Chronic Physical Diseases and Depressive Symptoms: Insight into the Association of Long QT Syndrome and Type 2 Diabetes with Depressive Symptoms

Karolina Wesołowska

ACADEMIC DISSERTATION
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# CONTENT

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>5</td>
</tr>
<tr>
<td>TIIVISTELMÄ</td>
<td>7</td>
</tr>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>10</td>
</tr>
<tr>
<td>LIST OF ORIGINAL PUBLICATIONS</td>
<td>12</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>13</td>
</tr>
<tr>
<td>1. INTRODUCTION</td>
<td>15</td>
</tr>
<tr>
<td>1.1. Depressive symptoms</td>
<td>15</td>
</tr>
<tr>
<td>1.2. Chronic physical diseases</td>
<td>17</td>
</tr>
<tr>
<td>1.2.1. Long QT syndrome</td>
<td>17</td>
</tr>
<tr>
<td>1.2.2. Type 2 diabetes</td>
<td>18</td>
</tr>
<tr>
<td>1.3. Risk factors for arrhythmic events in LQTS mutation carriers</td>
<td>18</td>
</tr>
<tr>
<td>1.4. Carrying a LQTS-causing mutation and the risk of depressive symptoms</td>
<td>20</td>
</tr>
<tr>
<td>1.5. Sex differences in the association between LQTS and depressive symptoms</td>
<td>21</td>
</tr>
<tr>
<td>1.6. T2D and depressive symptoms</td>
<td>22</td>
</tr>
<tr>
<td>1.6.1. The link between chronically elevated glucose and depressive symptoms—previous studies</td>
<td>22</td>
</tr>
<tr>
<td>1.6.2. Chronically elevated glucose as a risk factor for depressive symptoms—potential mechanisms</td>
<td>24</td>
</tr>
<tr>
<td>1.6.3. Depressive symptoms as a risk factor for chronically elevated glucose—potential mechanisms</td>
<td>24</td>
</tr>
<tr>
<td>1.6.4. What can be the next step?</td>
<td>25</td>
</tr>
<tr>
<td>2. AIMS OF THE STUDY</td>
<td>28</td>
</tr>
<tr>
<td>3. METHODS</td>
<td>30</td>
</tr>
<tr>
<td>3.1. LQTS study</td>
<td>30</td>
</tr>
<tr>
<td>3.1.1. Participants</td>
<td>30</td>
</tr>
</tbody>
</table>
3.1.2. Measures .............................................................................................................. 31

3.2. The Cardiovascular Risk in Young Finns Study .................................................... 32

3.2.1. Participants .......................................................................................................... 32
3.2.2. Measures ............................................................................................................. 34

3.3. Statistical analyses ................................................................................................ 36

3.3.1. Study I ................................................................................................................ 36
3.3.2. Study II ................................................................................................................. 37
3.3.3. Study III .............................................................................................................. 38

4. RESULTS .................................................................................................................. 40

4.1. The association of LQTS mutation carrier status and symptomatic LQTS with depressive symptoms (Study I) .................................................................................. 41
4.2. The direction of the association between depressive symptoms and glucose (Study II).... 44
4.3. Elevated glucose as a causal risk factor for depressive symptoms? (Study III) .......... 50

5. DISCUSSION ............................................................................................................. 54

5.1. LQTS mutation carrier status and the risk of depressive symptoms ...................... 54
5.2. Depressive symptoms and the risk of arrhythmic events in LQTS ............................. 54
5.3. The role of depressive symptoms in disturbed glucose metabolism ....................... 58
5.4. The role of increased glucose in the development of depressive symptoms .......... 60
5.5. Methodological considerations and directions for future research ......................... 63
5.6. Conclusions and practical implications .................................................................. 67

REFERENCES .............................................................................................................. 70
ABSTRACT

Individuals diagnosed with chronic physical diseases, such as coronary artery disease (i.e., a cardiac condition being a risk factor for ventricular arrhythmias) and type 2 diabetes (T2D; i.e., a metabolic condition characterized by high glucose levels), are at risk of developing mental health problems. In parallel, people with mental health problems, including depressive symptoms, have an increased risk of being diagnosed with a chronic physical disease. The co-occurrence of physical and mental conditions is a major public health concern, since it can significantly decrease quality of life, contribute to worse health outcomes and a higher rate of mortality, and bring enormous economic costs to society. Thus, identifying the concomitance of physical and mental health problems as well as understanding its underlying mechanisms are primary steps in developing strategies to prevent and treat the incidence of comorbid conditions. The main aim of this study was to examine: 1) whether long QT syndrome (LQTS; i.e., a genetic heart condition which can predispose to ventricular arrhythmias) mutation carrier status is associated with the risk of depressive symptoms (Study I); 2) whether depressive symptoms are associated with the risk of arrhythmic events in women and men with LQTS (Study I); 3) whether depressive symptoms predict glucose levels, or vice versa, in women and men (Study II); 4) whether changes in body fat, inflammation, alcohol consumption, or tobacco or cigarette smoking are likely to mediate these possible associations (Study II); and 5) whether elevated glucose is likely to be a causal risk factor for depressive symptoms (Study III).

In Study I, the participants were derived from the Finnish LQTS registry (the 2011 follow-up). The sample consisted of 782 participants. There were 369 genetically defined LQTS mutation carriers (169 with and 200 without arrhythmic events). The control group comprised 413 relatives without a familial LQTS mutation. Depressive symptoms were assessed using the Beck Depression Inventory-II. The participants in Study II (n = 2534; data from the 2001, 2007, and 2012 follow-ups) and Study III (n = 1217; data from 2012) were from the Cardiovascular Risk in Young Finns
Study, a Finnish prospective, population-based study. Depressive symptoms were assessed with a modified Beck Depression Inventory. Blood glucose levels were based on the single measurement of fasting serum glucose concentrations.

The results of Study I revealed that LQTS mutation carrier status was not associated with the risk of depressive symptoms. Depressive symptoms were, however, associated with an increased risk of arrhythmic events in men but not in women with LQTS. Furthermore, Study II showed that depressive symptoms in 2001 were positively associated with glucose in 2012 in women but not in men. This sex difference was significant. Glucose in 2001 did not predict depressive symptoms in 2012 in either sex. Moreover, changes (from 2001 to 2007) in body fat, inflammation, alcohol consumption, or tobacco or cigarette smoking did not mediate the observed association in women. In Study III, glucose was not associated with depressive symptoms in the standard linear regression, but the instrumental-variable regression showed a negative association between glucose and depressive symptoms. The difference between the estimates derived from these two regression models was significant.

The findings suggest that depressive symptoms can be a risk factor for arrhythmic events in men but not in women with LQTS. Further, the results indicate that women with depressive symptoms but not men may have elevated glucose concentrations, and thus may be at increased risk for the development of T2D. The mechanisms underlying this association, however, still remain unclear. Moreover, elevated glucose is unlikely to be a causal risk factor for depressive symptoms. Therefore, the association from T2D to depressive symptoms might not be due to chronically elevated glucose. It is, however, possible that this relationship may result from low glucose concentrations. Given these findings, prevention and treatment of depressive symptoms might be beneficial for prevention of arrhythmic events in men with LQTS and blood glucose abnormalities among women in the general population.
TIIVISTELMÄ

Krooniset fyysiset sairaudet, kuten sepelvaltimotauti (sydämen rytmihäiriön riskitekijä) tai tyyppi 2 diabetes (jolle on ominaista korkeat verensokeriarvot), altistavat mielenterveysongelmien kehittymiselle. Toisaalta mielenterveysongelmat, kuten masennus, voivat vastaavasti kohottaa kroonisten fyysisten sairauksien riskiä. Fyysisten sairauksien ja mielenterveysongelmien yhteisesiintyvyys eli komorbiditeetti on vakava kansanterveyden ongelma, koska useita sairauksia samanaikaisesti sairastavilla on tavanomaista heikompi elämänlaatu ja korkeampi kuolleisuus, ja näiden sairauksien hoidosta aiheutuu mittavia kustannuksia yhteiskunnalle. Tässä väitöskirjatutkimuksessa tarkasteltiin masennusoireiden ja fyysisen sairastavuuden komorbiditeettia sekä pyrittiin tunnistamaan sitä mahdollisesti selittäviä tekijöitä. Tutkimuksessa haettiin vastausta seuraaviin kysymyksiin: 1) onko pitkä QT-oireyhtymän (LQTS) mutaation kantajilla korkeampi alttius masennusoireiden kokemiselle (osatutkimus I), 2) ovatko masennusoireet yhteydessä sydämen rytmihäiriöihin pitkä QT-oireyhtymää sairastavilla (osatutkimus I), 3) ennustavatko masennusoireet verensokeritasoja vai verensokeritasot masennusoireita (osatutkimus II), 4) välittävätko muutokset kehon rasvassa, tulehdusarvoissa, alkoholin kulutuksessa tai tupakoinnissa näitä yhteyksiä (osatutkimus II), ja 5) ovatko kohonneet verensokeriarvot kausaalinen riskitekijä masennusoireille (osatutkimus III).


Väitöskirjatutkimuksen perusteella masennusoireiden ennaltaehkäisyllä ja hoidolla voidaan parhaimmillaan ennaltaehkäistä sydämen rytmihäiriöitä kehittymistä enkä enkä pitkä QT-oireyhtymän mutaation kantamiehille sekä pienentää riskiä häiriointyneelle sokeriaineenvaihdunnalle erityisesti naisilla.
To those who are affected by depressive symptoms, long QT syndrome, and type 2 diabetes.

In moments of doubts, frustration, and tiredness, the thought that this work might be of value to you motivated me to complete it. This thesis is, above all, for you.
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Helsinki, 1st of September, 2018

Karolina Wesołowska
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:


The publications are referred to in the text by their Roman numerals.
## LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>$b$</td>
<td>Unstandardized regression coefficient</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Standardized regression coefficient</td>
</tr>
<tr>
<td>BDI</td>
<td>Beck Depression Inventory</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>CFI</td>
<td>Comparative fit index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>FIML</td>
<td>Full information maximum likelihood</td>
</tr>
<tr>
<td>GMM</td>
<td>Generalized method of moment</td>
</tr>
<tr>
<td>GWAS</td>
<td>Genome-wide association study</td>
</tr>
<tr>
<td>HbA$_{1C}$</td>
<td>Glycated hemoglobin</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>High-sensitivity C-reactive protein</td>
</tr>
<tr>
<td>ICE</td>
<td>Imputation by chained equations</td>
</tr>
<tr>
<td>LQT1</td>
<td>Long QT syndrome subtype 1</td>
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<td>LQT2</td>
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<td>LQT3</td>
<td>Long QT syndrome subtype 3</td>
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<tr>
<td>LQTS</td>
<td>Long QT syndrome</td>
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</tbody>
</table>
\( M \)  
Mean

MI  
Myocardial infarction

MSPSS  
Multidimensional Scale of Perceived Social Support

\( n \)  
Number of cases

OR  
Odds ratio

\( p \)  
Probability

PMM  
Pattern mixture modeling

QTc  
Corrected QT interval

\( R^2 \)  
Fraction of explained variance

RMSEA  
Root mean squared error of approximation

SD  
Standard deviation

SEM  
Structural equation modeling

SES  
Socioeconomic status

SNP  
Single nucleotide polymorphism

T1D  
Type 1 diabetes

T2D  
Type 2 diabetes

TLI  
Tucker-Lewis index

\( \chi^2 \)  
Chi-square statistic
1. INTRODUCTION

It is well-established that the body and the mind are inextricably connected. People with chronic physical diseases, such as coronary artery disease (CAD; i.e., a cardiac condition that can be a risk factor for ventricular arrhythmias) and diabetes mellitus, have an increased risk of developing mental health problems (Rotella & Mannucci, 2013b; Virtanen et al., 2017). In parallel, individuals with mental health problems, including depression\(^1\), tend to experience a wide range of chronic physical diseases (Currier & Nemeroff, 2014; Hein, Lanquart, Loas, Hubain, & Linkowski, 2017; O’Neil et al., 2016). The co-occurrence of physical and mental conditions is a major public health concern as it can significantly decrease quality of life (Gadalla, 2008), and contribute to worse health outcomes (Moussavi et al., 2007) and a higher rate of mortality (Herrmann et al., 1998). It is also associated with a huge economic burden to society due to impaired work performance and sickness absenteeism (Buist-Bouwman, Graaf, Vollebergh, & Ormel, 2005; Druss, Rosenheck, & Sledge, 2000; Merikangas et al., 2007), as well as increased use of health care services (Brilleman et al., 2013). For these reasons, identifying the concomitance of physical and mental health problems as well as understanding its underlying mechanisms are primary steps in developing strategies to treat and prevent the incidence of comorbid conditions.

Given the above, the aim of the present thesis was to examine the link of chronic physical conditions, such as congenital long QT syndrome (LQTS) and type 2 diabetes (T2D), with depressive symptoms.

1.1. Depressive symptoms

Major depression is one of the most common psychiatric disorders (Steel et al., 2014). Its lifetime prevalence has been estimated to be 14.6% in high-income countries and 11.1% in low-middle-income countries (Kessler & Bromet, 2013). At a global level, over 300 million people have been

\(^1\) In the present thesis, the term “depression” has referred to a formal diagnosis of major depressive disorder/major depression. Otherwise, the term “depressive symptoms” has been used.
reported to have depression, equivalent to 4% of the world’s population (World Health Organization, 2017). It has been estimated that depression will be the second leading cause of disease burden in the world (the first in high-income countries) by 2030 (Mathers & Loncar, 2006). According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association, 2013), the diagnosis of clinical depression requires the presence of at least five depressive symptoms—at least one of the symptoms needs to be either depressed mood or loss of interest or pleasure—for a minimum of two weeks. Other symptoms can be as follows: a significant weight change or appetite disturbance, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, decreased concentration, and recurrent suicidal thoughts or a suicide attempt.

Many people with depressive symptoms do not exhibit a sufficient number of symptoms to meet the criteria of clinical depression. Such “subclinical” or “subthreshold” depressive symptoms have been documented to have a much higher prevalence than clinical depression (Judd, Schettler, & Akiskal, 2002; Meeks, Vahia, Lavretsky, Kulkarni, & Jeste, 2011). Depression is currently the main cause of disability worldwide (World Health Organization, 2017). However, numerous studies (Cuijpers, 2004; Cuijpers et al., 2007; Judd et al., 2002; Lewinsohn, Solomon, Seeley, & Zeiss, 2000; Meeks et al., 2011) have reported that the presence of less than the five depressive symptoms required for full-blown depression can also lead to a significant level of functional impairment. For instance, “subthreshold” depressive symptoms have been shown to be associated with lower quality of life, physical health problems, cognitive decline (Meeks et al., 2011), and various aspects of functional disability including, among others, limitations in physical, social, and role functioning (Cuijpers, 2004; Cuijpers et al., 2007; Judd et al., 2002; Lewinsohn et al., 2000).

Most studies on risk factors for the development of depressive symptoms have focused on the predictors of the onset of major depression. A number of consistently significant risk factors have
been reported, such as female sex, lack of social support, childhood adversity, personality traits, family history (e.g., psychiatric disorders in a family; Kessler, 2003), and low socioeconomic status (Lorant et al., 2003). Furthermore, the risk of being depressed has been found to be highest in young adulthood and in older age (Sutin et al., 2013). In addition, it is well-documented that stressful life events (Kessler, 2003), including the diagnosis of serious chronic physical condition (Schneiderman, Ironson, & Siegel, 2005), may contribute to the development of depression. Thus, not only can depressive symptoms result in physical health problems (as mentioned in the previous paragraph), but they can also occur as their consequence.

1.2. Chronic physical diseases

Chronic disease has been defined as one that is persisting or recurring over a long period of time (Bernell & Howard, 2016). Such conditions as congenital LQTS and T2D are considered as chronic diseases. In Finland, the prevalence of LQTS has been documented to be 1:250 (Marjamaa et al., 2009), which is considerably higher than the generally estimated prevalence of the syndrome in other populations (1:2000; Schwartz et al., 2009). Thus, research in the field of LQTS can be especially relevant to Finnish public health concerns. As regards T2D, globally, approximately 378 million people (equivalent to 5% of the world’s population) are estimated to have T2D (International Diabetes Federation, 2015). In addition, the disease has been projected to be the seventh leading cause of mortality worldwide (fourth in highly industrialized countries, including Finland) by the year 2030 (Mathers & Loncar, 2006). Therefore, T2D constitutes one of the major public health problems in the world.

1.2.1. Long QT syndrome

Congenital LQTS is an inherited heart condition characterized by a prolonged QT interval observed in the electrocardiogram (ECG) that can predispose an individual to life-threatening ventricular arrhythmias (hereinafter also referred to as symptoms or cardiac/arrhythmic events) and sudden cardiac death (Schwartz, Periti, & Malliani, 1975). The disorder is caused by genetic mutations in
cardiac ion-channel proteins (Morita, Wu, & Zipes, 2008). Depending on a mutated gene, the syndrome has been classified into subtypes, of which LQT1, LQT2, and LQT3 are the most prevalent (Morita et al., 2008). The occurrence of changes in the potassium channel genes \textit{KCNQ1} and \textit{KCNH2} (HERG) results in LQT1 and LQT2, respectively, whereas mutations in the sodium channel gene \textit{SCN5A} are a cause of the LQT3 subtype (Morita et al., 2008). The high prevalence of LQTS in the Finnish population, mentioned in the previous paragraph, has been suggested to be due to four identified LQTS founder mutations, \textit{KCNQ1} G589D, \textit{KCNQ1} IVS7-2A>G (c.1129-2A>G), \textit{KCNH2} L552S, and \textit{KCNH2} R176W, which have been spread in this isolated population (Fodstad et al., 2004).

1.2.2. Type 2 diabetes

T2D is the most common form of diabetes; in high-income countries, it accounts for around 91% of all diabetes cases (International Diabetes Federation, 2015). The condition is characterized by high glucose levels resulting from deficiency in insulin secretion, secondary to insulin resistance (Rudenski et al., 1988). T2D has been suggested to be caused by the combination of genetic and environmental influences (Murea, Ma, & Freedman, 2012). Obesity and physical inactivity are major risk factors for the development of this metabolic disease (DeFronzo & Abdul-Ghani, 2011). The condition mostly occurs after the age of 40 (but has been increasingly seen in young adults and adolescents; Mokdad et al., 2001), in men (Kautzky-Willer, Harreiter, & Pacini, 2016), and among individuals with low socioeconomic status (Agardh, Allebeck, Hallqvist, Moradi, & Sidorchuk, 2011). T2D may lead to long-term complications, including CAD, stroke, nephropathy, neuropathy (which can result in foot amputation), and retinopathy (which may cause vision impairment and blindness; Fowler, 2011).

1.3. Risk factors for arrhythmic events in LQTS mutation carriers

For many years, it was taken for granted that LQTS is characterized by complete penetrance, that is, that all individuals with a LQTS-causing mutation manifest clinical/phenotypic symptoms of the
disorder. This assumption was challenged in 1980 by Schwartz who suggested that a number of LQTS mutation carriers who exhibit cardiac symptoms might have been lower than what had been expected. At present, it is known that the penetrance of the syndrome can range from 25% (Priori, Napolitano, & Schwartz, 1999) to 100% (Viadero, Rubin, Amigo, & Gonzalez-Lamuno, 2011) in the same family. The reasons for reduced penetrance in people with the same LQTS-causative mutation remain unclear (Giudicessi & Ackerman, 2013).

Patients of a given LQTS-causing mutation tend to experience arrhythmias under specific circumstances (Schwartz et al., 2001). Most of the cardiac events in LQT1 are triggered by physical activity (e.g., swimming), whereas in the LQT2 subtype, symptoms are mainly due to sudden emotional stress (e.g., stressful events; Schwartz et al., 2001). In LQT3, the risk of arrhythmias seems to be highest during rest or sleep in the absence of any arousal (Schwartz et al., 2001). The greater tendency of having cardiac events under one condition does not, however, eliminate the possibility of becoming symptomatic due to other triggers (Schwartz et al., 2001).

The effect of sex, age, and genotype on the probability of arrhythmias (Zareba et al., 2003) and the trend in heart rate-corrected QT intervals (QTc; Vink et al., 2017) among LQTS mutation carriers has also been reported. During childhood, LQT1 males have shown to exhibit a higher risk for cardiac event, whereas in adulthood, LQT2 females have shown to be at higher risk (Zareba et al., 2003). In LQT1, after the age of 12 years, male mutation carriers have been found to have a significantly shorter QTc interval compared with female carriers. In LQT2, until 5 years of age and from 14 to 26 years, male mutation carriers have been shown to have a significantly shorter QTc interval than female mutation carriers. Between the age 5 and 14 years, however, LQT2 men have had significantly longer QTc interval than LQT2 women (Vink et al., 2017).

The findings from cross-sectional studies based on the Finnish LQTS registry have shown that prolonged mental stress, stressful life events (i.e., death or illness of a family member, financial
difficulties, significant interpersonal conflicts, and mental and physical assaults; Hintsa et al., 2010), and work stress (Hintsa et al., 2013) are associated with the risk of arrhythmias in LQTS mutation carriers. One study (Hintsa et al., 2009) has reported that depressive symptoms may also be a risk factor for cardiac events in LQTS independently of sex and age. This study, based on the baseline data of the Finnish LQTS registry, did not, however, include a measure of depressive symptom dimensions, and did not control for medications (β-blockers and antidepressants), social support, or education. To establish depressive symptoms as a risk factor for arrhythmic events in LQTS, β-blockers (Verbeek, van Riezen, de Boer, van Melle, & de Jonge, 2011), antidepressants (Sicouri & Antzelevitch, 2008), social support (Barth, Schneider, & von Kanel, 2010; Huffman, Celano, Beach, Motiwala, & Januzzi, 2013), and education (Huffman et al., 2013; Loucks et al., 2009) need to be taken into account as they have been associated with both depressive symptoms and cardiac conditions. Furthermore, the inclusion of three dimensions of depressive symptoms (i.e., affective, cognitive, and somatic) could help to examine if the potential association between depressive symptoms and the risk of arrhythmic events in LQTS is mostly due to psychological depressive symptoms (i.e., affective and cognitive) or whether this association is mainly due to somatic depressive symptoms (e.g., fatigue) which may well be secondary to the syndrome itself.

1.4. Carrying a LQTS-causing mutation and the risk of depressive symptoms

Serious physical conditions have repeatedly been shown to increase the risk of developing mental health problems, including depressive symptoms (Dickens et al., 2004; Prince et al., 2007; Scott et al., 2010). Thus, carrying a LQTS-causing mutation could predispose a person to experience depressive symptoms. So far, however, little is known about whether being diagnosed with LQTS may increase the risk of developing depressive symptoms. Previous studies (Maattanen et al., 2011, 2013a) have shown that LQTS mutation carriers exhibit higher temperamental vulnerability to stress compared with the general population. Screening for a LQTS-causing mutation has been
found to induce mental distress (van Langen, Hofman, Tan, & Wilde, 2004) which, in turn, has been associated with depression (Hammen, Kim, Eberhart, & Brennan, 2009). Furthermore, LQTS mutation carriers have reported to be worried about the probability of having passed the mutation to next generations (Farnsworth, Fosyth, Haglund, & Ackerman, 2006; van Langen et al., 2004) and the risk of sudden cardiac death of those family members who harbor the same familial mutation (Andersen, Oyen, Bjorvatn, & Gjengedal, 2008; Farnsworth et al., 2006). The uncertainty regarding the diagnosis of LQTS (Andersen et al., 2008; Hendriks et al., 2008) and limitations in daily life caused by avoidance of potential triggers of arrhythmias (Andersen et al., 2008) can be a source of additional stressors. Moreover, as in some LQTS mutation carriers engagement in strenuous exercise (especially among those genotyped as LQT1) or competitive sports (in LQT1 mutation carriers and in all patients with a high risk of cardiac events, e.g., in those with QTc > 500 ms) is restricted due to the risk of cardiac events (Priori et al., 2013), those individuals may be physically less active. Physical inactivity, in turn, has been documented to be a risk factor for depressive symptoms (Mammen & Faulkner, 2013). Based on these findings, it is reasonable to assume that LQTS mutation carrier status may be associated with an increased risk of developing depressive symptoms.

1.5. Sex differences in the association between LQTS and depressive symptoms?

Current evidence suggests that there can be sex differences in the association of cardiac conditions with depression (Shanmugasegaram, Russell, Kovacs, Stewart, & Grace, 2012) and depressive symptoms (Doyle et al., 2015; Parashar et al., 2009; Shah et al., 2014). Consistent with the general population, the prevalence of depressive symptoms has been documented to be higher in women than in men with CAD (Shah et al., 2014; Shanmugasegaram et al., 2012) and myocardial infarction (MI; Doyle et al., 2015; Parashar et al., 2009). Further, depressive symptoms have been associated with an increased risk of mortality in women but not in men with CAD (Shah et al., 2014) and a
higher risk of adverse outcomes after MI (especially rehospitalization and angina) in female but not male patients (Parashar et al., 2009). Contrary to these findings, however, a recent literature review and meta-analysis (Doyle et al., 2015) has shown that the association between depressive symptoms and poor cardiac prognosis can be stronger in men than in women with MI. Moreover, depression has been suggested to partly reflect cardiovascular disease severity in men but not in women with this heart condition (Doyle et al., 2015). In overall, given the above, sex differences in the potential association of LQTS mutation carrier status and symptomatic LQTS status with depressive symptoms may be assumed.

1.6. T2D and depressive symptoms

There is ample evidence that T2D and depressive symptoms are associated (Cosgrove, Sargeant, & Griffin, 2008; Knol et al., 2006; Mezuk, Eaton, Albrecht, & Golden, 2008; Nouwen et al., 2010). Thus far, however, the temporal or causal direction of this association and the underlying mechanisms, such as elevated glucose levels, remain unclear (Tabak, Akbaraly, Batty, & Kivimaki, 2014).

1.6.1. The link between chronically elevated glucose and depressive symptoms—previous studies

Most previous studies that examined the association between glycemia (i.e., the concentration of glucose in the blood) and depressive symptoms have been based on cross-sectional data. The findings from one cohort, cross-sectional study (Kivimaki et al., 2009) have revealed that there can be an increased risk of depressive symptoms in individuals with very high and very low blood glucose concentrations in both sexes. This U-shape association was not, however, supported by data from the Vietnam Experience Study (Gale et al., 2010). Further, the Hertfordshire Cohort Study showed a positive association of depressive symptoms with glucose levels in women and men without a previous diagnosis of diabetes (Holt et al., 2009). This study also found that depressive symptoms are associated with both diagnosed and undiagnosed diabetes in women and men,
suggesting that the relationship between depressive symptoms and diabetes is not solely due to psychological distress resulting from the disease diagnosis. However, a meta-analysis of 13 cross-sectional studies (Nouwen et al., 2011) reported that only diagnosed T2D is associated with an increased risk of depressive symptoms, whereas the risk of depressive symptoms in people with undiagnosed T2D and prediabetes is similar to that of individuals with normal glucose metabolism; these findings imply that disturbed glucose homeostasis may not contribute to depressive symptoms, but rather, that depressive symptoms in T2D may reflect psychosocial stress associated with being diagnosed with T2D, and the burden of coping with T2D and its complications. As only few studies included in the meta-analysis reported sex-specific results, potential differences between women and men in the association between glucose levels and depressive symptoms could not be explored.

So far, there has been little prospective research on the association between glycemia and depressive symptoms. The results from the English Longitudinal Study of Aging (Hamer, Batty, & Kivimaki, 2011) suggested that higher glucose levels could be a risk factor for depressive symptoms, especially in men. The findings from the Whitehall II study (Akbaraly et al., 2013) showed, however, no association between glucose levels and depressive symptoms in either women or men. Moreover, a prospective, cohort study of U.S. adults (Golden et al., 2008) found an increased risk of depressive symptoms in individuals with treated T2D—but a decreased risk in those with prediabetes and untreated T2D. As regards the association of interest in the opposite direction, longitudinal evidence from a Swedish population-based study (Eriksson et al., 2008) reported that depressive symptoms may increase the risk of prediabetes and T2D in men but not in women.

As can been seen from the above, previous research of the association between glycemia and depressive symptoms has provided mixed results. A recent literature review (Tabak et al., 2014) concluded that there is no convincing evidence that depressive symptoms directly increase the risk
of T2D development or that pathophysiological changes preceding the onset of T2D, such as increased glucose concentrations, are causes of depressive symptoms. Inconsistencies between studies might have potentially been influenced, among others, by differences: in study designs (i.e., cross-sectional or longitudinal study), in ways of operationalizing glycemia and depressive symptoms (i.e., continuous or categorical variables), in utilized measures of glycemia (i.e., fasting glucose, 2-hour post-load glucose, or glycated hemoglobin (HbA1C)) and depressive symptomatology, characteristics of the study participants (e.g., age), or by whether sex differences were taken into account or not. Additionally, methodological limitations of observational research, including bias due to residual or unobserved confounding or reverse causality, may have contributed to discrepancies between studies.

1.6.2. **Chronically elevated glucose as a risk factor for depressive symptoms—potential mechanisms**

Elevated glucose could contribute to depressive symptoms through somatic symptoms associated with negative mood, such as overall sense of fatigue, sleepiness, and concentration difficulty (Adriaanse et al., 2005). Moreover, elevated glucose levels may lead to a broad range of disabling complications, including cardiovascular events (e.g., MI and stroke), heart failure, overt nephropathy, and death (Gerstein et al., 2005); fear of complications and the burden of dealing with complications could elicit depressive symptoms (Egede, 2005). Another possibility is that elevated glucose concentrations induce inflammatory processes (de Rekeneire et al., 2006; Esposito, 2002) that can result in the reduction of brain-derived neurotrophic factor and, in turn, in decreased neuronal plasticity (Calabrese et al., 2014) and depression (Brunoni, Lopes, & Fregni, 2008).

1.6.3. **Depressive symptoms as a risk factor for chronically elevated glucose—potential mechanisms**

Depressive symptoms could lead to elevated glucose levels directly through its association with increased activity of the hypothalamic-pituitary-adrenal (HPA) axis (Stetler & Miller, 2011) and the
sympathetic nervous system (SNS; Udupa et al., 2007), resulting in an excessive release of cortisol, which subsequently stimulates enhanced glucose production and lipolysis; this, in turn, has been suggested to be implicated in the development of obesity, insulin resistance, and T2D (Champaneri, Wand, Malhotra, Casagrande, & Golden, 2010). Furthermore, depressive symptoms may promote inflammation (Kiecolt-Glaser, Derry, & Fagundes, 2015), which has been associated with the risk of insulin resistance and T2D (Esser, Legrand-Poels, Piette, Scheen, & Paquot, 2014). Biological alterations in the HPA axis and the SNS, and inflammation have not, however, consistently been associated with the risk of T2D (Tabak et al., 2014).

Depressive symptoms could also lead to elevations in glucose levels indirectly by, among others, being involved in worsening adherence to healthy diet (Alhazmi, Stojanovski, McEvoy, & Garg, 2014; Gonzalez et al., 2007) and exercise regimens (Gonzalez et al., 2007; Jeon, Lokken, Hu, & van Dam, 2007), by contributing to excess body adiposity (Ganz et al., 2014; Luppino et al., 2010), or by increasing health-risk behaviors, including smoking (Fergusson, Goodwin, & Horwood, 2003; Liu, Wang, Maisonet, Wang, & Zheng, 2016) and alcohol use (Liu et al., 2016; Wang & Patten, 2001). So far, the impact of depressive symptoms on health behaviors and the role of health behaviors in the development of T2D have been examined separately in previous population-based studies. Therefore, it remains unknown whether behavioral factors mediate the association between depressive symptoms and increased glucose levels.

1.6.4. What can be the next step?

To overcome the limitations of previous studies that have attempted to determine the temporal ordering of the association between glucose levels and depressive symptoms, the next step could be to conduct a prospective study that examines this relationship in both directions within the same population, taking sex differences into account, and treating measures of glycemia and depressive symptoms as continuous variables. The latter is suggested as in diabetes risk prediction, glycemic measures (fasting glucose, 2-hour post-load glucose, and HbA1c) may perform better if treated as
continuous traits rather than categorical variables (Rathmann et al., 2010); the reasons for that can be that categorization of continuous variables may lead to a loss of statistical power and an imprecise estimation (Bennette & Vickers, 2012) and that higher fasting plasma glucose levels within the normoglycemic range have been shown to be an independent risk factor for T2D (Tirosh et al., 2005). Moreover, a population-based study examining factors mediating the potential association between depressive symptoms and glucose concentrations would also be of value.

To determine the causal role of increased glucose concentrations in the development of depressive symptoms, further step could be the implementation of instrumental-variable regression with a genetic instrument (also known as Mendelian randomization). Instrumental-variable regression with a genetic instrument is a statistical method that can help to reduce the possibility of bias resulting from residual and unobserved confounding, and reverse causation by using genetic variants as an instrument for the risk factor (in this case glucose levels). This means that the health-related outcome (in this case depressive symptoms) is predicted only with the proportion of variance in the risk factor that is attributable to the genetic variants used as the instrument for the risk factor. Considering that alleles are randomly assigned from parents to offspring at the time of gamete formation, genetic variants are, in general, independent of factors that commonly confound associations between risk factors and health-related outcomes in non-experimental studies. Also, since the allocation of alleles is determined at conception and cannot be influenced by later outcomes, associations between genetic variants and health-related outcomes cannot be explained by reverse causation. Therefore, instrumental-variable regression with genetic variants as a proxy for risk factors can strengthen causal inference (Lawlor, Harbord, Sterne, Timpson, & Smith, 2008; Smith & Ebrahim, 2004). Figure 1 presents the assumptions underlying instrumental-variable regression with more detail.
Figure 1. Assumptions of instrumental-variable regression. Genetic variants can serve as an instrument for a risk factor if they: a) are strongly associated with the risk factor; b) are independent of any factors that confound the association between the risk factor and the outcome; and c) affect the outcome only through the risk factor.
2. AIMS OF THE STUDY

The first aim of the present study was to cross-sectionally examine: 1) whether LQTS mutation carrier status is associated with the risk of depressive symptoms or any of their dimensions (affective, cognitive, or somatic); 2) whether depressive symptoms or their dimensions are associated with the risk of arrhythmic events in LQTS after the adjustment for age, β-blockers, antidepressants, social support, and education; and 3) whether there are sex differences in these potential relationships.

The second objective of this study was to prospectively investigate: 1) whether depressive symptoms predict glucose levels, or vice versa; 2) whether there are sex differences in these plausible associations; and 3) whether changes in body fat, inflammation, alcohol consumption, or tobacco or cigarette smoking are likely to mediate these possible associations.

The final aim of the current study was to determine using instrumental-variable regression: 1) whether elevated glucose is likely to be a causal risk factor for depressive symptoms; and, additionally, 2) whether women and men may differ in this potential association.

Figure 2 outlines the focus of the present study.
Figure 2. The focus of the present study.
3. METHODS

In the present research, data from two separate studies were used: the Finnish LQTS registry (Study I) and the Cardiovascular Risk in Young Finns Study (Studies II–III).

3.1. LQTS study

3.1.1. Participants

The LQTS study participants were from the Finnish LQTS registry, which includes people who have been referred for genetic testing for LQTS to the Helsinki University Central Hospital from all over the country since year 1993. Those members of the registry who fulfilled the following criteria participated in psychological assessment: a molecularly confirmed or excluded familial LQTS mutation, age greater than or equal to 18 years, permanent residency in Finland, and a written informed consent.

The baseline data collection phase in 2006 included 1443 attendees. The participants of the present study were from the follow-up performed in 2011 (n = 1081). Those individuals who had missing information on any of the study variables (n = 254) were excluded from the final analyses. As older adults can experience depressive symptoms due to ageing-related declines in physical health (Sutin et al., 2013), which could bias our results, individuals who were 75 years of age or older (n = 45) were not included in the study population. Thus, the final sample consisted of 782 participants (n = 252 men). There were 369 LQTS mutation carriers (263 KCNQ1, 87 KCNH2, 12 SCN5A, and six KCNJ2 mutation carriers, and one carrier of both KCNQ1 and KCNH2 mutations). The control group comprised 413 relatives who did not carry a familial LQTS mutation.

To identify LQTS mutations, direct DNA sequencing and restriction enzyme assays were used as previously described (Fodstad et al., 2004, 2006). The classification of the mutations was conducted in compliance with the recommendations of Richards et al. (2015) using information from the following databases: ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/), dbSNP (http://www.ncbi.nlm.nih.gov/snp/), ExAC (http://biorxiv.org/content/early/2015/10/30/030338),
ExAC (http://exac.broadinstitute.org/), Exome Variant Server (http://evs.gs.washington.edu/EVS/), HGMD (http://www.hgmd.cf.ac.uk/ac/index.php), HGMD (Stenson et al., 2003), and SISu (http://www.sisuproject.fi/). Only pathogenic and likely pathogenic mutations, and variants of unknown significance were included in the study. Two mutant channels SCN5A R104Q and SCN5A E1784K were excluded as they have previously been found to be associated with both LQTS and Brugada syndrome (Moric et al., 2003). The study was approved by the Helsinki University Central Hospital.

3.1.2. Measures

Information on arrhythmic events (i.e., symptoms) was self-reported when an individual became a member of the LQTS registry. These data were updated in the 2011 follow-up study. LQTS mutation carriers with a documented LQTS-type syncopal episode and/or aborted cardiac arrest (i.e., with arrhythmic events) were classified as symptomatic and those without arrhythmic events as asymptomatic LQTS mutation carriers.

Depressive symptoms were assessed with the Beck Depression Inventory-II (BDI-II; Beck, Steer, & Brown, 1996), which is a measure used to screen for major depressive disorder on the basis of the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-4; American Psychiatric Association, 1994). The questionnaire consists of 21 items with four alternative statements each (except for items referring to change in sleeping and eating habits with seven statements). The study participants were asked to describe how they have been feeling during the past 2 weeks. The scale reliability (Cronbach’s α) was .92. Severity score of depressive symptoms was calculated as the sum score of responses. Additionally, each participant was categorized into one of the two groups depending on whether he/she screened positive or negative for depressive disorder. Following the recommendations presented in the manual (Beck et al., 1996), the cut-off score of 14 points was used. This allowed to estimate the prevalence of depressive disorder in the study population.
The three dimensions of depressive symptoms were based on the three-factor model of the BDI-II (Beck, Steer, Brown, & Van der Does, 2002). The affective dimension was measured with five items (1, 2, 4, 9, and 12), the cognitive dimension—with seven items (3, 5–8, 13, and 14), and the somatic dimension—with nine items (10, 11, and 15–21). Reliability of the subscales was high (affective dimension Cronbach’s α = .80, cognitive dimension Cronbach’s α = .87, and somatic dimension Cronbach’s α = .82).

Social support was assessed with the Multidimensional Scale of Perceived Social Support (MSPSS; Zimet, Dahlem, Zimet, & Farley, 1988). The measure comprises 12 items such as: There is a special person with whom I can share my joy and sorrows, I can talk about my problems with my family, or I can count on my friends when things go wrong. The attendees were asked to rate how well each item describes them using a 5-point response scale (instead of the original 7-point scale) ranging from 1 = totally disagree to 5 = totally agree. Reliability of the measure (Cronbach’s α) was .96. The level of social support was calculated as the mean score of responses.

Information concerning the use of β-blockers and antidepressants was collected with a medical questionnaire, which was enclosed to the psychological measures sent to the participants in 2011.

The individuals were asked to report their level of education as the highest completed degree. Thereafter, we classified them into two groups: with lower (basic/vocational education including degrees obtained at a university of applied sciences) and higher (university degree) education level.

3.2. The Cardiovascular Risk in Young Finns Study

3.2.1. Participants

The Cardiovascular Risk in Young Finns Study is an ongoing, prospective, population-based study aimed to investigate risk factors of cardiovascular diseases in Finland (Akerblom et al., 1991; Raitakari et al., 2008). The baseline study consisted of randomly selected 3596 children and adolescents from six birth cohorts (aged 3, 6, 9, 12, 15, and 18 years). To select a broadly
representative sample of the Finnish population, the country was divided into five areas according to the locations of university cities with a medical school (Helsinki, Kuopio, Oulu, Tampere, and Turku). In each area, urban and rural girls and boys were selected using their unique personal social security numbers. Since the baseline, eight follow-up studies have been performed (years: 1983, 1986, 1989, 1992, 1997, 2001, 2007, and 2012). The study was approved by the ethics committees of each of the five participating universities. A written informed consent was obtained from participants aged 9, 12, 15, and 18 years and from the parents of participants aged 3 and 6 years.

Study II included data from the 2001, 2007, and 2012 follow-ups (all six cohorts). In the main model (two measurement points: 2001 and 2012), individuals with information on either depressive symptoms or glucose levels in 2001 or 2012, and information on socioeconomic status (SES) measured in 2001 were included. We excluded the participants with type 1 diabetes (T1D) or T2D in 2001 (n = 26). The final sample comprised 2534 individuals.

The additional model tested in Study II (three measurement points: 2001, 2007, and 2012) was based on a sample consisting of people with data on either depressive symptoms or glucose levels in at least one of the follow-ups, and information on SES in 2001. Those participants who had T1D or T2D in 2001 were excluded (n = 23). The analytic sample included 2549 individuals.

The mediation model in Study II was tested only among women. All female participants who had data on at least one of the variables used in this model, except for women with the diagnosis of T1D or T2D in 2001 (n = 12), were included. The final sample consisted of 1820 participants.

Study III was based on information from the latest data collection phase (i.e., 2012) consisting of 2063 participants (all six cohorts). Those individuals who did not have complete information on all the study variables (n = 796) or who were diagnosed with T1D (n = 7) or T2D (n = 43) were excluded. The final sample comprised 1217 participants.
3.2.2. Measures

Depressive symptoms in Studies II–III (years: 2001, 2007, and 2012) were assessed with a modified version of the Beck Depression Inventory-I (BDI-I; Beck & Steer, 1987). The original version of the scale comprises 21 items with four alternative response options for each item (ranging from absence to severe depressive symptoms). In the modified version of the BDI-I, adopted for use in the Cardiovascular Risk in Young Finns Study (Elovainio et al., 2015; Katainen, Raikkonen, Keskivaara, & Keltikangas-Jarvinen, 1999a), the items are the second mildest statements of the original inventory with a five 5-point Likert scale ranging from 1 = totally disagree to 5 = totally agree. This scoring system has been suggested to most accurately capture a wider variance in depressive symptoms in the general population and to be less time-consuming compared with the original measure (Katainen et al., 1999a; Rosenstrom et al., 2012). So far, however, there has been no explicit empirical evidence that would support this rationale. Depressive symptom severity score was calculated as the mean score of responses. The scale reliability (Cronbach’s α) was .92 in 2001, and .93 in 2007 and 2012. The validity of the modified BDI-I has been supported, among others, by its correlation with the BDI-II, which is a tool to screen for depressive disorder (Rosenstrom et al., 2012), and its association with depression-related psychosocial characteristics, including low level of sociability, negative emotionality (Katainen, Raikkonen, & Keltikangas-Jarvinen, 1999b), harm avoidance (Josefsson, Merjonen, Jokela, Pulkki-Raback, & Keltikangas-Jarvinen, 2011), perseveration, and emotional reactivity (Hintsa et al., 2016a).

Fasting serum glucose levels in Studies II–III (years: 2001, 2007, and 2012) were measured with the enzymatic hexokinase method (Glucose reagent, Beckman Coulter Biomedical) using an AU400 instrument (Olympus, Japan). To reduce positive skewness, glucose values were log transformed in the main analyses of Study II.

The genome-wide association study (GWAS) analysis in the Cardiovascular Risk in Young Finns Study population (n = 2627) was conducted in 2009 using the 670K Illumina platform
In genotype imputation, SHAPEIT (Delaneau, Marchini, & Zagury, 2011) and IMPUTE2 software (Howie, Donnelly, & Marchini, 2009), and the 1000G Phase I Integrated Release Version 3 Haplotypes (The 1000 Genomes Project Consortium, 2010) were used as a reference panel. A weighted genetic risk score for fasting glucose used in Study III included 35 previously published risk single nucleotide polymorphisms (SNPs) for fasting glucose (Dupuis et al., 2010; Manning et al., 2012; Scott et al., 2012). The score was calculated as the sum of genotyped risk alleles or imputed allele dosages carried by an individual, each multiplied by the effect size (the natural log of the odds ratios) using R software version 2.15.3.

Serum high-sensitivity C-reactive protein (hs-CRP) in Study II (years: 2001 and 2007) was used as an indicator of inflammation. It was measured with an automated analyzer (Olympus AU400, Olympus, USA) and a highly sensitive turbidimetric immunoassay kit (CRP-UL-assay, Wako Chemicals, Neuss, Germany).

The current alcohol consumption in Study II (years: 2001 and 2007) was assessed by one question (i.e., frequency of consumption of six or more alcohol portions within one day) with six alternative answers (1 = twice a week or more often, 2 = once a week, 3 = twice or three times a month, 4 = once a month, 5 = twice to six times a year, and 6 = rarely or never). Alcohol consumption was recoded so that higher values indicated higher frequency.

The measurement of frequency of current tobacco or cigarette smoking in Study II (years: 2001 and 2007) was based on a single question consisting of five response options. The answer choices were as follows: 1 = once a day or more often, 2 = once a week or more often but not every day, 3 = less than once a week, 4 = I quit smoking, and 5 = I have never smoked. The variable was recoded in like manner as alcohol consumption (i.e., the higher value, the higher frequency).

SES in Study II (year 2001) was measured by education. High SES was indicated by a completed academic or polytechnic degree or by studying at a university, intermediate SES—by
secondary education as the highest degree, and low SES—a primary school or less as the highest level of education.

Body fat in Studies II–III (years: 2001, 2007, and 2012) was measured with body mass index (BMI), which is calculated as weight (kg) divided by height$^2$ (m$^2$). Height was measured with a wall-stated stadiometer and weight—with Seca scales.

Physical activity in Study III (year 2012) was assessed using a short self-report questionnaire, which includes five questions referring to: the intensity of physical activity, frequency of rigorous physical activity, time spent on rigorous physical activity, duration of a physical activity session, and participation in organized physical activity (for details concerning this instrument, see Telama et al., 2005). Physical activity index was calculated as the sum score of responses.

### 3.3. Statistical analyses

#### 3.3.1. Study I

The association of LQTS mutation carrier status with depressive symptoms and their three dimensions (continuous variables) was examined using binary logistic regression, in which LQTS mutation carriers were compared with the control group. Since there was no significant interaction effect of LQTS mutation carrier status and sex on depressive symptoms ($p = .30$) in the two-way analysis of variance (ANOVA), this relationship was tested combining women and men. The association of depressive symptoms and their dimensions (continuous variables) with the risk of arrhythmic events in LQTS was tested using multinomial (comparison of symptomatic and asymptomatic LQTS mutation carriers with the control group) and binary (comparison of symptomatic LQTS mutation carriers with asymptomatic LQTS mutation carriers) logistic regression. Due to the fact that a marginally significant interaction of symptom status and sex on depressive symptoms was observed ($p = .059$), the association between depressive symptoms and the risk of arrhythmic events was tested for women and men separately. All the models were
adjusted for age, β-blocker and antidepressant use, social support, and, additionally, for education (since 186 participants had missing information on education, the analyses including this variable were conducted in a sample of 596 individuals). To examine the differences between women and men in the study variables and to conduct an attrition analysis, the chi-square test ($\chi^2$) and the t-test were used. The statistical analysis was performed with PASW 18.0.2. software.

3.3.2. Study II

The temporal direction of the association between depressive symptoms and glucose levels, and sex differences in this potential association were measured with multiple-group cross-lagged analysis in structural equation modeling (SEM) controlling for baseline age and SES. First, the model with two measurement points was tested (2001 and 2012). The model with three measurement points (2001, 2007, and 2012) was tested additionally. Since our population was relatively young ($M = 42.54$ in the latest follow-up), considering that prevalence of T2D begins to increase on the threshold of midlife (Wild, Roglic, Green, Sicree, & King, 2004), the plausible relationship between depressive symptoms and glucose levels, or possible differences between women and men in this association were more likely to be detected within a longer time lag (i.e., 11 years instead of 6 or 5 years).

To examine whether the association between depressive symptoms (2001) and glucose concentrations (2012) was mediated by changes in BMI, hs-CRP, alcohol consumption, or tobacco or cigarette smoking (from 2001 to 2007), we used parallel multiple mediation in SEM. The reason for choosing this approach was the fact that it is robust to unmeasured common causes of two or more mediators and that it takes into account that the mediators can affect one another (VanderWeele & Vansteelandt, 2014). The model was adjusted for baseline age and SES, and the baseline scores of the tested mediators and the outcome. The bootstrapping procedure with 1000 repetitions was used to obtain confidence intervals (normal-based 95% CI) as recommended by Preacher and Hayes (2008).
To reduce the possibility of biased results due to missing values, we implemented the full information maximum likelihood estimation (FIML; “mlmv” option; Dong & Peng, 2013). The method estimates parameters using all available information (i.e., also from participants with incomplete data). The FIML maximizes the likelihood function of incomplete cases in parameter estimation. The approach assumes that the data are at least missing at random. As this assumption is uncheckable empirically, pattern mixture modeling (PMM) was used to tackle informative (i.e., non-ignorable) attrition (Dantan, Proust-Lima, Letenneur, & Jacqmin-Gadda, 2008). PMM requires creating a new variable that provides information on a drop-out pattern and further controlling it in the analysis. Thus, missing data mechanism does not need to be non-informative. There are different ways to create the attrition indicator; in Study II, this covariate was based on the number of follow-ups, in which the participant provided data on either glucose or depressive symptoms.

Goodness-of-fit of the models was evaluated using: the $\chi^2$, the root mean squared error of approximation (RMSEA), the comparative fit index (CFI), and the Tucker-Lewis Index (TLI) following Acock (2013), Hoe (2008), and Kenny, Kaniskan, and McCoach (2015). Further, the model fit comparison was based on the difference in $\chi^2$ test ($\Delta\chi^2$). Statistically significant changes in the $\chi^2$ values ($p < .05$; Byrne, 2001) were an indicator that the model with fewer equality constrains across sex provided a better fit to the data.

Sex differences in the study variables were examined using the $t$-test and the Mann-Whitney $U$ test. The attrition analysis, which included data from three measurement points, was performed with multilevel mixed-effects logistic regression (QR decomposition). All the analyses were conducted with Stata/SE 13 software.

### 3.3.3. Study III

Stata/SE 13 software was used to analyze all the data. First, the association between fasting glucose and depressive symptoms was tested with standard linear regression. Then, we used instrumental-variable regression (the generalized method of moment estimation, GMM; Baum, Schaffer, &
Stillman, 2003) with the genetic risk score for fasting glucose as an instrument for fasting glucose allowing for heteroscedasticity of the error term (“wmatrix (robust)” option; Baum et al., 2003). The analysis was performed for women and men combined. The models were adjusted for sex, age, BMI, and physical activity. To compare estimates of the standard linear regression and the instrumental-variable regression, the difference-in-Sargan test (the C statistic) was used (Baum et al., 2003). Linear and binary logistic regression were used to examine the association between the genetic risk score and the study covariates. The evaluation of the strength of the genetic risk score as an instrument for fasting glucose was based on the $F$-statistic from the first-stage regression analysis. The criterion of the $F$-value greater than 10 as evidence that an instrument is sufficiently strong was used following Staiger and Stock (1997). The attrition analysis was performed with the $t$-test and the $\chi^2$ test.

Thereafter, we additionally imputed missing values using the variables included in the analysis with Stata imputation by chained equations (ICE; Royston & White, 2011) to examine whether it is possible that the results derived from the analysis of the incomplete data could be biased due to the attrition (sensitivity analysis). Multiply imputed values were generated for the participants of the Young Finns Study who had information on the genetic risk score for fasting glucose and who were not diagnosed with T1D or T2D in the 2012 follow-up ($n = 2527$). Randomly selected multiply imputed datasets ($n = 50$) were analyzed with “misum” and “mibeta” commands and with the same main statistical methods mentioned in the previous paragraph using “mi estimate” option.

We were not able to perform our analyses separately for women and men on the incomplete dataset, in which there was a significant interaction effect of glucose and sex on depressive symptoms ($p = .039$). The reason for that was a small sample size ($n = 500$ women and $n = 717$ men). Thus, sex-specific analyses were conducted on the imputed dataset ($n = 1371$ women and $n = 1156$ men). They were, however, treated as an additional material.
4. RESULTS

The characteristics of the study populations are presented in Table 1 (Study I) and Table 2 (Studies II–III).

### Table 1

*The Characteristics of the Participants Included in Study I*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women</th>
<th>Men</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>530</td>
<td>252</td>
<td>.024</td>
</tr>
<tr>
<td><strong>Group status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LQTS mutation carrier status</td>
<td>256</td>
<td>113</td>
<td></td>
</tr>
<tr>
<td>Symptomatic LQTS</td>
<td>131</td>
<td>38</td>
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<tr>
<td>Asymptomatic LQTS</td>
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<td>75</td>
<td>.002&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Control group</td>
<td>274</td>
<td>139</td>
<td></td>
</tr>
<tr>
<td><strong>Depressive disorder (screening)</strong></td>
<td></td>
<td></td>
<td>.011</td>
</tr>
<tr>
<td>Yes</td>
<td>84</td>
<td>23</td>
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</tr>
<tr>
<td>No</td>
<td>446</td>
<td>229</td>
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<tr>
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<td></td>
<td></td>
<td>&lt;.001</td>
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<td>530</td>
<td>252</td>
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<td><strong>Affective dimension</strong></td>
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<td>.020</td>
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<td>530</td>
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<td>500</td>
<td>200</td>
<td></td>
</tr>
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<td><strong>Cognitive dimension</strong></td>
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<td></td>
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<tr>
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<td>252</td>
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</tr>
<tr>
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<td>500</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td><strong>Somatic dimension</strong></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
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<td>530</td>
<td>252</td>
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<td><strong>Medication</strong></td>
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</tr>
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<td>β-blockers</td>
<td>530</td>
<td>252</td>
<td>&lt;.001</td>
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<td>205</td>
<td></td>
</tr>
<tr>
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<td>174</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
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<td>252</td>
<td>.061</td>
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<td>Yes</td>
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</tr>
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<td>No</td>
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<td>15</td>
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<td><strong>Social support</strong></td>
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<tr>
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<td>151</td>
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<tr>
<td>Higher</td>
<td>117</td>
<td>47</td>
<td>.15</td>
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<td><strong>Education</strong></td>
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<tr>
<td>Lower</td>
<td>308</td>
<td>178</td>
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<tr>
<td>Higher</td>
<td>222</td>
<td>72</td>
<td></td>
</tr>
</tbody>
</table>

Note: LQTS = long QT syndrome; M = mean; n = number of participants; SD = standard deviation.

<sup>a</sup>P-value for a difference between women and men.

<sup>b</sup>The chi-square test used to compare proportions of women and men with and without LQTS-related symptoms.
Table 2
The Characteristics of the Participants and Variables of Interest in Studies II–III

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women n (%)</th>
<th>Study II</th>
<th>Men n (%)</th>
<th>Study III</th>
<th>All n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1406 (55.5)</td>
<td>1217</td>
<td>1128 (44.5)</td>
<td>717 (58.9)</td>
<td>1217</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>1406</td>
<td>1128</td>
<td>823</td>
<td>722</td>
<td>1217</td>
</tr>
<tr>
<td>Depressive symptoms in 2001</td>
<td>1152</td>
<td>1090</td>
<td>1007</td>
<td></td>
<td>1217</td>
</tr>
<tr>
<td>Depressive symptoms in 2007</td>
<td>1093</td>
<td>1007</td>
<td>843</td>
<td></td>
<td>1217</td>
</tr>
<tr>
<td>Depressive symptoms in 2012</td>
<td>913</td>
<td>823</td>
<td>727</td>
<td></td>
<td>1217</td>
</tr>
<tr>
<td>Glucose (mmol/L) in 2001</td>
<td>1242</td>
<td>1092</td>
<td>907</td>
<td></td>
<td>1217</td>
</tr>
<tr>
<td>Glucose (mmol/L) in 2007</td>
<td>1093</td>
<td>1007</td>
<td>843</td>
<td></td>
<td>1217</td>
</tr>
<tr>
<td>Glucose (mmol/L) in 2012</td>
<td>1002</td>
<td>907</td>
<td>843</td>
<td></td>
<td>1217</td>
</tr>
<tr>
<td>Genetic risk score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SES in 2001</td>
<td>1406</td>
<td>1128</td>
<td>785</td>
<td>5.50 (0.70)</td>
<td>1217</td>
</tr>
<tr>
<td>Low</td>
<td>126 (9.0)</td>
<td>97 (8.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>885 (62.9)</td>
<td>762 (67.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>395 (28.1)</td>
<td>269 (23.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²) in 2012</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity in 2012</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. BMI = body mass index; M = mean; n = number of participants; SD = standard deviation; SES = socioeconomic status.

The characteristics presented here are for the model with two measurement points (2001 and 2012), except for depressive symptoms and glucose in 2007 included in the model with three measurement points (2001, 2007, and 2012).

P-value for a difference between women and men.

Age in Study II is shown for year 2001 and in Study III—for year 2012.

The genetic risk score expressed in standard score.

4.1. The association of LQTS mutation carrier status and symptomatic LQTS with depressive symptoms (Study I)

The participants of the study (n = 782) were younger compared with the individuals lost due to attrition (49.40 vs. 54.86, p < .001). The groups did not differ in social support, depressive symptoms, β-blocker intake, or the prevalence of depressive disorder (ps > .05). The participants were more often users of antidepressants than those who dropped out (13.6% vs. 7.3%, p = .006).

The binary logistic regression showed no association between LQTS mutation carrier status and overall depressive symptoms in the model adjusted for sex, age, β-blockers, antidepressants, and social support (OR = 1.01, 95% CI [0.99, 1.04], p = .38, R² = 18.8%). There was also no association between LQTS mutation carrier status and any of the dimensions of depressive symptoms
(affective: \( OR = 1.01, 95\% \text{ CI } [0.92, 1.11], p = .85, R^2 = 18.7\% \); cognitive: \( OR = 1.06, 95\% \text{ CI } [0.99, 1.13], p = .12, R^2 = 19.1\% \); somatic: \( OR = 1.01, 95\% \text{ CI } [0.96, 1.06], p = .64, R^2 = 18.8\% \). When the models were adjusted additionally for education, the results remained unchanged (\( ps > .05 \)).

In the multinomial logistic regression (Table 3), overall depressive symptoms (\( p = .007 \)), cognitive symptoms (\( p = .013 \)), and somatic symptoms (\( p = .005 \)) were associated with an increased risk of arrhythmic events in men independently of age, \( \beta \)-blockers, antidepressants, and social support. The association between the affective dimension and the risk of arrhythmic events was marginally significant (\( p = .054 \)). After the additional adjustment for education, the association of overall depressive symptoms (\( OR = 1.09, 95\% \text{ CI } [1.02, 1.16], p = .008, R^2 = 20.1\% \)), cognitive symptoms (\( OR = 1.24, 95\% \text{ CI } [1.05, 1.47], p = .011, R^2 = 19.6\% \)), and somatic symptoms (\( OR = 1.20, 95\% \text{ CI } [1.05, 1.37], p = .006, R^2 = 20.3\% \)) with an increased risk of arrhythmic events in LQTS remained significant. In parallel, the affective dimension continued to be associated with symptomatic LQTS at the marginal level of significance (\( OR = 1.24, 95\% \text{ CI } [0.99, 1.54], p = .061, R^2 = 16.9\% \)). No associations between depressive symptoms or their three dimensions and the risk of arrhythmic events in LQTS were found in women (\( ps > .05 \)).
The results of the binary logistic regression (Table 4) showed that overall depressive symptoms ($p = .009$), and affective ($p = .017$), cognitive ($p = .020$), and somatic symptoms ($p = .009$) were associated with the risk of arrhythmic events in men after controlling for age, β-blockers, antidepressants, and social support. When we controlled additionally for education, the association of overall depressive symptoms ($OR = 1.14$, 95% CI [1.03, 1.25], $p = .011$, $R^2 = 23.7\%$), and cognitive ($OR = 1.37$, 95% CI [1.03, 1.83], $p = .032$, $R^2 = 21.3\%$) and somatic depressive symptoms ($OR = 1.29$, 95% CI [1.08, 1.54], $p = .005$, $R^2 = 24.6\%$) with an increased risk of arrhythmias in LQTS remained significant. The association between affective symptoms and symptomatic LQTS

### Table 3

*The Results of the Multinomial Logistic Regression Examining the Association of LQTS Symptom Status With Depressive Symptoms and Their Three Dimensions (n = 782; n = 530 Women and n = 252 Men)*

<table>
<thead>
<tr>
<th>Group status</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td><strong>Overall depressive symptoms</strong></td>
<td>Model</td>
<td>27.3</td>
</tr>
<tr>
<td>Control group</td>
<td>274</td>
<td>1.00</td>
</tr>
<tr>
<td>Asymptomatic LQTS</td>
<td>125</td>
<td>1.01 (0.97, 1.04)</td>
</tr>
<tr>
<td>Symptomatic LQTS</td>
<td>131</td>
<td>1.00 (0.96, 1.04)</td>
</tr>
<tr>
<td><strong>Affective dimension</strong></td>
<td>Model</td>
<td>27.3</td>
</tr>
<tr>
<td>Control group</td>
<td>274</td>
<td>1.00</td>
</tr>
<tr>
<td>Asymptomatic LQTS</td>
<td>125</td>
<td>0.99 (0.86, 1.13)</td>
</tr>
<tr>
<td>Symptomatic LQTS</td>
<td>131</td>
<td>0.98 (0.84, 1.14)</td>
</tr>
<tr>
<td><strong>Cognitive dimension</strong></td>
<td>Model</td>
<td>27.5</td>
</tr>
<tr>
<td>Control group</td>
<td>274</td>
<td>1.00</td>
</tr>
<tr>
<td>Asymptomatic LQTS</td>
<td>125</td>
<td>1.04 (0.94, 1.14)</td>
</tr>
<tr>
<td>Symptomatic LQTS</td>
<td>131</td>
<td>1.06 (0.96, 1.17)</td>
</tr>
<tr>
<td><strong>Somatic dimension</strong></td>
<td>Model</td>
<td>27.5</td>
</tr>
<tr>
<td>Control group</td>
<td>274</td>
<td>1.00</td>
</tr>
<tr>
<td>Asymptomatic LQTS</td>
<td>125</td>
<td>1.01 (0.94, 1.08)</td>
</tr>
<tr>
<td>Symptomatic LQTS</td>
<td>131</td>
<td>0.96 (0.89, 1.04)</td>
</tr>
</tbody>
</table>

Note. CI = confidence interval; LQTS = long QT syndrome; $n$ = number of participants; OR = odds ratio; $R^2$ (Nagelkerke) = fraction of explained variance. Model adjusted for age, β-blockers, antidepressants, and social support. Reference group = control group.
was attenuated to marginally significant \((OR = 1.31, 95\% \text{ CI } [0.97, 1.76], p = .080, R^2 = 16.4\%)\). These associations were not observed in women \((ps > .05)\).

### Table 4

*The Results of the Binary Logistic Regression Examining the Association of LQTS Symptom Status With Depressive Symptoms and Their Three Dimensions \((n = 369; n = 256 \text{ Women and } n = 113 \text{ Men})\)*

<table>
<thead>
<tr>
<th>Group status</th>
<th>Model</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Overall depressive symptoms</td>
<td></td>
<td>20.6</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic LQTS</td>
<td></td>
<td>125</td>
<td>1.00</td>
</tr>
<tr>
<td>Symptomatic LQTS</td>
<td></td>
<td>131</td>
<td>0.99 (0.95, 1.03)</td>
</tr>
<tr>
<td>Affective dimension</td>
<td></td>
<td>20.5</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic LQTS</td>
<td></td>
<td>125</td>
<td>1.00</td>
</tr>
<tr>
<td>Symptomatic LQTS</td>
<td></td>
<td>131</td>
<td>0.98 (0.83, 1.16)</td>
</tr>
<tr>
<td>Cognitive dimension</td>
<td></td>
<td>20.5</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic LQTS</td>
<td></td>
<td>125</td>
<td>1.00</td>
</tr>
<tr>
<td>Symptomatic LQTS</td>
<td></td>
<td>131</td>
<td>1.01 (0.91, 1.12)</td>
</tr>
<tr>
<td>Somatic dimension</td>
<td></td>
<td>21.0</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic LQTS</td>
<td></td>
<td>125</td>
<td>1.00</td>
</tr>
<tr>
<td>Symptomatic LQTS</td>
<td></td>
<td>131</td>
<td>0.96 (0.88, 1.04)</td>
</tr>
</tbody>
</table>

*Note.* CI = confidence interval; LQTS = long QT syndrome; \(n\) = number of participants; OR = odds ratio; \(R^2\) (Nagelkerke) = fraction of explained variance.

Model adjusted for age, \(\beta\)-blockers, antidepressants, and social support.

Reference group = asymptomatic LQTS.

### 4.2. The direction of the association between depressive symptoms and glucose (Study II)

The results of the attrition analysis showed that higher glucose concentrations \((OR = 18.57, 95\% \text{ CI } [4.42, 77.90], p < .001)\), lower SES \((OR = 2.45, 95\% \text{ CI } [1.84, 3.27], p < .001)\), and female sex \((OR = 3.97, 95\% \text{ CI } [2.95, 5.36], p < 0.001)\) were associated with higher drop-out. Older participants were less likely to drop out \((OR = 0.94, 95\% \text{ CI } [0.91, 0.97], p < .001)\). Higher depressive
Depressive symptoms were not associated with attrition \((OR = 1.07, 95\% \text{ CI} [0.86, 1.34], p = .54)\). Regarding the pattern of missing values, there were 1934 (64.0\%) participants who had information on either glucose or depressive symptoms in three follow-ups, 284 (9.4\%) in 2001, 272 (9.0\%) in 2001 and 2007, 200 (6.6\%) in 2007 and 2012, 137 (4.5\%) in 2001 and 2012, 108 (3.6\%) in 2007, and 89 (2.9\%) in 2012.

The multiple-group cross-lagged model with two measurement points is shown in Figure 3. In this adjusted for baseline age and SES model, we imposed equality constraints across sex on paths b and d as those paths were not statistically different between women and men \((ps > .05)\). The model did not provide a statistically worse fit to the data than the saturated fully unconstrained model \((\Delta \chi^2 (2) = 0.28, p = .87)\). Further, the model fit difference between this model and the fully constrained model was statistically significant \((\Delta \chi^2 (2) = 9.94, p = .007)\). Thus, the partially constrained model was retained.

Figure 3. The cross-lagged model with two measurement points (2001 and 2012).
The final model was a good fit to the data ($\chi^2 (2) = 0.28$; RMSEA = .00; CFI = 1.00; TLI = 1.01). The results (Table 5) showed that depressive symptoms in 2001 were associated with glucose levels in 2012 in women ($\beta = .07, p = .023, R^2 = 16.4\%$) but not in men ($\beta = -.03, p = .45, R^2 = 15.9\%$). The sex difference in this path was statistically significant ($p = .042$). We also found that glucose levels in 2001 did not predict depressive symptoms in 2012 in either sex (women: $\beta = .00, p = .96, R^2 = 34.7\%$; men: $\beta = .00, p = .96, R^2 = 38.3\%$).

Table 5

The Results of the Multi-Group Cross-Lagged Analysis With Data From the 2001 and 2012 Follow-Up (n = 2534; n = 1406 Women and n = 1128 Men)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$</td>
<td>$b$</td>
</tr>
<tr>
<td>Autoregressive paths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms in 2001</td>
<td>.59</td>
<td>.57</td>
</tr>
<tr>
<td>Glucose in 2012</td>
<td>.39</td>
<td>.52</td>
</tr>
<tr>
<td>Cross-lagged paths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms in 2012</td>
<td>.00</td>
<td>.01</td>
</tr>
<tr>
<td>Glucose in 2012</td>
<td>.07</td>
<td>.01</td>
</tr>
</tbody>
</table>

Note. $b$ = unstandardized regression coefficient; $\beta$ = standardized regression coefficient; CI = confidence interval. Glucose values logarithmically transformed. The significance levels presented here are for the unstandardized regression coefficients. Model adjusted for baseline age and socioeconomic status.

The additional multiple-group cross-lagged model (with three measurement points) adjusted for baseline age and SES is depicted in Figure 4. First, we allowed all the paths to vary across sex. The model, however, was not a good fit to the data ($\chi^2 (8) = 154.61$; RMSEA = .12; CFI = .95; TLI = 0.83). Therefore, we included a correlation between depressive symptoms in 2001 and depressive symptoms in 2012 (path l) in this model to obtain a significant improvement in its fit ($\chi^2 (6) = 52.62$; RMSEA = .08; CFI = .99; TLI = 0.93). The model showed that the only paths that differed
The model fit difference between the improved, unconstrained model and the model with equality constraints imposed across sex on all paths, except paths b, c, and e ($\chi^2 (14) = 67.13; \text{RMSEA} = .06; \text{CFI} = .98; \text{TLI} = 0.97$), was not significant ($\Delta\chi^2 (8) = 14.51, p = .069$). Thus, the model with equality constraints was retained. When equality constraints were imposed on all the paths, the model fit difference between the fully constrained model and the partially constrained model was significant ($\Delta\chi^2 (3) = 13.15, p = .004$), indicating that the latter should be selected.

![Figure 4](image)

*Figure 4.* The cross-lagged model with three measurement points (2001, 2007, and 2012).

The results of the final model are presented in Table 6. Depressive symptoms in 2001 were associated with glucose levels in 2007 in women ($\beta = .06, p = .027, R^2 = 19.5\%$) but not in men ($\beta = $...
.02, \ p = .61, \ R^2 = 27.3\%). \ The \ sex \ difference \ was \ non-significant (p = .32). \ Depressive \ symptoms \ in
2007 \ did \ not \ predict \ glucose \ levels \ in \ 2012 \ in \ either \ sex \ (women: \ \beta = -.01, \ p = .56, \ R^2 = 38.4\%;
men: \ \beta = -.01, \ p = .56, \ R^2 = 33.9\%). \ Moreover, \ neither \ glucose \ levels \ in \ 2001 \ were \ associated \ with
depressive \ symptoms \ in \ 2007 \ (women: \ \beta = .01, \ p = .51, \ R^2 = 40.6\%; \ men: \ \beta = .01, \ p = .51, \ R^2 =
41.2\%), \ nor \ glucose \ levels \ in \ 2007 \ predicted \ depressive \ symptoms \ in \ 2012 \ (women: \ \beta = .02, \ p = .42, \ R^2 = 52.0\%; \ men: \ \beta = .01, \ p = .42, \ R^2 = 55.6\%).

Table 6

The Results of the Multi-Group Cross-Lagged Analysis With Data From the 2001, 2007, and 2012
Follow-Up (n = 2549; n = 1414 Women and n = 1135 Men)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women</th>
<th>Men</th>
<th>p-value</th>
<th>p-value for a difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoregressive paths</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms in 2001</td>
<td>\beta = 0.64, 95% CI (0.60, 0.67)</td>
<td>\beta = 0.64, 95% CI (0.60, 0.67)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Glucose in 2001</td>
<td>\beta = 0.43, 95% CI (0.44, 0.57)</td>
<td>\beta = 0.52, 95% CI (0.53, 0.67)</td>
<td>&lt;.001</td>
<td>.048</td>
</tr>
<tr>
<td>Depressive symptoms in 2012</td>
<td>\beta = 0.52, 95% CI (0.45, 0.56)</td>
<td>\beta = 0.57, 95% CI (0.55, 0.68)</td>
<td>&lt;.001</td>
<td>.004</td>
</tr>
<tr>
<td>Glucose in 2012</td>
<td>\beta = 0.27, 95% CI (0.21, 0.31)</td>
<td>\beta = 0.24, 95% CI (0.21, 0.31)</td>
<td>&lt;.001</td>
<td>-</td>
</tr>
<tr>
<td>Glucose in 2007</td>
<td>\beta = 0.62, 95% CI (0.64, 0.73)</td>
<td>\beta = 0.58, 95% CI (0.64, 0.73)</td>
<td>&lt;.001</td>
<td>-</td>
</tr>
<tr>
<td>Cross-lagged paths</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms in 2007</td>
<td>\beta = 0.01, 95% CI (-0.19, 0.38)</td>
<td>\beta = 0.01, 95% CI (-0.19, 0.38)</td>
<td>.51</td>
<td>-</td>
</tr>
<tr>
<td>Glucose in 2007</td>
<td>\beta = 0.06, 95% CI (0.00, 0.02)</td>
<td>\beta = 0.02, 95% CI (-0.01, 0.01)</td>
<td>.61</td>
<td>.32</td>
</tr>
<tr>
<td>Depressive symptoms in 2012</td>
<td>\beta = 0.02, 95% CI (-0.14, 0.34)</td>
<td>\beta = 0.01, 95% CI (-0.14, 0.34)</td>
<td>.42</td>
<td>-</td>
</tr>
<tr>
<td>Glucose in 2007</td>
<td>\beta = -0.01, 95% CI (-0.01, 0.01)</td>
<td>\beta = -0.01, 95% CI (-0.01, 0.01)</td>
<td>.56</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: \ \beta = \text{unstandardized regression coefficient}; \ \beta = \text{standardized regression coefficient}; \ CI = \text{confidence interval}.
Glucose values logarithmically transformed.
The significance levels presented here are for the unstandardized regression coefficients.
Model adjusted for baseline age and socioeconomic status.
Due to the fact that the association of depressive symptoms with glucose levels was found in women but not in men, the mediation analysis was conducted only for the female participants. The characteristics of the sample are summarized in Table 7.

Table 7

The Characteristics of the Women Included in the Mediation Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>%</th>
<th>M</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) in 2001</td>
<td>1820</td>
<td>31.52</td>
<td>4.99</td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms in 2001</td>
<td>1203</td>
<td>2.17</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Glucose (mmol/L) in 2001</td>
<td>1247</td>
<td>4.87</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>Glucose (mmol/L) in 2012</td>
<td>1107</td>
<td>5.21</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>SES in 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>130</td>
<td>9.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>902</td>
<td>63.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>396</td>
<td>27.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²) in 2001</td>
<td>1429</td>
<td>24.47</td>
<td>4.56</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²) in 2007</td>
<td>1176</td>
<td>25.38</td>
<td>5.07</td>
<td></td>
</tr>
<tr>
<td>hs-CRP (mg/L) in 2001</td>
<td>1247</td>
<td>2.23</td>
<td>4.23</td>
<td></td>
</tr>
<tr>
<td>hs-CRP (mg/L) in 2007</td>
<td>1203</td>
<td>2.04</td>
<td>3.56</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption in 2001</td>
<td>1407</td>
<td>2.09</td>
<td>1.18</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption in 2007</td>
<td>1215</td>
<td>2.00</td>
<td>1.20</td>
<td></td>
</tr>
<tr>
<td>Tobacco or cigarette smoking in 2001</td>
<td>1398</td>
<td>2.23</td>
<td>1.58</td>
<td></td>
</tr>
<tr>
<td>Tobacco or cigarette smoking in 2007</td>
<td>1218</td>
<td>2.00</td>
<td>1.44</td>
<td></td>
</tr>
</tbody>
</table>

Note. BMI = body mass index; hs-CRP = high-sensitivity C-reactive protein; M = mean; n = number of participants; SD = standard deviation; SES = socioeconomic status.

The results of the parallel multiple mediator model adjusted for baseline age and SES, and the baseline values of the tested mediators and glucose levels are shown in Table 8. The goodness-of-fit indexes indicated that the model was a good fit to the data ($\chi^2$ (22) = 193.99, RMSEA = .07, CFI = .95, TLI = 0.89). We found that the total indirect effect was statistically non-significant ($\beta = .01, p = .13$). Moreover, changes in BMI ($\beta = .01, p = .15$), hs-CRP ($\beta = -.00, p = .83$), alcohol consumption ($\beta = .00, p = .46$), or tobacco or cigarette smoking ($\beta = .00, p = .85$) did not mediate the association between depressive symptoms and glucose levels.
### Table 8

The Results of the Parallel Multiple Mediator Model in Women (n = 1820)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>( \beta )</th>
<th>( b )</th>
<th>95% CI</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms -&gt; Glucose</td>
<td>.04</td>
<td>0.01</td>
<td>(−0.00, 0.02)</td>
<td>.21</td>
</tr>
<tr>
<td>Depressive symptoms -&gt; BMI</td>
<td>.03</td>
<td>0.22</td>
<td>(−0.07, 0.51)</td>
<td>.13</td>
</tr>
<tr>
<td>Depressive symptoms -&gt; hs-CRP</td>
<td>−.01</td>
<td>−0.03</td>
<td>(−0.31, 0.25)</td>
<td>.81</td>
</tr>
<tr>
<td>Depressive symptoms -&gt; Alcohol consumption</td>
<td>.02</td>
<td>0.04</td>
<td>(−0.06, 0.15)</td>
<td>.43</td>
</tr>
<tr>
<td>Depressive symptoms -&gt; Tobacco or cigarette smoking</td>
<td>.02</td>
<td>0.05</td>
<td>(−0.04, 0.14)</td>
<td>.30</td>
</tr>
<tr>
<td>BMI -&gt; Glucose</td>
<td>.39</td>
<td>0.01</td>
<td>(0.00, 0.01)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>hs-CRP -&gt; Glucose</td>
<td>.03</td>
<td>0.00</td>
<td>(−0.00, 0.00)</td>
<td>.44</td>
</tr>
<tr>
<td>Alcohol consumption -&gt; Glucose</td>
<td>.08</td>
<td>0.01</td>
<td>(0.00, 0.01)</td>
<td>.025</td>
</tr>
<tr>
<td>Tobacco or cigarette smoking -&gt; Glucose</td>
<td>.01</td>
<td>0.00</td>
<td>(−0.01, 0.01)</td>
<td>.85</td>
</tr>
<tr>
<td><strong>Total effect</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms -&gt; Glucose</td>
<td>.05</td>
<td>0.01</td>
<td>(−0.00, 0.02)</td>
<td>.12</td>
</tr>
<tr>
<td><strong>Total of the indirect effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms -&gt; Glucose</td>
<td>.01</td>
<td>0.00</td>
<td>(−0.00, 0.01)</td>
<td>.13</td>
</tr>
<tr>
<td><strong>Specific indirect effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms -&gt; BMI -&gt; Glucose</td>
<td>.01</td>
<td>0.00</td>
<td>(−0.00, 0.00)</td>
<td>.16</td>
</tr>
<tr>
<td>Depressive symptoms -&gt; hs-CRP -&gt; Glucose</td>
<td>−.00</td>
<td>−0.00</td>
<td>(−0.00, 0.00)</td>
<td>.83</td>
</tr>
<tr>
<td>Depressive symptoms -&gt; Alcohol consumption -&gt; Glucose</td>
<td>.00</td>
<td>0.00</td>
<td>(−0.00, 0.00)</td>
<td>.46</td>
</tr>
<tr>
<td>Depressive symptoms -&gt; Tobacco or cigarette smoking -&gt; Glucose</td>
<td>.00</td>
<td>0.00</td>
<td>(−0.00, 0.00)</td>
<td>.85</td>
</tr>
</tbody>
</table>

*Note. \( \beta \) = standardized linear regression coefficient; BMI = body mass index; hs-CRP = high-sensitivity C-reactive protein. The significance levels presented here are for the unstandardized regression coefficients. Glucose values logarithmically transformed. Model adjusted for baseline: age, socioeconomic status, BMI, hs-CRP, alcohol consumption, tobacco or cigarette smoking, and glucose.

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### 4.3. Elevated glucose as a causal risk factor for depressive symptoms? (Study III)

Individuals included in the final sample (\( n = 1217 \)) and people lost due to attrition did not differ in age, the genetic risk score for fasting glucose, or physical activity (\( ps > .05 \)). However, the groups differed in depressive symptoms (2.04 vs. 2.22, \( p < .001 \)), glucose levels (5.26 vs. 5.42, \( p < .001 \)), and BMI (26.07 vs. 26.94, \( p < .001 \)). Moreover, men tended to drop out more often compared with women (45.4% vs. 33.9%, \( p < .001 \)).

There was no association of the genetic risk score with sex, age, BMI, or physical activity (\( ps > .05 \)). The genetic risk score was associated with glucose (\( b = 0.09, 95\% CI [0.07, 0.12], R^2 = 3.8\% \),
$p < .001$) and depressive symptoms ($b = -0.04, 95\% \text{ CI } [-0.07, -0.005], R^2 = 0.4\%, p = .025$). The $F$-value of the association between the genetic risk score and glucose while controlling for above-mentioned potential confounders was greater than 10 ($F = 69.72, R^2 = 22.3\%$).

The results of the standard linear regression adjusted for sex, age, BMI, and physical activity showed that glucose levels were not associated with depressive symptoms ($b = -0.04, 95\% \text{ CI } [-0.12, 0.04], p = .34$). In the instrumental-variable regression, however, the association between glucose and depressive symptoms was negative and statistically significant after the adjustment for the plausible confounders ($b = -0.43, 95\% \text{ CI } [-0.79, -0.07], p = .020$). The difference between estimates derived from the standard linear regression and the instrumental-variable regression models was statistically significant ($p = .026$).

Descriptive statistics of the participants and the association of the genetic risk score with the study covariates across multiply imputed datasets are summarized in Table 9 and Table 10 (both for women and men combined and stratified by sex).

Table 9

*Descriptive Statistics of the Participants Across the 50 Multiply Imputed Datasets (n = 2527; n = 1371 Women and n = 1156 Men)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>Women</th>
<th>Men</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$M$</td>
<td>$SD$</td>
<td>$M$</td>
<td>$SD$</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42.49</td>
<td>5.00</td>
<td>42.53</td>
<td>4.99</td>
</tr>
<tr>
<td></td>
<td>42.44</td>
<td>5.02</td>
<td>.95</td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>2.06</td>
<td>0.63</td>
<td>2.07</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>2.06</td>
<td>0.63</td>
<td>.95</td>
<td></td>
</tr>
<tr>
<td>Genetic risk score</td>
<td>$-0.01$</td>
<td>1.00</td>
<td>$-0.002$</td>
<td>1.02</td>
</tr>
<tr>
<td></td>
<td>$-0.02$</td>
<td>0.98</td>
<td>$-0.02$</td>
<td>0.98</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.29</td>
<td>0.49</td>
<td>5.15</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>5.44</td>
<td>0.47</td>
<td>.79</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.26</td>
<td>4.80</td>
<td>25.86</td>
<td>5.16</td>
</tr>
<tr>
<td></td>
<td>26.73</td>
<td>4.28</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td>9.01</td>
<td>1.88</td>
<td>9.13</td>
<td>1.86</td>
</tr>
<tr>
<td></td>
<td>8.86</td>
<td>1.89</td>
<td>.004</td>
<td></td>
</tr>
</tbody>
</table>

*Note: BMI = body mass index; $M$ = mean; $SD$ = standard deviation.  
*P-value for a difference between women and men.  
The genetic risk score expressed in standard score.
The $F$-statistic in the regression of glucose on the genetic risk score while controlling for sex, age, BMI, and physical activity was 98.20 ($R^2 = 21.8\%$). In the standard linear regression, glucose levels were not associated with depressive symptoms after adjusting for the above covariates ($b = -0.02$, 95% CI $[-0.11, 0.06]$, $p = .58$). On the other hand, the results of the fully adjusted instrumental-variable regression model showed a negative association between glucose levels and depressive symptoms ($b = -0.42$, 95% CI $[-0.76, -0.08]$, $p = .015$). The difference between the estimates of these two models were statistically significant in 48 out of 50 imputed dataset ($ps < .05$). In overall, this sensitivity analysis replicated the results obtained from the analysis of the incomplete dataset.

In the additional, sex-specific analysis, $F$-value from the first-stage regression analysis was 47.40 ($R^2 = 15.7\%$) in women and 29.96 ($R^2 = 12.7\%$) in men. There was no association between glucose levels and depressive symptoms in either women ($b = 0.02$, 95% CI $[-0.08, 0.13]$, $p = .66$) or men ($b = -0.08$, 95% CI $[-0.19, 0.04]$, $p = .19$) in the standard linear regression adjusted for age, BMI, and physical activity. In women, the results of the instrumental-variable regression showed a negative association between glucose levels and depressive symptoms while controlling for age, BMI, and physical activity ($b = -0.45$, 95% CI $[-0.87, -0.03]$, $p = .034$). When the estimates of the

---

### Table 10

The Association Between the Genetic Risk Score and the Study Covariates Across the 50 Multiply Imputed Datasets ($n = 2527$; $n = 1371$ Women and $n = 1156$ Men)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>All</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$b$</td>
<td>95% CI</td>
<td>p-value</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.02</td>
<td>(-0.10, 0.06)</td>
<td>.63</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.17</td>
<td>(-0.36, 0.03)</td>
<td>.088</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>-0.20</td>
<td>(-0.42, 0.01)</td>
<td>.068</td>
</tr>
<tr>
<td>Physical activity</td>
<td>-0.03</td>
<td>(-0.12, 0.06)</td>
<td>.53</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>0.09</td>
<td>(0.07, 0.11)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>-0.04</td>
<td>(-0.08, -0.01)</td>
<td>.012</td>
</tr>
</tbody>
</table>

Note: $b$ = unstandardized regression coefficient; BMI = body mass index; CI = confidence interval.
standard linear regression were compared with the estimates of the instrumental-variable regression in women within 10 first multiply imputed datasets, the difference was statistically significant ($ps < .05$). In men, glucose levels were not associated with depressive symptoms in the instrumental-variable regression ($b = −0.37, 95\% \text{ CI } [−0.84, 0.10], p = .12$) as could be expected in the absence of the association between the genetic risk score and depressive symptoms ($p = .12$). The fact that in the instrumental-variable regression the mean of men overlapped with the 95\% confidence interval of women, and vice versa, suggests that sex differences in the association between glucose and depressive symptoms might not exist. It is likely that the lack of the relationship between glucose and depressive symptoms in the instrumental-variable regression in men was a result of insufficient statistical power due to an inadequate number of participants ($n = 1156$ men compared with $n = 1371$ women).
5. DISCUSSION

5.1. LQTS mutation carrier status and the risk of depressive symptoms

The first aim of Study I was to examine whether LQTS mutation carrier status is associated with an increased risk of depressive symptoms or their affective, cognitive, or somatic dimension. The results showed that carrying a LQTS-causing mutation was not associated with depressive symptoms or any of their dimensions. These findings are in line with a previous study (Hintsa et al., 2009), which found no association between being aware of LQTS mutation carrier status and the risk of depressive symptoms. Moreover, some research (Andersen et al., 2008; Hendriks et al., 2008) showed that uncertainty related to the diagnosis of LQTS rather than knowledge of the syndrome can contribute to the development of depressive symptoms.

5.2. Depressive symptoms and the risk of arrhythmic events in LQTS

The second objective of Study I was to investigate whether there is an association of depressive symptoms or any of their three dimensions with an increased risk of arrhythmic events in LQTS, and whether women and men differ in these plausible associations. The study found that depressive symptoms and all the dimensions were associated with the risk of arrhythmias in LQTS mutation carrier men independently of age, β-blockers, antidepressants, social support, and education. Women scored higher than men on depressive symptoms and all their dimensions. Furthermore, a greater number of women than men screened positive for depressive disorder and had had arrhythmic events. Despite this, neither depressive symptoms nor any of the dimensions were associated with symptomatic LQTS in women.

The results are consistent with previous studies, which provided evidence for the association of prolonged mental stress, a history of stressful life events (Hintsa et al., 2010), and work stress (Hintsa et al., 2013) with the risk of arrhythmias in LQTS mutation carriers. The present findings are also in agreement with two earlier investigations (Hintsa et al., 2016b; Maattanen et al., 2013b),
which revealed that compared with asymptomatic LQTS mutation carriers, symptomatic LQTS patients appear to be more sensitive to respond with emotional distress (Maattanen et al., 2013b) and depressive symptoms to stressful life events (Hintsa et al., 2016b). Those four studies, however, did not report sex-specific results. In line with our observations, a recent systematic literature review and meta-analysis (Doyle et al., 2015) concluded that the prevalence of depressive symptoms in women with MI is higher than in men, although depressive symptoms can be more strongly associated with poor cardiac prognosis among men than women and reflect cardiovascular disease severity in men but not in women.

Those LQTS mutation carriers who are genotyped as LQT1 (the most prevalent (71.3%) LQTS subtype within our study sample) and those with a high risk of cardiac events are advised to avoid engagement in some forms of physical activity (Priori et al., 2013). As a result, they may be physically less fit and therefore experience greater and more frequent fatigue than others. The syndrome itself may also lead to a feeling of tiredness (Andersen et al., 2008). Thus, the association between depressive symptoms and the risk of arrhythmic events in LQTS observed in Study I could mainly be due to fatigue resulting from lower levels of physical activity or cardiac symptoms themselves. The inclusion of the three dimensions of depressive symptoms showed, however, that this was not the case; the risk of arrhythmic events in LQTS was more strongly associated with psychological depressive symptoms (i.e., affective and cognitive) than with somatic depressive symptoms.

It is possible that depressive symptoms are a risk factor for cardiac events in LQTS mutation carrier men but not in women. Depressive symptoms (Grippo, 2004; Watkins et al., 2006; Whang et al., 2005) have repeatedly been shown to be associated with the risk of ventricular arrhythmias. One plausible explanation for this relationship could be altered autonomic nervous system function. There is evidence that depression is associated with excessive sympathetic and reduced parasympathetic activity (Wang et al., 2013), which in turn, has been found to predispose
individuals with CAD to myocardial ischemia, ventricular tachycardia, ventricular fibrillation, and sudden cardiac death (Carney, Freedland, Miller, & Jaffe, 2002). Furthermore, there seem to be sex differences in the function of the autonomic nervous system: women exhibit higher cardiac parasympathetic responsiveness, while men show higher cardiac sympathetic responsiveness (Dart, Du, & Kingwell, 2002). Therefore, LQTS mutation carrier men but not women may be sensitive to proarrhythmic effects of depressive symptoms.

Moreover, depressive symptoms could increase the risk of arrhythmic events in LQTS mutation carrier men through physical inactivity and inflammatory processes. Depressive symptoms are a risk factor for decreased levels of physical activity (Roshanaei-Moghaddam, Katon, & Russo, 2009), and low levels of physical activity have been shown to account for a significant proportion of the risk of cardiovascular mortality due to depressive symptoms (Win et al., 2011). Since physical activity of long duration has been suggested to protect against depressive and anxiety states in men but not in women (Bhui & Fletcher, 2000), it is likely that physical activity may also play a more important role in maintaining physical health of men than of women, perhaps by preventing inflammation (Hamer et al., 2012). As regards inflammatory processes, depressive symptoms have been associated with systemic inflammation in men but not in women (Elovainio et al., 2009), which in turn, has a critical impact on the development of cardiovascular disease (Willerson, 2004). Further, depressive symptoms have been linked to coagulation markers implicated in the pathogenesis of CAD (Panagiotakos et al., 2004). Thus, the association between depressive symptoms and an increased risk of cardiac events in LQTS mutation carrier men could be explained, besides physical inactivity, by inflammatory mechanisms.

In addition to the possibility that depressive symptoms may be a trigger for arrhythmias in LQTS mutation carrier men but not women, it is likely that symptomatic LQTS may lead to depressive symptoms. The association seen in this direction and the observed sex differences could be explained by differences between women and men in the self-concept (Cross & Madson, 1997)
and stress responses (Stroud, Salovey, & Epel, 2002). First, women have been suggested to construct and maintain a self-definition, which involves close personal bonds and pursuit of harmony (i.e., interdependent self-construal), while self-definition in men tends to be based on their unique personality characteristics, distinctive abilities, and pursuit of independence (i.e., independent self-construal; Cross & Madson, 1997). Second, women are physiologically more reactive to social rejection stressors, whereas men exhibit higher physiological reactivity to achievement stressors (Stroud et al., 2002). Bearing this in mind, it seems likely that cardiac symptoms in LQTS may have an especially adverse effect on mental health of men since the syndrome can limit major life activities due to extreme fatigue, headaches, palpitations, and the need to avoid activities that could precipitate arrhythmic events (Andersen et al., 2008). The symptoms can particularly have an impact on working life as they can result in not being able to attend all work activities, being late, or having to take a day off (Andersen et al., 2008). This, in combination with higher costs of health care, and limitations in achievement strivings and financial independence could lead to increased occupational stress, being an independent risk factor for depression (Wang, 2005), in men but not in women.

Furthermore, it is possible that LQTS mutation carrier men but not women may have an increased risk of depressive symptoms due to restrictions concerning levels of physical activity (Priori et al., 2013). As mentioned before, physical activity has been found to be a protective factor against depressive states in men but not in women (Bhui & Fletcher, 2000). The effect of exercise on depressive symptoms can be mediated by the three major monoamine neurotransmitters, that is, dopamine, noradrenaline, and serotonin (Lin & Kuo, 2013). It has also been shown that physical inactivity can induce inflammation (Hamer et al., 2012), which in turn, may result in the development of depressive symptoms in men but not in women (Elovainio et al., 2009).
5.3. The role of depressive symptoms in disturbed glucose metabolism

In Study II, one of the objectives was to investigate the association in the direction from depressive symptoms to glucose levels in women and men, and mechanisms underlying this association. First, we prospectively examined whether depressive symptoms predict glucose levels and whether there are sex differences in this association. Then, we tested whether the observed relationship is likely to be mediated by changes in BMI, hs-CRP, alcohol consumption, or tobacco or cigarette smoking. The results of the two multiple-group cross-lagged models showed that depressive symptoms in 2001 predicted glucose levels in 2007 and 2012 independently of baseline age and SES in women but not in men. Depressive symptoms in 2007, however, were not associated with glucose levels in 2012 in either sex. Therefore, women with depressive symptoms at the beginning of the fourth decade of life may especially be at risk for the future development of glucose abnormalities, including T2D. Moreover, the observed sex difference was statistically significant only in the model with an 11-year time lag, suggesting that the development or emergence of the difference between women and men in the association of interest is likely to occur over a longer period of time. Further, the effect of depressive symptoms in 2001 on glucose levels in 2012 in women was not mediated by BMI, hs-CRP, alcohol consumption, or tobacco or cigarette smoking measured in 2007 after the adjustment for baseline age and SES, and baseline levels of the studied mediators and the outcome.

Unlike the conclusions of a recent literature review (Tabak et al., 2014), our results demonstrating a positive association between depressive symptoms and glucose concentrations supported the notion that depressive symptoms can directly increase the risk of T2D. This direct effect seems not to be due to chronic inflammation, since we did not observe that changes in levels of hs-CRP mediated the association between depressive symptoms and glucose levels in women. However, depression-related biological alterations in the HPA and the SNS, which could not have been taken into account in our study, might be a mechanism underlying this association.
Furthermore, we found that the association going from depressive symptoms to glucose concentrations was not mediated by changes in BMI, alcohol consumption, or tobacco or cigarette smoking. This is not in agreement with the results of a U.S. study (Chiu, Wray, Beverly, & Dominic, 2010), in which the mediating role of changes in BMI and smoking in the relationship between depressive symptoms and glycemia was observed. This study, however, did not control for baseline levels of glucose and was performed in a clinical sample of people with the diagnosis of T2D; therefore it could not have determined the full causal pathway from depressive symptoms to glucose concentrations. Given this, the contribution of our study to the current evidence base is significant.

Moreover, our results showed that the association between depressive symptoms and glucose levels was present in women but not in men. This is in line with the findings of a cross-sectional study (Adriaanse et al., 2008) indicating an increased risk of prediabetes and T2D (both defined with fasting glucose or 2-hour post-load) in women but not in men with depressive symptoms. Contrary to our results, longitudinal evidence from a Swedish population-based study (Eriksson et al., 2008) showed that psychological distress (depressive symptoms, apathy, fatigue, insomnia, and anxiety) increases the risk of prediabetes and T2D (both indicated by 2-hour post-load glucose) in men but not in women (except for an increased risk of prediabetes in the middle index group of distress). The use of an instrument including only five items (suggesting its low reliability) to measure stress in the Swedish study could possibly contribute to this discrepancy.

The presence of the association between depressive symptoms and glucose levels in women but not in men could be explained by sex differences in coping with stress/depressive symptoms. Specifically, men tend to engage in exercise and instrumental activities in response to depressive symptoms (Piccinelli & Wilkinson, 2000), while women are less physically active and more likely to ruminate about a problem (Piccinelli & Wilkinson, 2000; Tamres, Janicki, & Helgeson, 2002). The latter strategy of the female coping repertoire has been found to be involved in the etiology and
maintenance of depression and depressive symptoms (Nolen-Hoeksema, 2000). Furthermore, distress has been associated with unhealthy food consumption (i.e., less frequent consumption of fruits and vegetables, and higher consumption of carbohydrate dense foods, such as sweets, cookies, snacks, and fast food) in women but not in men (Mikolajczyk, El Ansari, & Maxwell, 2009). Low levels of physical activity and unhealthy dietary patterns could, in turn, lead to the development of T2D (Alhazmi et al., 2014; Jeon et al., 2007). Thus, depressive symptoms may result in an increased diabetes risk in women but not in men.

5.4. The role of increased glucose in the development of depressive symptoms

Another objective of Study II was to examine the association in the direction from glucose levels to depressive symptoms. Specifically, we prospectively examined whether glucose levels predict depressive symptoms and whether women and men differ in this association. In Study III, we implemented instrumental-variable regression with a genetic risk score for fasting glucose used as an instrument for fasting glucose to examine whether elevated glucose levels may be a causal risk factor for depressive symptoms (in women and men combined and then, additionally, separately for both sexes).

Study II found that glucose levels in 2001 did not predict depressive symptoms in 2007 and 2012, and that glucose levels in 2007 did not predict depressive symptoms in 2012 after the adjustment for baseline age and SES in either women or men. The results of the standard linear regression in Study III showed that glucose levels were not associated with depressive symptoms when controlling for sex, age, BMI, and physical activity. The instrumental-variable regression showed an inverse association between glucose levels and depressive symptoms in the fully adjusted model. The difference between the estimates derived from the two regression models was statistically significant. In overall, these findings suggest that increased glucose levels are unlikely to be a causal risk factor for depressive symptoms in people with T2D. The association between
T2D and depressive symptoms might be due to low glucose levels. Alternatively, the protective effect of increased glucose levels against depressive symptoms in people with T2D might also be possible.

The above results of Study III were replicated only for women in the additional, sex-specific analysis. In men, the association between glucose and depressive symptoms was non-significant in either the standard linear regression or the instrumental-variable regression. The lack of the association between glucose and depressive symptoms in the instrumental-variable regression in men was likely to be due to underpowered tests resulting from an insufficient number of participants. Therefore, drawing clear and robust conclusions about sex differences in the association of interest based on these results is not possible.

Our finding that elevated glucose may not to be causally linked to higher depressive symptoms is consistent with the results of previous cross-sectional studies (i.e., a meta-analysis and a single study; Mezuk et al., 2013; Nouwen et al., 2011) and the conclusion of a recent systematic literature review (Tabak et al., 2014), which suggested that elevated glucose concentrations may not cause depressive symptoms but that depressive symptoms in individuals with T2D may be attributable to factors related to disease management. In line with the present investigation, a prospective, cohort study (Akbaraly et al., 2013) reported no association between fasting glucose levels and depressive symptoms in either women or men. However, the English Longitudinal Study of Aging (Hamer et al., 2011) found that increased glucose levels (treated as a continuous variable and measured with HbA1C) are a risk factor for depressive symptoms, especially in men. This inconsistency could result from different measures of blood glucose as the English study also showed that T2D, when defined with both HbA1C and fasting glucose, and prediabetes, when defined with HbA1C but not fasting glucose, increase the risk of depressive symptoms. Similarly, one cross-sectional study (Holt et al., 2009) documented a positive relationship of depressive symptoms with glucose levels defined
by 2-hour post-load glucose in both women and men without previously diagnosed diabetes; this association was not observed in either sex when fasting glucose was used as a measure of glycemia.

Surprisingly, we found a negative association between glucose levels and depressive symptoms. To our knowledge, there have only been two studies (Golden et al., 2008; Icks et al., 2008), which suggested that increased glucose levels may protect against depressive symptoms, although individuals with diagnosed or treated T2D can be at higher risk of developing depressive states. The first study (Icks et al., 2008), based on cross-sectional data, showed that the prevalence of depressive symptoms in women with previously diagnosed T2D (assessed by self-report: physician’s diagnosis or the use of medications for T2D) and with undiagnosed T2D (defined using fasting glucose) was similar to those without T2D. In men, the prevalence of depressive symptoms in those with diagnosed T2D did not differ from those without T2D. However, depressive symptoms in men with undiagnosed T2D were less frequent compared with those without T2D. The second study (Golden et al., 2008), with a longitudinal design and the diabetes status based on fasting glucose or receiving treatment, found that treated T2D is positively associated with depressive symptoms, whereas untreated T2D and prediabetes (defined by fasting glucose) are inversely associated with depressive symptoms (people with normal fasting glucose as a reference group).

The protective effect of elevated glucose levels against depressive symptoms was not supported by cross-sectional research of the British Whitehall II study (Kivimaki et al., 2009), which found an increased risk of depressive symptoms in individuals with very high and very low blood glucose (measured with fasting glucose, 2-hour post-load glucose, and HbA1C). Thus, it is possible that depressive symptoms in people with T2D could result from low levels of glucose. There is some evidence that hypoglycemia (i.e., concentrations of glucose in the blood below the normoglycemic range), reported by 23% of individuals with T2D (Green, Fox, & Grandy, 2012), is associated with the risk of depressive symptoms in this group of patients (Green et al., 2012; Kikuchi et al., 2015).
Nevertheless, further studies are needed to determine whether increased glucose levels can confer protection against depressive symptoms or whether low glucose levels can contribute to the development of depressive symptoms, and whether there are sex differences in these potential associations.

### 5.5. Methodological considerations and directions for future research

Our findings should be interpreted in light of methodological limitations. Study I was cross-sectional, thus the direction of the association between depressive symptoms and symptomatic LQTS cannot be inferred. Further, depressive symptoms were self-reported and depressive disorder was not based on a formal psychiatric diagnosis. The use of a self-report measure for depressive symptoms could result in some reporting bias. Considering, however, that depressive symptoms were measured with a validated instrument, it is unlikely that they were considerably affected by reporting bias. Moreover, the self-reported cardiac events in LQTS mutation carriers may have included some that were not the disease-specific ventricular arrhythmias. Finally, relatives who did not carry a familial LQTS mutation (control group) may not have been validly comparable to the cases. This is due to the fact that they could worry about family members carrying a LQTS-linked mutation, feel stressed about caregiving duties, or experience “survivor’s guilt”, that is, feel guilty towards affected relatives for not having the familial LQTS mutation.

The above limitations of Study I revealed the need for longitudinal studies in order to establish the direction of the association between depressive symptoms and symptomatic LQTS. Moreover, we suggest that future research could focus on identifying mechanisms underlying this relationship. Studies including a psychiatric diagnosis of depressive disorder and a control group of heathy people randomly derived from population-based samples could also be of value. Further, we recommend to examine whether depressive symptoms are related to higher severity of cardiac events in carriers of a LQTS-causing mutation.
The limitations of Studies II and III need also to be acknowledged. First, depressive symptoms were measured using a self-report instrument. Thus, it is possible that some reporting bias could arise. Second, the studies did not include clinically diagnosed depression but depressive symptoms in the general population. Therefore, the association between glucose levels and clinical depression requires future investigations. Third, our measurement of glucose concentrations was based on a single test of fasting serum glucose. Due to the fact that the use of fasting glucose might be a less robust and reliable method to diagnose T2D than 2-hour post-load glucose (Pomerleau, McKeigue, & Chaturvedi, 1999) or HbA1C (Bonora & Tuomilehto, 2011), further research could include these two measures of blood sugar, together with fasting glucose, in order to verify our results. Last, Studies II and III were based on a relatively young population (age range of 35 to 50 years in the latest follow-up, M = 42.73). Considering that the number of cases of T2D begins to increase rapidly in midlife (Wild et al., 2004), our results might have underestimated the strength of the association between glucose levels and depressive symptoms in older people, and thus, they need to be replicated in future studies conducted on older populations than ours.

In addition to these limitations, Study II used BMI which might not have accurately captured adiposity change in our participants. We suggest that further research could include more direct measures of body fat in order to confirm our finding that the association going from depressive symptoms to glucose levels is unlikely to be mediated by changes in adiposity. Moreover, in Study II, cumulative exposure (i.e., the effect of exposure intensity and duration) to elevated body fat, inflammation, or health-risk behaviors was not taken into account when examining whether these factors can mediate the association between depressive symptoms and glucose concentrations. As a result, their mediating role might have been underestimated. Therefore, cumulative exposure should be considered when replicating our findings in future studies. We were also not able to investigate whether physical inactivity or unhealthy dietary patterns can be mechanisms underlying the effect...
of depressive symptoms on glycemia. Thus, more research is needed to determine their role in the association of interest.

In Study III, we implemented instrumental-variable regression, whose key assumption is that the only mechanism by which the instrumental variable can affect the outcome is through its effect on the risk factor of interest (Lawlor et al., 2008). In other words, the instrument cannot influence the outcome directly or indirectly through other factors besides the risk factor of interest. This main assumption is empirically unverifiable (Morgan & Winship, 2007). Potential factors that could violate it include, among others, population stratification and pleiotropy.

Population stratification (i.e., population heterogeneity) was unlikely to bias the results of Study III as the study sample comprised only native Finns. However, there is a possibility that the association between the genetic risk score used in this investigation and fasting glucose differs between different ethnicities. Therefore, the results of Study III might not be applicable to other ethnic groups.

Moreover, the association between fasting glucose and depressive symptoms observed in Study III could result from genetic pleiotropic effects, that is, from the fact that the genetic instrument for fasting glucose could influence depressive symptoms directly or indirectly through other factors than fasting glucose. If that was the case, this study would overestimate the causal relationship between glucose levels and depressive symptoms. Thus, the shared genetic origins of glucose and depressive symptoms require a more thorough examination. Future instrumental-variable regression studies need to also give closer attention to identifying other factors than fasting glucose that may mediate the association between the genetic risk score for fasting glucose and depressive symptoms in order to control for them in their analyses.

The present study has a number of strengths. Study I included a large cohort of molecularly genotyped LQTS mutation carriers. Further, it took into account three dimensions of depressive
symptoms and potential confounding factors, such as β-blocker and antidepressant use, social support, and education. Study I also considered sex-specific results regarding the association between depressive symptoms and the risk of arrhythmic events. Moreover, it used a validated tool to measure depressive symptoms and to screen for depressive disorder.

With regard to the strengths of Study II, the inclusion of three repeated measurements of depressive symptoms and fasting glucose collected over a span of 11 years allowed to investigate the long-term association between depressive symptoms and glucose concentrations simultaneously in both directions. Moreover, Study II enabled to examine the mediating effect of body fat, inflammation, tobacco or cigarette smoking, and alcohol consumption on the relationship in the direction from depressive symptoms to glucose levels in women, which had not been tested in previous population-based studies.

The major strength of Study III laid within its statistical method (i.e., instrumental-variable regression with a genetic instrument), in which genetic information was used in order to reduce bias resulting from residual and unobserved confounding, and reverse causality. This, in turn, helped to strengthen causal inference concerning the role of elevated glucose in the development of depressive symptoms.

Besides those strengths of Studies II and III, the use of a large population-based sample and continuous measures of fasting glucose and depressive symptoms gave more statistical power to our tests. Furthermore, we included a relatively young population, which can be perceived not only as a limitation but also as a strength. The earlier the risk for the development of depressive symptoms or T2D is identified, the less aggressive and more cost-efficient preventive interventions can be. Given that the majority of previous investigations examining the association between depressive symptoms and blood glucose were based on older populations, Studies II and III constitute a contribution to this area of research. In addition, both studies considered sex-specific differences in
the association of interest and used methods helping to deal with missing values (FIML and multiple imputation), and thus, to minimize the possibility of attrition bias.

5.6. Conclusions and practical implications

The present study found that being a carrier of a LQTS-linked mutation is not associated with the risk of depressive symptoms. In LQTS mutation carrier men, depressive symptoms and their three dimensions (i.e., affective, cognitive, and somatic) may increase the risk of arrhythmic events independently of age, the use of β-blockers and antidepressants, social support, and education level. These increased risks appear not to exist in women, although arrhythmic events can be more common in women with LQTS than men. Moreover, women in overall were shown to experience higher levels of depressive symptoms and more frequently than men screen positive for depressive disorder. This female preponderance could result from the fact that women may simply be more willing than men to reveal distress and health problems (Barsky, Peekna, & Borus, 2001).

These findings can be especially beneficial to the Finnish health care system, given that the prevalence of LQTS in Finland has been reported to be the highest in the world (Marjamaa et al., 2009; Schwartz et al., 2009). The results suggest that prevention and treatment of depressive symptoms might be an important component of the health care of men with a LQTS-causing mutation. If depressive symptoms are proven to trigger arrhythmias in men with LQTS, future studies, in particular clinical trials, will need to examine whether routine screening for depressive symptoms in LQTS mutation carriers and the management of those patients who exhibit depressive symptoms would be safe and efficient in preventing cardiac events. Considering benefits of genetic counseling for coping with distress and depressive symptoms in individuals with hypertrophic cardiomyopathy (i.e., a genetic disease predisposing to sudden cardiac death; Ingles, Lind, Phongsavan, & Semsarian, 2008), this form of psychotherapy (Austin, Semaka, & Hadjipavlou, 2014) could be of value in LQTS mutation carriers and their family members. This, however, needs to be first verified in clinical trials. Moreover, as women in our sample scored higher on depressive
symptoms compared with men, further research is required to investigate whether LQTS mutation
carrier women and female relatives without a familial LQTS mutation are more depressed than
women in the general population.

The results of the present study also suggest that elevated glucose levels are unlikely to be a
mechanism underlying the association in the direction of T2D leading to depressive symptoms. It
seems possible, however, that this association might be due to low concentrations of glucose or that
increased glucose levels might protect against depressive symptoms. These conclusions, however,
need to be treated cautiously, considering the methodological limitations of the Mendelian
randomization approach, and replicated in future studies. Furthermore, our findings provide
evidence that depressive symptoms can be a risk factor for elevated glucose levels, and thus, for the
development of T2D in women but not in men, and that this association may not be mediated by
changes in body fat, inflammation, alcohol consumption, or tobacco or cigarette smoking.

The above findings are relevant to current public health concerns given the steadily increasing
rates of T2D worldwide. Health care providers should be aware that women with depressive
symptoms may be at risk of increased glucose concentrations, and thus may have an increased risk
for T2D development. We recommend that future research, especially clinical trials, should
examine whether the initiation of routine screening for depressive symptoms in women at the
beginning of the fourth decade of life could be beneficial for prevention of abnormal blood glucose.
Studies that examine the effects of screening for glucose abnormalities in women already at the end
of the fourth decade of life could also be of value.

Our results do not preclude the possibility that the relationship going from T2D to depressive
symptoms can result from distress associated with the diagnosis of T2D, management of this
disease, and its complications (Tabak et al., 2014). Given this, if following the recommendation of
the American Association of Clinical Endocrinologists (Handelsman et al., 2015) and the Canadian
Diabetes Association (Robinson, Luthra, & Vallis, 2013), all individuals diagnosed with T2D should continue to be screened for depressive symptoms.
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