control have health status comparable to persons with higher socioeconomic status (40). Furthermore, there are cultural differences in sense of control, and differences in the experiences of persons with lower sense of control across cultures. For example, the relationship between low sense of control and negative experiences does not seem to be present for Asian individuals, which has been suggested to be related to values (38).

High internal locus of control is related to good health (38). Health locus of control is associated with health behaviour, where high internality is associated with healthier behaviours, high chance locus of control is associated with lower levels of healthy behaviours, and associations for powerful others locus are less clear (41). The construct of locus of control has been studied extensively in both depression and in management of type 2 diabetes, and in health behaviour in general (42).

Contructs concerning control have been measured and defined in several ways (43). One of the most widely used assessments of health locus of control is the Multidimensional Health Locus of Control Scale (MHLC) with 18 items (36). A single question to measure internal health locus of control (IHLC) has been used in a few population-based studies (44-46).

1.4 DEPRESSION

Depressive symptoms can be defined as low mood and low interest in activities and people, often combined with feelings of worthlessness and hopelessness, and cognitive, behavioural, and somatic symptoms. Major depressive disorder (47) is a clinical diagnosis that describes depressive symptoms above a certain level, defined in the International Statistical Classification of Disease and related health problems (ICD) (48). The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM) (49) by the American Psychiatric Association is also widely used by clinicians as a complement to the ICD to diagnose psychiatric disorders, although the ICD is the classification used for the registration of diagnoses in Sweden. The Swedish version of the ICD currently used is called ICD-10-SE (50).

Symptom intensity and its effects on function range widely and major depressive disorder is divided into mild, moderate, and severe depression. A mild depression affects the person, but most daily activities can still be carried out. A moderate major depressive disorder usually affects function clearly. In severe depression, symptoms are marked and agonizing, recurrent thoughts of death or suicide are common and sometimes become an imminent risk of suicide. The ability to function in daily activities in life is often seriously reduced. Concentration and memory difficulties, fatigue, lack of initiative and stamina, emotional lability, insomnia, and anxiety are frequent disabilities due to depression. The restricted abilities often become obvious in decision-making and planning. The lifetime prevalence of depressive disorder is between 25-45 per cent for women and 13-27 per cent for men (51, 52). The point prevalence of depression in a Swedish population was found to be 5.2 per cent in 2009 (53). Recurrent depressive episodes are common, and the more episodes a person has had, the more likely additional episodes are (54).

1.5 TREATMENT FOR DEPRESSION

According to the current national guidelines for depression and anxiety syndromes in Sweden, healthcare should offer availability for early assessment and examination of patients with suspected depression, including assessment of suicide risk (55). Patients with depressive disorder should also be offered follow-up and assessment of somatic symptoms, since individuals with depressive disorder have a higher risk of somatic morbidity and mortality. According to the recommendations, adults who have mild to moderate depressive disorder should be offered cognitive behavioural therapy (CBT), interpersonal psychotherapy, and/or pharmacological treatment with antidepressants (55). CBT currently has the highest priority of the three standard treatments. Physical activity, short-term psychodynamic psychotherapy and care management “can” be offered to adults who have mild to moderate depressive disorder, where “can” denotes a lower priority. The choice between treatment alternatives should be made with respect to the severity of the depressive disorder, and in dialogue with the patient. Other types of treatment are recommended for patients with severe depression, and repetitive transcranial stimulation is recommended for adults with moderate to severe depressive disorder. These treatments are generally offered in psychiatric clinics. Patients with recurring depressive disorder should be offered relapse prevention treatment after remission, either pharmacological treatment with antidepressants or relapse preventative CBT (55). Psychological treatment of depression in primary care is preferred by the majority of patients, and seems to have longer lasting effects compared with pharmacological therapy (56).

The national guidelines in Sweden also state that access to psychological treatment in Swedish healthcare is low, primarily due to lack of personnel with competence to deliver the treatment in public healthcare (55). Furthermore, they also state that the healthcare for depressive disorders and anxiety syndromes is underfinanced.

1.5.1 INTERNET-BASED COGNITIVE BEHAVIOURAL THERAPY

Internet-based Cognitive Behavioural Therapy, ICBT in short, refers to cognitive behavioural therapy delivered through internet, commonly as a predefined internet-based treatment programme asynchronically accessible with a password. There are internet-delivered psychological treatments based on other types of psychotherapy, but CBT is by far the most common. Briefly, CBT can be described as a type of psychotherapy based on learning psychology, cognition psychology, and social psychology (57). Individual behaviours, cognitions, and emotions in relation to the context are in focus. CBT is sometimes called an umbrella term spanning many methods and interventions, with the largest subcategories perhaps being cognitive therapy and behavioural therapy.

The ICBT programmes are usually available for computers, tablets, and smartphones. The term ICBT is used as a broad term, sometimes including the type of ICBT programmes described above, but also internet-delivered video psychotherapy, sometimes called online CBT (58), referring to traditional psychological treatment through a screen, synchronically. Computerized therapy is another term, referring to formats such as treatment programmes for stationary computers with or without access to internet (59). Yet another is bibliotherapy, in which psychological treatment is delivered as text files or as a printed book. Printed treatment material and text files are still common, both as material used between live sessions with a psychologist/psychotherapist, and as books also available for the public at bookstores.

There is strong evidence for ICBT for adults with depressive disorder (60). However, ICBT research has mainly been carried out in community settings with patients recruited through advertisement or at specialized clinics, and comparing treatment with waiting lists. Few studies have been conducted in the primary care setting. This may be explained by the complexity and the known difficulties often present in research trials conducted in ordinary primary healthcare clinics (61).

1.6 PREVENTION

Disease prevention refers to interventions aiming to decrease burden of disease and risk factors, and can target individuals and populations (62). Prevention on the individual level typically offers interventions for high-risk individuals, for example by identifying high-risk individuals by screening and offering treatment. Population-based prevention aims to lower risk factors in the whole population. Examples of population-based interventions are alcohol taxes to reduce alcohol consumption, regulations on seat belts for traffic safety, and recreation areas to enhance physical activity, i.e. interventions aiming to lowering the mean value of risk factors in the whole population. The change may not be perceived as beneficial on an individual level but is very powerful on a population level (63). Lowering the population mean value of systolic blood pressure by 4 units predicts a 25 per cent lower number of individuals with hypertension, according to Rose (64) with reference to the Intersalt study (65). This is because the distribution of risk factors in the population is generally approximately normal, displaying a continuity of risk, which means that lowering the mean value of a risk factor reduces the burden of disease for the whole population.

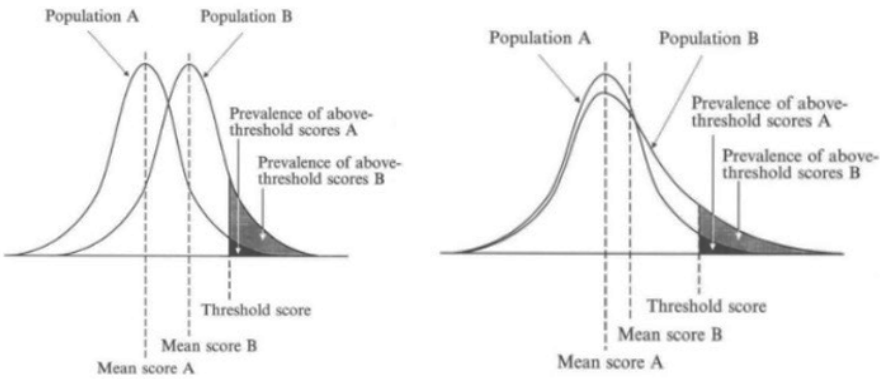

Figure 1. Figures from the publication by Anderson, Huppert and Rose in 1993(30), with permission granted. The distribution in the population as a continuum. The dark areas visualize the difference in number of high-risk individuals with different levels of exposure in the whole population.

2 AIMS

2.1 GENERAL AIM

The aim of this thesis was to explore psychological distress (PD) and internal health locus of control (IHLC) in individuals with regard to impaired glucose metabolism, and to investigate the effectiveness of ICBT as a treatment alternative in primary care. Moreover, we aimed to investigate the validity of the IHLC scale.

2.2 SPECIFIC AIMS

- To assess the associations between low IHLC, PD, and insulin resistance, and to assess the joint effect of low IHLC and PD on insulin resistance

- To examine whether ICBT differed from treatment-as-usual in reducing depressive symptoms after 3 months

- To evaluate long-term effects of ICBT treatment for depression compared with treatment-as-usual in primary care settings

- To investigate the correlation between IHLC and the Multidimensional Health Locus of Control Scale and to assess how IHLC relates to the General Self-Efficacy scale in a primary care setting

3 METHODS

The papers in this thesis are from three different projects. Paper I is based on data from the Vara-Skövde Cohort, a random population sample in the Skaraborg Project. Papers II and III are from the PRIM-NET project, a randomized controlled trial in primary care. Paper IV is based on a data collection for the purpose of a validation of the global scale Internal Health Locus of Control.

3.1 THE VARA-SKÖVDE COHORT

The Vara-Skövde Cohort is a population cohort in The Skaraborg Project. Between 2002 and 2005, a computer-generated random sample of 2,816 persons between 30 and 74 years old were examined in the municipalities of Vara and Skövde in south-west Sweden. The sample was stratified by gender and by 5-year age groups, and was aimed at a three-fold over-sampling in ages below 50 years. In Vara, 1,811 individuals were included (81% participation) and in Skövde 1,105 individuals (70% participation). Experienced and specially trained study nurses carried out a physical examination. Height and weight to the nearest 0.1 kg were measured with light clothes and no shoes. Blood samples were drawn in the morning after an overnight fast (≥10 hours). An oral glucose tolerance test with a 75g standard glucose load was performed. Participants filled in questionnaires regarding socioeconomic status and lifestyle, including physical activity, alcohol consumption and smoking habits.

For Paper I, participants with diabetes mellitus and/or cardiovascular disease (atrial fibrillation, myocardial infarction, angina pectoris, stroke and heart failure, n=249), and participants with missing information for the questionnaires (IHLC or GHQ-12, or HOMA-ir, n=128) were excluded. In total, 2,439 participants were included. Associations between low internal health locus of control (IHLC), psychological distress (GHQ-12) and insulin resistance (HOMA-ir) were assessed. Adjustments were made for possible confounding factors included age, sex, education, alcohol consumption, smoking, BMI, and leisure time physical activity (LTPA).

Internal Health Locus of Control (IHLC). The IHLC is phrased "Do you believe that you can do anything yourself in order to preserve good health?" and has three response alternatives: 1) "yes, to a very high extent"; 2) "Yes, to some extent"; and 3) "No, it is not possible to influence your own health" (44, 46). IHLC was dichotomized by merging 2 and 3, due to the response pattern, and labelled high/low IHLC. **Psychological distress (PD)** was measured by the validated 12-item General Health Questionnaire, with four-point Likert

scale (GHQ-12) (33, 34, 66). Dichotomization with the cut-off at 12 points or more was employed (34). **Insulin resistance (HOMA-ir)** was estimated by the homeostasis model assessment of insulin resistance, (HOMA-ir) (fasting glucose x fasting insulin/22.5) (29). **Age** was calculated based on the patients' social security number. **Sex** was calculated based on the participants' social security number. **Educational level** was assessed by a question with ten response alternatives, presented as the three groups primary school, high school, and higher education. **Alcohol consumption** was assessed by questions concerning the quantities consumed during the past 30 days of beer, wine, or spirits, respectively, and presented in total grams per week (67). **Smoking.** Current smoking was defined based on the question "Do you smoke?" with the answer alternatives: No, I have never smoked; No, I have smoked but have given it up; Yes, I smoke. **Body Mass Index (BMI).** Body weight was measured with participants in light clothes to the nearest 0.1 kg, standing height to the nearest centimetre, and body mass index (BMI) was calculated (weight in kg/height in meters, squared) (68). **Leisure time physical activity (LTPA)** was measured by the question: "How physically active are you during your leisure time? The four response alternatives are: *Sedentary leisure time*: reading, watching television, stamp collecting or other sedentary activity; *Light leisure time physical activity*: walking, cycling, or other physical activity during at least four hours per week; *Moderate leisure time physical activity*: running, swimming, tennis, aerobics, heavier gardening, or similar physical activity during at least 2 hours a week; *Heavy training or competitive sport*: heavy training or competitions in running, skiing, swimming, football, etc., carried out regularly and several times a week (69).

Statistical analyses were performed in SPSS, version 26. All tests were two-sided, and statistical significance was assumed at $p<0.05$. Descriptive statistics were calculated with standard methods. Differences in means were estimated using general linear models with HOMA-ir log transformed due to an abnormal distribution of data. Adjustments were made for possible confounding factors based on theoretical assumptions. Analyses with interaction terms were carried out, and stratified analyses were carried out in the presence of significant interaction. A combined variable was computed based on dichotomized values for PD and IHLC.

Ethics: The Ethical Committee at the University of Gothenburg, Sweden, approved the study: Dnr 199-01, and Dnr 036-12. All participants signed informed consent.

3.2 THE PRIM-NET PROJECT

The PRIM-NET project was a randomized controlled trial in primary care. A total of 90 adult patients were enrolled between March 2010 and March 2013 at 16 primary care centres located in the south-west region of Sweden. Patients 18 years and older with depressive symptoms who attended the study primary care centres were recruited by the general practitioners and nurses, who were instructed to invite all patients they suspected for mild to moderate depression who had not started or changed antidepressant medication the last month.

Before inclusion, a licensed psychologist/psychotherapist carried out a one-hour interview including a diagnostic process based on structured assessment interviews, validated instruments, and scales. Inclusion required diagnosis of depression according to Mini International Neuropsychiatric Interview Swedish version 6.0.0b (MINI) (70), a score below 35 on the Montgomery-Åsberg Depression Rating Scale – self-rating version (MADRS-S) (71), and access to a computer with speakers or headphones. Patients with medium-high suicide risk, prior suicide attempt, or a diagnosis according to MINI of substance dependence, alcohol abuse, bipolar disorder, psychotic disorders, or any other severe psychiatric disorder were excluded. Diagnosed anxiety disorders were allowed if secondary to the depression. No somatic comorbidity was excluded in the study. Patients with cognitive disability or communication difficulties were also excluded. Patients included thereafter met a nurse to fill in questionnaires, including socioeconomic status and sick leave during the past year. The patients were consecutively randomized to either ICBT or treatment as usual (TAU) by an independent research unit. The ICBT group received login and password to the internet treatment called Depressionshjälpen ®, consisting of 7 modules. They also received therapist support from the same therapist who carried out the initial assessment. The therapist followed the patient's progress actively and communicated with the patient every week via a secure email and three telephone contacts (starting up treatment, in the middle and at the end of the treatment). The therapist encouraged the patient to provide feedback about the progress experienced. TAU consisted of the treatments for depression typically provided at the primary care centres (ICBT excluded). There were no restrictions in additional care offered to the patients after inclusion, except for no ICBT for patients in the TAU group, and no psychotherapy at the study primary care centre in the ICBT group. The responsibility for the patients' treatment remained with the primary care centres. After the treatment period, all patients met a nurse at the PCC for a 3-month follow-up. Evaluation with the same instruments was repeated after 6 and 12 months by sending the instruments and prepaid envelopes to the patients. The study protocol has been described in detail in Kivi et al (72).

After a year of difficulties recruiting patients to the project, partly due to organizational changes, a broad vaccination project, and perceived additional workload caused by the research project, an alternative design was set up in which patients were randomized to ICBT or waiting list and offered ICBT after three months. The patients in the alternative design were recruited in primary care centres by general practitioners and nurses the same way as the original design and were patients at their usual primary care centres while waiting for ICBT delivered by the project. After the 3 months, the project organized access to the internet treatment, therapist support and research questionnaires at a central unit.

Papers II and III included 90 patients diagnosed with mild-moderate depression. The number of patients in the two arms differ between Papers II and III due to the different design that was added to the PRIM-NET project after difficulties in recruiting patients. In all, 90 patients were included, 44 patients allocated to ICBT, 38 patients to TAU and eight patients were allocated to the TAU-waiting list (TAU-WL). The eight patients allocated to TAU-WL received ICBT after 3 months. Paper II examined differences between ICBT and TAU at post-treatment after 3 months and included the eight patients in the TAU group. Paper III evaluated long-term effects after 3, 6 and 12 months. The eight patients in TAU-WL received ICBT after the three months waiting list and were consequently included in the ICBT group in Paper III.

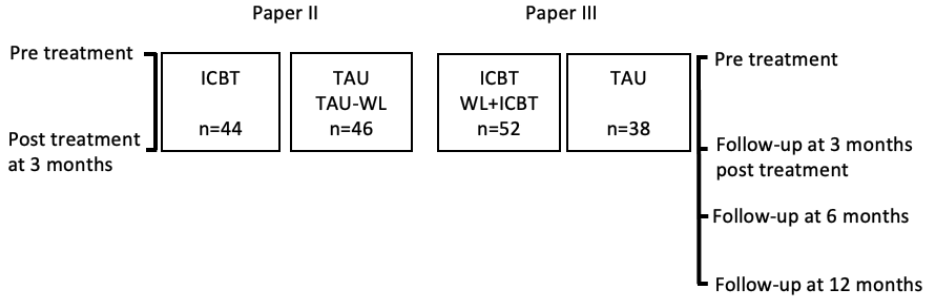

Figure 2. Differences between the groups ICBT and TAU in Papers II and III.

Paper II examined wheather ICB differed from TAU in reducing depressive symptoms after 3 months. Paper III, evaluated the long-term effects of ICBT for depression compared with TAU.

Depressive symptoms were measured with the Beck Depression Inventory II (BDI-II) (73, 74), and with Montgomery-Åsberg Depression Rating Scale – self-rating version (MADRS-S) (71). **Depression.** BDI-II was used for indication of major depression, with a cut-off of ≥14p (73). **Anxiety symptoms** were measured with the Beck Anxiety Inventory (75). **Psychological distress (PD)** was measured by the validated 12-item General Health Questionnaire, with four-point Likert scale (GHQ-12) (33, 34, 66). Likert scoring (0, 1, 2, 3) was used in Paper III (76). **Quality of life (EQ-5D)** was measured by the validated Quality of Life instrument EQ-5D with British tariff (77) and calculated according to Dolan (78). **Antidepressant medication.** Information on use of antidepressants (yes/no) was collected by questionnaire. **Sedative medication.** Information on use of sedatives (yes/no) was collected by questionnaire. **Sick leave** (yes/ no) and number of days of sick leave during 0–3, 4–6 and 7–12 months in PRIM-NET were collected by questionnaires. **Primary care centre contacts (PCC contacts)** The study nurse registered patients' PCC visits to GPs, therapists, and nurses. Visits to GPs and nurses were also collected from electronic patient records (EPR) after the study. In Paper III, data regarding visits to therapists and nurses was obtained from the study protocol, and data regarding GP visits was obtained from EPR. **Age** was calculated based on the participants' and patients' social security number. **Sex** was defined based on the patients' social security number. **Educational level** was assessed by a question with 3 levels: primary school, high school and higher education.

Statistical analyses were carried out in SPSS, version 20. All tests were two-sided, and statistical significance was assumed at $p<0.05$. Descriptive statistics were calculated with standard methods. In **Paper II**, changes in BDI-II, BAI and MADRS-S scores between the groups were calculated for complete cases using univariate ANCOVA adjusted for baseline scores. Within-group changes of scores were analyzed with paired samples t-tests. Furthermore, between- and within-group effect sizes (Cohen's d) were calculated. Finally, differences between groups in recovery rate, with a score of 13 or below on the BDI-II were assessed with χ^2 test. In **Paper III**, differences between the groups concerning depressive symptoms, psychological distress and quality of life were analyzed comparing means of intra-individual change using t-test. Differences in medication, sick leave, and primary care centre contacts were assessed with χ^2 test. Days of sick leave were compared between groups using the Mann–Whitney U test. Effect sizes (Cohen's d) were calculated between and within groups.

Ethics: PRIM-NET The Regional Medical Ethics Review Board in Gothenburg, Sweden approved the protocol (Dnr: 696- 09, T692-11). Written informed consent was obtained from all participants.

3.3 THE VALIDATION STUDY

The validation study included primary care patients, aged 18 and older, attending one of three Primary Care Centres in southwest Sweden. The patients were consecutively asked to participate anonymously in the study during June - October 2018. In all, 534 patients filled in the questionnaire (participation rate 73%).

The patients were offered written information and the possibility to ask questions about the study before giving informed consent. The patients accepting participation were given the questionnaire and instructed to return the questionnaire to a sealed box in the waiting room. The questionnaires were numbered, and personnel were instructed to put the questionnaire in the box when a patient declined to participate, which allowed for calculation of participation rate. The questionnaire contained items concerning birth year, sex, education, occupation, the global scale Internal Health Locus of Control, the Multidimensional Health Locus of Control (MHLC), and the General Self-Efficacy scale (GSE). No data that could identify specific individuals was collected.

A total of 519 participants, aged 18 and older were included in Paper IV after excluding 15 patients due to high amount of missing data. The validity of the global scale IHLC was investigated against the MHLC, and the GSE by assessing strength of correlations and predictive values.

Internal Health Locus of Control (IHLC). The IHLC is phrased "Do you believe that you can do anything yourself in order to preserve good health?" and has three response alternatives: 1) "Yes, to a very high extent"; 2) "Yes, to some extent"; and 3) "No, it is not possible to influence your own health" (44, 46). IHLC was dichotomized by merging 2 and 3, due to the response pattern, and labelled high/low IHLC. **Multidimensional Health Locus of Control (MHLC)** The MHLC (Form A) was used in the validation of the IHLC. The MHLC measures health locus of control and contains 18 questions in three scales of six questions each, called Internality, Powerful Others-Externality, and Chance-Externality (36). A Swedish translation with a five-point Likert scale was used (79). **Self-efficacy** was measured with the General Self-Efficacy scale (GSE) which contains ten questions with response alternatives on a four-point Likert scale (80). A validated Swedish version was used (81). **Age** was calculated based a question of year of birth. **Sex** was measured by a question with the response alternatives male/female. **Educational level** was assessed by a question with 3 levels: primary school, high school and higher education.

Statistical analyses were carried out in SPSS, version 26. All tests were two-sided, and statistical significance was assumed at $p<0.05$. Descriptive statistics were calculated with standard methods. Correlations (r_{rho}) were calculated between the IHLC and the three scales of the MHLC and the GSE, respectively. Logistic regression models were used to test the predictive value of the scales of the MHLC and the GSE for reporting high IHLC. The logistic regression models were carried out controlling for study site.

Ethics: The Ethics Board decided that the study did not formally need any review from them and had no concerns about the conduction of the study: Dnr 307-18, May 18, 2018.

3.4 SUMMARY OF DESIGNS IN PAPERS I-IV

Paper	Design	Subjects	Exposure	Outcome	Statistical methods
I	Cross-sectional study	Population cohort, N=2439	Low Internal health locus of control, and psychological distress	Insulin resistance	General linear models
II	Randomised controlled trial	Primary care patients, N=90	ICBT for depression	Depressive symptoms, diagnosis of depression and symtoms of anxiety after treatment	Univariate ANCOVA, t-test
III	Randomised controlled trial Follow-up at 3-, 6- & 12 months	Primary care patients, N=90	ICBT for depression	Depressivve symptoms, psychological distress, quality of life, use of medication and sick leave at 3-, 6- and 12 months	T-test, $\chi 2$, Mann-Whitney U
IV	Cross-sectional validation study	Participants recruited in primary care, N=519	The IHLC, the MHLC, and the GSE scales	Correlations and predictive values	Correlation, logistic regression
IHLC: Internal health locus of control, MHLC: Multidimensional health locus of control scale, GSE: General self-efficacy scale.					

Figure 3. Summary of design, subjects, and methods in Papers I-IV.

4 RESULTS

4.1 PAPER I

In Paper I, a total of 2,439 participants were included. Mean age was 46 years and 51 per cent were women. Thirteen per cent were retired and 78 per cent were employed. A third (33%) reported higher education, 41 per cent had completed high school, 24 per cent reported an educational level of primary school only. The study population had a mean BMI of 26.5 (SD=4.3) and 18.5 per cent had a BMI of 30 or more. Seven per cent reported a sedentary leisure time physical activity (LTPA), 56 per cent reported low LTPA, 31 per cent reported moderate LTPA, and three per cent reported high LTPA. Figure 4 presents a histogram of the scores the of GHQ-12. The participants were allocated into 4 groups based on reported values for PD and IHLC, as presented in Figure 5.

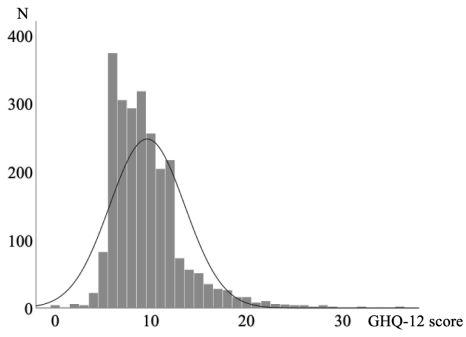

Figure 4. Histogram of the 12 item General Health Questionnaire in the Vara Skövde Cohort (n=2439.

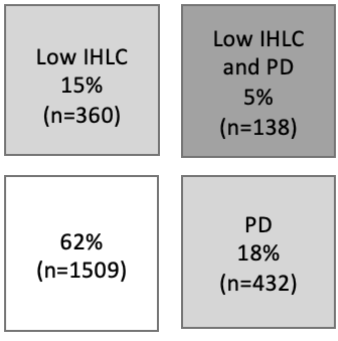

Figure 5. Internal Health Locus of Control and Psychological Distress combined into 4 groups.

A significant association between IHLC and logHOMA-ir was found (Crude: Mean difference=0.04, 95%CI:0.02-0.07, p=0.002). Participants with low IHLC had higher logHOMA-ir. The association remained significant after adjusting for sex, age, alcohol consumption, smoking, education, and BMI, but disappeared when physical activity was included in the model. We carried out an analysis with an interaction term of IHLC x LTPA, which revealed a significant interaction between IHLC and physical activity ($p<0.001$). In stratified analyses, the association between IHLC and HOMA-ir was weak and

insignificant in individuals with high LTPA. However, in individuals with low LTPA there was a strong and statistically significant association between IHLC and HOMA-ir, also after adjusting for age, sex, education, smoking, alcohol consumption and BMI (Mean difference=0.03, 95% CI: 0.00-0.06, p=0.026). A strong and significant association was found between PD (≥12p) and logHOMA-ir, also when adjusting for sex, age, alcohol consumption, smoking, education, and physical activity (Mean difference=0.04, 95% CI: -0.01-0.07, p=0.001). The association was almost statistically significant after also including BMI in the model (Mean difference=0.02, 95%CI: -0.01-0.43, p=0.062).

The presence of both low IHLC and PD was strongly associated with a higher logHOMA-ir also in the final model, adjusting for age, sex, education, smoking, alcohol consumption, BMI, and physical activity (Mean difference=0.11, 95% CI:0.00-0.09, p=0.033).

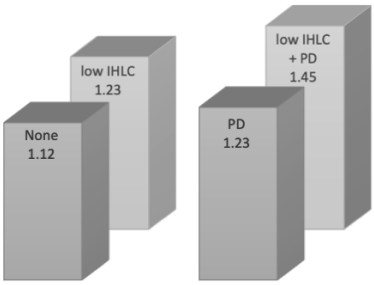

Figure 6. Levels in HOMA-ir in the groups PD, low IHLC and low IHLC and PD combined.

4.2 PAPER II

In Paper II, 90 patients were included. Eight patients allocated to ICBT and three patients allocated to TAU withdrew from participation. The mean age was 36.6 years and 66 per cent (n=52) were women. According to depressive symptoms reported in the BDI-II at baseline, 6 per cent (n=5) had a minimal depression, 19 per cent (n=15) had a mild depression, 34 per cent (n=27) had a moderate depression and 41 per cent (n=32) had a severe depression.

ICBT for depression in primary care was equally effective as TAU at post treatment in the PRIM-NET randomized controlled trial. No significant differences were found between the ICBT group and the TAU group regarding changes in depressive symptoms in scores measured with BDI-II, or with MADRS-S, either during treatment or post treatment. There was no difference

between the groups in symptoms of anxiety after treatment. Possible negative treatment effects were also assessed, and 6% of the patients in the study deteriorated during the treatment period, 10% (n=3) in ICBT and 3% (n=1) in TAU. All seven modules of the ICBT were completed during the 12 weeks by 56% (n=20) of the patients in the ICBT group. Five (5.1) modules were completed on average (q1-3: 2.6-7). In the TAU group, 19 % (n=8) received psychological treatment. As expected, there were no differences between the randomized groups at baseline. Eleven patients in each group had antidepressant medication at inclusion.

4.3 PAPER III

In Paper III, intention-to-treat-analysis was employed, and included all the 90 patients in the analyses. The analyses in Paper III showed that ICBT for depression at primary care centres was equally effective as TAU regarding long-term effects on depressive symptoms and psychological distress (Figure 7). The effect sizes (Cohen's d) between the groups differed only marginally. The within-group effect sizes for both the ICBT group and the TAU group were large (presented in Table 1).

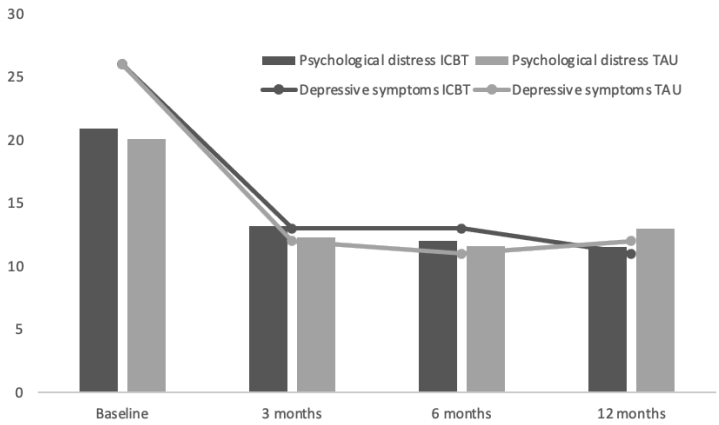

Figure 7. Mean score for psychological distress and depressive symptoms for ICBT and TAU, at baseline, 3, 6, and 12 months, respectively.

Cohen's d	3 months	6 months	12 months
Between groups	0.09	0.18	0.09
Within ICBT	1.17	1.23	1.42
Within TAU	1.31	1.43	1.29

Table 1. Effect sizes (Cohen's d) between and within groups based on scores on BDI-II in the PRIM-NET trial.

As expected, patients in TAU had significantly more visits to therapists compared to patients in ICBT. There was no difference between the groups concerning visits to GPs or nurses or telephone contacts. At 3 months, significantly fewer patients in the ICBT group were on antidepressant medication. Patients with antidepressant medication increased in TAU and decreased in ICBT. At 6 and 12 months however, there was again no difference in antidepressant medication between the groups. There was a significant difference at baseline concerning number of patients using sedatives (none in TAU, 5 in ICBT). At the 3-month follow-up, there was no longer any difference between the groups concerning sedatives. There were no significant differences between the groups concerning number of days on sick leave or concerning number of patients on sick leave. Both groups experienced an improved quality of life. The dropout analysis revealed that living alone was more common in patients lost to follow-up.

The seven WL-ICBT patients had a lower mean score on BDI-II when initiating ICBT and a smaller reduction of scores during the treatment period compared to patients in ICBT or TAU. No differences in main results were found either when the WL-ICBT patients were excluded or regarded as TAU pre-post treatment and then excluded, except for some differences for quality of life.

4.4 PAPER IV

A total of 519 participants, aged 18 and older and recruited in the primary care setting were included in Paper IV. The mean age was 52 years and 54 per cent were women. A fourth of the sample were retired and 64 per cent were employed/self-employed. Fourteen per cent reported an educational level of primary school only, 37 per cent reported having completed high school and 49 per cent reported having higher education. In the total sample, 16 per cent (n=86) of the patients reported low IHLC.
In Paper IV, support was found for the global question as a measurement of Internal Health Locus of Control. The correlations were statistically significant

but weak between IHLC and the three scales of the MHLC and the GSE, respectively.

The odds ratios for Internality, Chance-Externality and Powerful Others-Externality (from the MHLC) for the likelihood that patients would report high IHLC were all statistically significant. An increase of one point on the Internality Scale of the MHLC gave an odds ratio of 1.19 (95%CI: 1.11-1.28) for reporting high IHLC, and thus a more than doubled likelihood of reporting high IHLC with a five-point increase on Internality, OR: 2.40, CI 1.67-3.46. Similar results were found for the GSE.

5 DISCUSSION

5.1 PSYCHOLOGICAL HEALTH AND INSULIN RESISTANCE

There was a strong association showing that participants with both psychological distress (PD) and low internal health locus of control (IHLC) had higher levels of insulin resistance, which was statistically significant also in the final model adjusting for age, sex, education, smoking, alcohol consumption, BMI, and physical activity. Further, PD was associated with higher insulin resistance in a random population sample, which was almost statistically significant in the full model including adjustment for BMI. Moreover, low IHLC was associated with higher levels of logHOMA-ir, but the statistical significance disappeared when physical activity was included in the final model. Finally, stratified analysis revealed that the association was statistically significant for the group with low physical activity in the final model, but not for the group with high level of physical activity.

Our results for PD are in line with a previous study in which PD predicted prediabetes and type 2 diabetes 10 years later in men (15). The results were however weaker in women and predictive only for prediabetes. These results were all adjusted for socioeconomic position, family history of diabetes, smoking, BMI and physical activity (15). In that study, PD was measured differently with a scale of 5 questions about depression, anxiety, insomnia, fatigue, and apathy. A longitudinal study with repeated measurements analyzing associations between psychosocial stress and depressive symptoms and HOMA-ir in boys and girls in years 2, 6 and 10 found cross-sectional associations between depression and HOMA-ir in boys only, and non-significant trends longitudinally (82).

The literature concerning the association between depression and insulin resistance is inconclusive (83, 84). Observational studies have found associations, while longitudinal findings so far have been less convincing. Central adiposity has been suggested to mediate association between depression and insulin resistance (85). Furthermore, a study exploring insulin resistance in patients with a diagnosis of depression receiving treatment, found increased insulin sensitivity in patients after remission (86).

Low IHLC was associated with insulin resistance, the association however disappearing in the fully adjusted model including physical activity, suggesting a central role of physical activity in explaining the association

between IHLC and insulin resistance. Locus of control is known to be associated with physical activity (87, 88), and a dose-response relationship between physical activity and insulin resistance has been demonstrated (89).

The presence of both low IHLC and PD was independently associated with insulin resistance, also in the final model adjusting for age, sex, education, smoking, alcohol consumption, BMI and physical activity. This may suggest that the combination of low IHLC and PD captures a group of individuals that over time have a disposition that increases vulnerability to developing insulin resistance. Or else perhaps individuals with low IHLC during a period of psychological distress have a stronger neuroendocrine stress activation (90, 91) which in turn could lead to a stronger impact on insulin resistance (92). Both sense of control and especially psychological distress can vary over time (39), and a recent study has shown that negative events and depressive symptoms predict low sense of control, and that low sense of control can predict depressive symptoms and anxiety (93).

5.2 ICBT FOR DEPRESSION IN ADULTS IN PRIMARY CARE

The findings in this thesis support the efficacy of ICBT with minimal support for depression in primary care. In the PRIM-NET trial, ICBT and TAU were equally effective in reducing depressive symptoms and symptoms of anxiety at post treatment. At follow-up after one year, the levels of depressive symptoms, psychological distress, quality of life, anti-depressive medication, and days of sick leave were very similar. The PRIM-NET trial was carried out at team-based primary care centres, and TAU consisted of common treatments or combinations of treatments for depression provided at the primary care centres, including scheduled visits to GPs, nurses and other personnel, anti-depressant medication, face-to-face psychotherapy, and sick leave (ICBT excluded). The study included mild to moderate depression, and patients with a MADRS-S score of 35 or more were excluded. However, according to BDI-II, 39 per cent (n=35) of the patients in the study had a severe depression.

In 2009, when the PRIM-NET project started, empirical data about the efficacy of ICBT in primary care was very limited. Since then, several reviews on ICBT for depression have been published. For example, a meta-analysis on ICBT for depression in both clinical and community settings by Karyotaki et al. (60) found ICBT had greater effectiveness than control conditions, both short-term and long-term; that guided ICBT had greater effectiveness than unguided ICBT on moderate to severe depression; and that unguided ICBT had similar effectiveness on mild/subthreshold depression. The reviews and meta-analyses

generally include trials with primary care patients, but trials carried out in the primary care setting are still rare. Furthermore, inclusion criteria differ between trials, and treatment as usual also seems to differ, partly due to organizational differences in primary health care between countries. Most trials in primary care compare ICBT+TAU against TAU alone.

A Swedish RCT with patients recruited at primary care centres found that ICBT for depression with support was at least equally effective compared with TAU (94). The ICBT with support was more effective than TAU after three months and the effect remained at 12 months for the ICBT group, while at 12 months the effect in the TAU group had almost reached that of the ICBT. ICBT with support was more effective than TAU in a German study carried out in primary care (95), and ICBT both with and without support was more effective than TAU in a Spanish study (96). In the UK, an RCT (97) found ICBT to be more effective than TAU for patients with anxiety and/or depression in primary care and that the ICBT programme also had a positive effect on attributional style. However, another larger trial in the UK, comparing two different types of guided ICBT and TAU, found neither of the ICBT programmes with support to be efficacious in the primary care setting in the UK, with no differences between groups, except in favour of one of the ICBT programmes at 12 months (98).

Studies of the effectiveness of ICBT in the primary care setting may need to be considered in relation to factors like the availability of treatment in general, availability of psychological treatment specifically, and the possible impact of carrying out a trial at a primary care centre, for example regarding the degree of detection of patients with depression and the possible change in workload for the personnel.

5.3 HEALTH LOCUS OF CONTROL

The validation study found weak but positive support for using the question to measure IHLC. The question detected less variability compared with the MHLC, and the distribution of the single question was skewed and had a dichotomous shape.

In a publication by Lindström in 2006, the question was described as lack of belief in the possibility to influence health (46), and in a publication from 2011 as health locus of control (99). In a recent publication, it was referred to as internal health locus of control (44). Accordingly, it seemed natural to validate the question against a well-established scale of health locus of control.

However, the question seems also to relate to beliefs about the capacity to behave in ways to produce specific desired outcome. In English it is phrased "Do you believe that you can do anything yourself in order to preserve good health?" (46), and in the Vara-Skövde Cohort it is phrased (in Swedish): "Tror du att man kan göra någonting själv för att bevara en god hälsa?". The English version asks if "…you believe that *you* can do anything", and the Swedish, if "…you believe that *one* can do anything…". The phrasing of the question may be interpreted as referring to beliefs both about effects on future health and about ability to carry out health-related behaviours. Health locus of control refers to beliefs about locus of control concerning health. Self-efficacy refers to beliefs in one's ability to behave in ways conducive to achieving certain goals. It has its origin in Bandura's social learning theory (100, 101), and relates to individuals' experience of being able to handle different situations in life, in which an individual's expectations of results affects if and how the individual handles a situation. The individual's trust in being able to handle the situation affects the individual's effort, endurance, and approach to obstacles and resistance.

Thus we decided to include scales to measure both health locus of control and self-efficacy in the validation study. As hypothesized, the question correlated with both health locus of control and self-efficacy. The correlation and odds ratio were weak but statistically significant between IHLC and the scale Internality in MHLC. The results were similar for GSE. Bandura (102) and Wallston (103) have discussed the two constructs in relation to each other like this:

> *"Perceived self-efficacy and locus of control represent entirely different phenomena. Beliefs about whether one can produce certain outcomes (*perceived self-efficacy*) cannot, by any stretch of imagination, be considered the same as beliefs about whether actions affect outcomes (*locus of control*)."* and *"Perceived self-efficacy is a judgement of one's ability to organize and execute given types of performances, whereas an outcome expectation is a judgement of the likely consequence such performances will produce." (Bandura 1997, Self-efficacy: the exercise of control, p 20-21)*

> *"An internal HLC orientation is a necessary, but not a sufficient, condition for engaging in "proper" health behavior. One must believe, to at least some degree, that one's health status is dependent upon one's health behavior in order for one to act (assuming, of course, that one is motivated to do so by valuing the reinforcement that good health would bring). But just because the person values health and feels responsible for his/her health does not mean that the person feels capable of taking*

the right steps to control his/her health status. That is where perceived health competence (or perceived control over health) fits in beautifully." and *"the substitution of perceived control as the important generalized expectancy rather than simply locus of control. It is intended to be a rapprochement of two social learning theories, the one by Rotter and the one by Bandura." (Wallston, 1992: Hocus-Pocus, the focus isn't strictly on locus: Rotter's social learning theory modified for health, p 194)*

Smith, Wallston and Smith developed a scale for the construct perceived health competence (104). The scale has 8 items where two of them are phrased: "No matter how hard I try, my health just doesn't turn out the way I would like" and "I am able to do things for my health as well as most other people" (104). Possibly, the IHLC would tap into this construct, combining both outcome and behavioural expectancies. Figure 8 presents a slightly adapted picture of the interaction between self-efficacy and locus of control according to Bandura (102).

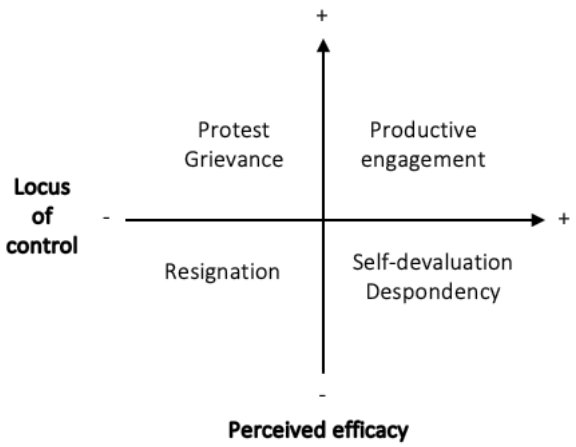

Figure 8. Simplified model of combinations of high/low locus of control and high/low self-efficacy based on Bandura, 1997, p 20.

5.4 METHODOLOGICAL DISCUSSION

The protocol employed in the PRIM-NET trial was comprehensive, with training for the primary care personnel, checklists, and supervision. The diagnostic assessment was carried out by licensed psychologists or psychotherapists with semi-structured interviews of an hour, including MINI and an assessment to ensure that depression was the primary diagnosis. Therapist support was delivered by a psychologists and psychotherapists with training in CBT.

After a long period with a low inclusion rate, despite the large number of patients with depression at the PCCs, we decided to set up an alternative design. At the time, with high costs and low prospects, it seemed better than to give up, and better than to add recruitment through advertisement. A centralized unit was formed, based at a primary care unit and with personnel from the project. The PCCs in PRIM-NET had experienced extra workload due to the project. It also seemed that the research project improved the detection of patients with mild-moderate depression at the PCCs. Treatment as usual is often known to be improved by research protocols (105). The alternative design removed most of the extra research work from the primary care personnel. Apart from that, the design was similar, with the exception that all patients included were offered ICBT, although for patients randomized to TAU, only after 12 weeks of TAU. It is worth noting that a waiting list for psychological treatment was common at primary care centres at the time. Despite all efforts, the inclusion still did not reach the initial power calculation. In retrospect, it would probably have been better to expand the project with more PCCs while still using the same protocol and not the alternative design. However, we have carried out all the calculations with and without the patients receiving ICBT after 12 weeks of TAU, with the same main results. The power of the study could also be regarded as sufficient for the analyses, based on the outcomes with very similar means and distribution.

Curiously, timepoints for follow-up in PRIM-NET turned out to cause some methodological confusion for a while in the interdisciplinary research group. From one perspective, time point zero was at inclusion, while from the other perspective at post-treatment. These approaches were such silent knowledge on both sides that we discussed follow-up after one year in agreement, only later realizing the three months' difference. Evaluation of pharmacological treatment commonly starts at baseline, while evaluations of psychological treatment often divide the timeline into pre-treatment, post-treatment, and follow-up.

Comorbidity of depression and type 2 diabetes has been called a prototypical example of mental/physical health issues, and psychological distress and insulin resistance still seem highly eligible for the purpose of exploring the development of public health illnesses related to lifestyle, and the role of psychology in them. The opportunity to investigate associations between psychological distress, internal health locus of control and insulin resistance in an existing representative population sample with a high participation rate has been advantageous. The results of Paper I suggest an independent dose-response relationship in which insulin resistance increases with PD and further with the presence of both PD and IHLC. However, the cross-sectional design employed in the present study cannot determine possible causality between IHLC, PD and insulin resistance. A longitudinal design would be able to conclude more about potential causality, or possible bidirectional associations.

Insulin resistance was measured with HOMA-ir, which has lower precision compared to the more expensive and time-consuming euglycemic clamp technique (involving intravenous infusion) which is gold standard for studies on small samples, while HOMA-ir is recommended for large epidemiological studies (106). Furthermore, it would have been preferable to use a response format with more response alternatives for IHLC to reduce the ceiling effect in the present format. Larger distribution and range in the variable would permit a better understanding of the association between IHCL and insulin resistance. The validated measure used for psychological distress (GHQ-12) also has the advantage of previous use in epidemiological studies. It also captures symptoms of stress that seem to be of importance in mechanisms in the development of both depression and of type 2 diabetes (92, 107).

Moreover, there are possible over-adjustments in the analyses. We found an interaction effect between IHLC and physical activity, and it would be interesting to continue with conditional process analysis to explore models of possible moderation and mediation. On the other hand, it is interesting that the associations remain statistically significant for presence of both IHLC and PD also in the final model, suggesting possible direct effects through neuroendocrine mechanisms on the HPA-axis.

6 CONCLUSIONS

6.1 GENERAL CONCLUSION

In conclusion, the presence of both low internal health locus of control (IHLC) and psychological distress (PD) was found to be associated with higher insulin resistance. The IHLC scale can be used to identify individuals with low IHLC. Internet-based cognitive behavioural therapy (ICBT) can be delivered as a routine treatment alternative in primary care if it can be implemented in a way that makes it time-saving and cost-effective. ICBT may also improve possibilities for preventative interventions on a larger scale. Preventative interventions for patients with PD and low IHLC may prevent or delay development of insulin resistance.

6.2 SPECIFIC CONCLUSIONS

- Presence of both IHLC and PD was strongly and independently associated with insulin resistance, also when adjusting for BMI and physical activity.

- There were no significant differences between the ICBT and treatment as usual at post treatment, either on BDI-II, MADRS-S, or BAI.

- ICBT with weekly minimal therapist support in primary care can be equally effective as treatment as usual among depressed patients also over a 12-month period

- Weak but statistically significant support for the IHLC scale as a measurement of internal health locus of control.

7 FUTURE PERSPECTIVES

The implications of this thesis are that psychological orientation is important in healthcare settings and that ICBT is a feasible treatment alternative for depressive symptoms in primary care. The prevalence of PD and low IHLC in the population and their relation to insulin resistance highlight the potential of preventative interventions.

Health prevention strategies often include both interventions for high-risk groups and interventions for the whole population. Geoffrey Rose has demonstrated that a reduction of the population mean body weight of 1 kg (1.25%) equals 25 per cent less obesity (BMI≥30) in the population (64), based on data from the Intersalt study with adults in the UK (65). Perhaps there is stigma involved when it comes to viewing psychological distress as a continuity of risk, but the potential is stunning (30). This is the case not only in relation to the number of patients with depressive disorders, anxiety syndromes and stress-related illness, but also in relation to insulin resistance. Insulin resistance is related to incident type 2 diabetes, which in turn is related to blindness, kidney failure, and cardiovascular diseases.

7.1 TREATMENT IN PRIMARY CARE

The results regarding ICBT in this thesis have already influenced primary care in Region Västra Götaland, as ICBT has been and continues to be implemented in regular healthcare. ICBT is an alternative to treatment delivered in person by a professional. To guarantee patient safety, just as the National Board of Health and Welfare issues licences for professions, ICBT programmes ought to be evaluated and licenced. ICBT programmes offered or recommended by the public healthcare system should be evaluated using research methods. Furthermore, research on the characteristics of primary care patients for whom ICBT is most effective would be helpful in the clinical situation at primary care centres in discussions with these patients about recommended treatment alternatives according to the national guidelines. Manualized treatment programmes do not adapt to patients as individual psychological treatment usually does. Variables to investigate in relation to ICBT could be the number of previous depressive episodes and their duration, as well as comorbidities, as previously suggested by Karyotaki (60). Furthermore, emphasis on differential diagnostic assessment is important, including assessment of primary diagnosis. The content in ICBT programmes for different diagnoses varies substantially. Consider for example treatments for social phobia, posttraumatic disorder, generalized anxiety disorder and depression, and suitable psycho-educative information and therapeutic interventions for these

patient groups. Moreover, since ICBT can be delivered with or without professional support or as blended treatment, where treatment consists of both traditional psychotherapy and predefined materials delivered through internet or in other formats, the level of competence in psychological treatment among personnel is crucial.

Further development of ICBT programmes for comorbidity has potential, especially for primary care where comorbidity is common. ICBT aiming to reduce psychological distress and increase healthy lifestyle behaviours may improve public health, considering the strong association between PD, IHLC and insulin resistance as shown in this thesis.

7.2 PREVENTION IN GENERAL POPULATION

What might preventative interventions for the whole population be, concerning psychological distress and internal health locus of control? Rose generally suggested we identify the factors affecting exposure in the population when considering preventative intervention for the whole population (64). Adding unnatural factors is much more difficult than removing or reducing unnatural exposure, i.e., we are more likely to succeed by focusing on trying to enhance people's efforts to increase healthy natural actions and to reduce unhealthy unnatural factors. This is also linked to change in norms, and perhaps redefining what is normal. Expectations about the progression in changing habits have been studied, in which relapse prevention has been suggested to be more often about relapse management (108). Furthermore, norms about ageing have been studied in relation to locus of control, in which beliefs about declining abilities seem to affect the sense of control in older age groups (109).

Influenced by Bandura (102), I suggest we organize healthcare in a way that enables and facilitates for primary care personnel to be responsive and supportive towards patients. Primary care personnel need to be able to teach patients health skills they need, and to help patients set personalized and reachable goals, to self-monitor and self-regulate in order to enhance their health status. Patients also need to learn to understand what is not controllable, and even more so – what they *can* control.

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