

From the DEPARTMENT OF PUBLIC HEALTH SCIENCES,
SECTION OF EPIDEMIOLOGY AND PUBLIC HEALTH
INTERVENTION RESEARCH
Karolinska Institutet, Stockholm, Sweden

**SOCIAL ENVIRONMENT AND
GENETICS AS
DETERMINANTS OF
DEPRESSION
OCCURRENCE AND ITS
CHRONICITY – A
LONGITUDINAL SURVEY**

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**Karolinska
Institutet**

Stockholm 2013

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ISBN 978-91-7549-072-4

*“Era un fantasma en una casa ajena
que de un día para otro se había vuelto
inmensa y solitaria, y en la cual vagaba
a la deriva, preguntándose angustiada
quién estaba más muerto: el que había
muerto o la que se había quedado.”*

El Amor en los Tiempos del Cólera.

© Gabriel García Márquez, 1985.

ABSTRACT

Depressive disorders are a set of heterogeneous disorders whose common characteristics are sadness and lack of interest, but varying regarding other symptoms, response to treatment and probability of recurrence and chronicity. They are a serious public health problem due to high prevalence and disability burden. Depression has a multifactorial causality with several genetic, behavioral and environmental factors playing a putative causal role. Thus, the aim of this thesis was to elucidate the interwoven effects of some environmental stressors, individual's characteristics and some genetic factors on the occurrence and the course of depressive disorders. The subjects were drawn from the PART study (In Swedish: Psykisk hälsa, Arbete och RelaTioner), a longitudinal study with three waves between 1998 and 2010, focused on mental health, work and relations among adult people residing in the Stockholm County, Sweden.

In Studies I and III, the relationship between polymorphisms in *COMT* and serotonin transporter genes and depressive disorders were explored using a case-control approach. Gene x environment interaction effects on depression risk were addressed focusing on *COMT* gene, childhood adversities and stressful life events in Study I; and focusing on serotonin transporter gene and objective life events (i.e. loss/separation) in Study III. Significant interactions were found between *COMT* and family problems during childhood and between serotonin transporter and partner's loss/separation.

In Study II, the association between the psychosocial work environment and depression was scrutinized in a follow-up design of people employed in the same job over three-years. The results showed a strong relationship between inadequate social climate and major depression among women three-years later, while there were no certain effects for the remaining exposure variables. Among men, the findings were controversial: high job demands and inadequate skill discretion appeared as protective factors against depression; thus, more studies using a similar approach are warranted.

In Study IV, the complex inter-relationships among personal characteristics and circumstances over different life periods, and their effects on the chronicity of depression, were explored in a follow-up study of depressed subjects over ten years. It was analyzed using structural equation modeling (SEM). The resulting model revealed two main mechanisms anchored on personality traits: an internalizing pathway and an externalized/adversity pathway; which are in line with studies about the onset of depression.

The effort in this doctoral thesis consisted in putting together some pieces of a big puzzle. It is necessary to develop integrative models from different disciplines (e.g. genetics, neurosciences and epidemiology) in order to elucidate the complex mechanisms behind the depressive disorders.

Keywords: Depressive disorders, *COMT* gene, Serotonin Transporter, Psychosocial Work Environment, Stressful Life Events, Recurrence, Chronicity

SAMMANFATTNING

Depression är inte en sjukdom utan en grupp av sjukdomar som har gemensamma symptom såsom nedstämdhet och minskat intresse men de varierar med avseende på andra symptom, hur de svarar på behandling och förlopp. Den höga förekomsten och den funktionsnedsättning som ofta ingår gör att de är ett folkhälsoproblem. Orsaken till depression är mångfacetterad och genetiska faktorer och miljöfaktorer samverkar.

Syftet med denna avhandling var att undersöka några av de genetiska, personlighets- och miljömässiga faktorer som kan tänkas påverka insjuknande i, och förlopp av, depression. De personer som ingår i studien var deltagare i PART-studien (Psykisk hälsa, Arbete och Relationer) som är en studie som pågått under åren 1998-2010 med tre undersökningstillfällen. Deltagarna var alla mantalsskrivna i Stockholms län och i åldern 20-64 år.

I studie I och III undersöktes relationen mellan funktionella polymorfier i generna som kodar för serotonin-transportören (5-HTT) samt enzymet COMT, miljöfaktorer och depressionssjukdomar med en fall-kontroll design. Studier av interaktionen mellan gen och miljöfaktorer visade att det fanns en signifikant interaktion mellan *COMT* och problem i familjen under barndomen och mellan *5-HTT* och separation från partner i vuxenlivet.

I studie II studerades betydelsen av krav-kontroll-socialt klimat inom yrkeslivet för förekomst av depression 3 år senare. Personer som hade samma arbete vid det första och andra undersökningstillfället (3 års tid) ingick i studien. Hos kvinnor fanns ett starkt samband mellan sämre socialt klimat på arbetet och insjuknande i depression tre år senare; detta sågs ej hos män.

I studie IV studerades personlighets- och miljömässiga faktorer för förloppet av depression över 10 år. Data från alla tre undersökningstillfällena användes och ordnades i olika tidsperioder under livet. Analysen visade att personlighetskaraktistika påverkade uppsättningen av riskfaktorer för att ha depression 10 år senare; för viss personlighet innebar internaliserande faktorer risk för återkommande depression, för annan personlighet var riskfaktorerna externaliserande. Liknande resultat har tidigare visats för insjuknande i depression.

Sammantaget visar studierna att för att undersöka varför man kan drabbas av depression måste man ta hänsyn både biologiska och miljöfaktorer.

Nyckelord: Depression, COMT, Serotonintransportören (5-HTT), Psykosocial arbetsmiljö, Stressande livshändelser, Förlopp.

RESUMEN

Los trastornos depresivos son un conjunto de trastornos heterogéneos, cuyas características comunes son la tristeza y la falta de interés, pero que varían con respecto a la presencia de otros síntomas, la respuesta al tratamiento y la probabilidad de recurrencia y cronicidad. Éstos son un grave problema de salud pública debido a su alta prevalencia y a la carga generada por la discapacidad. La depresión tiene una causalidad múltiple con diferentes factores genéticos, comportamentales y ambientales jugando un posible papel causal. Por lo tanto, el objetivo de esta tesis fue determinar los efectos interconectados de algunos estresores ambientales, de las características individuales y de algunos factores genéticos en la ocurrencia y evolución de los trastornos depresivos. Los sujetos de estudio provinieron del proyecto PART (en sueco: Psykisk Halsa, Arbete och Relationer), un estudio longitudinal con tres fases entre 1998 y 2010, que se centró en la salud mental, el trabajo y las relaciones entre personas adultas que residían en el condado de Estocolmo, Suecia.

En los Estudios I y III, las relaciones entre los polimorfismos en los genes *COMT* y transportador de la serotonina y los trastornos depresivos se analizaron utilizando un abordaje de casos y controles. Los efectos de las interacciones Gen x Medio Ambiente sobre el riesgo de depresión fueron abordados para el gen *COMT*, las adversidades en la niñez y los eventos vitales estresantes recientes en el Estudio I; y para el gen transportador de la serotonina y algunos eventos vitales objetivos (es decir, pérdidas y separaciones) en el Estudio III. Se encontraron interacciones significativas entre el gen *COMT* y los problemas familiares durante la infancia y entre el gen transportador de la serotonina y la pérdida o separación de la pareja.

En el estudio II, la asociación entre el entorno psicosocial del trabajo y la depresión fue analizada en un estudio de seguimiento de personas empleadas en el mismo trabajo a lo largo de tres años. Los resultados mostraron una fuerte relación entre un clima social inadecuado y la depresión mayor entre las mujeres, mientras que no se encontraron efectos significativos para las variables de exposición restantes. Entre los hombres, los resultados son controvertidos: las altas demandas laborales y una inadecuada discreción de las habilidades aparecieron como factores de protección contra la depresión, por lo tanto, se requieren estudios adicionales con un enfoque metodológico similar para comprobar estos resultados.

En el Estudio IV, las complejas interrelaciones entre las características personales y las circunstancias presentes en períodos diferentes de vida, y sus efectos sobre la cronicidad de la depresión, fueron exploradas en un estudio de seguimiento de sujetos deprimidos a lo largo de diez años. Estas relaciones se analizaron mediante modelos de ecuaciones estructurales (SEM). El modelo resultante reveló dos mecanismos principales anclados en los rasgos de personalidad: una vía de internalización y una vía externalizada / adversidad, que están en consonancia con los estudios acerca de la aparición de la depresión.

El esfuerzo en esta tesis consistió en poner algunas piezas de un gran rompecabezas juntas. Es necesario desarrollar modelos de integración de diferentes disciplinas (por

ejemplo, la genética, las neurociencias y la epidemiología) con el fin de dilucidar los complejos mecanismos detrás de los trastornos depresivos.

Palabras clave: trastornos depresivos, gen *COMT*, gen transportador de la serotonina, entorno psicosocial de trabajo, eventos estresantes de la vida, recurrencia, cronicidad.

LIST OF PUBLICATIONS/MANUSCRIPTS

- I. Åberg, E., **Fandiño-Losada, A.**, Sjöholm, L.K., Forsell, Y., Lavebratt, C., 2011. The functional Val¹⁵⁸Met polymorphism in catechol-O-methyltransferase (*COMT*) is associated with depression and motivation in men from a Swedish population-based study. *J Affect Disord* 129, 158-166.
- II. **Fandiño-Losada, A.**, Forsell, Y., Lundberg, I., 2012. Demands, skill discretion, decision authority and social climate at work as determinants of major depression in a 3-year follow-up study. *Int Arch Occup Environ Health*. 2012 Jul 4. [Epub ahead of print] doi: 10.1007/s00420-012-0791-3.
- III. **Fandiño-Losada, A.**, Wei, Y., Åberg, E., Sjöholm, L.K., Lavebratt, C., Forsell, Y., 2013. Influence of serotonin transporter promoter variation on the effects of separation from parent/partner on depression. *J Affect Disord* 144, 216-224.
- IV. **Fandiño-Losada, A.**, Bangdiwala, S.I., Lavebratt, C., Forsell, Y. A Path Analysis of the Chronicity of Depression using the Comprehensive Developmental Model Framework. [Manuscript Submitted].

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LIST OF ABBREVIATIONS

5-HT	Serotonin
5-HTT	Serotonin Transporter
5-HTTLPR	Serotonin Transporter Linked-Polymorphic Region
AP	Proportion Attributable to Interaction
APA	American Psychiatric Association
bp	base-pairs
BDNF	Brain-Derived Neurotrophic Factor
CDMF	Comprehensive Developmental Model Framework
CI	Confidence Interval
COMT	Catechol-O-methyltransferase
DSM	Diagnostic and Statistical Manual of Mental Disorders
GxE	Gene x Environment Interactions
GxGxE	Gene x Gene x Environment Interactions
GWAS	Genetic Wide-Association Studies
HWE	Hardy-Weinberg equilibrium
JDCSM	Job-Demands-Control-Support Model
MAOA	Monoamine oxidase A
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MDI	Major Depression Inventory
OR	Odds Ratio
RERI	Relative Excess Risk due to Interaction
S	Synergy Index
SEM	Structural Equation Modeling
SLE	Stressful Life Event
SNP	Single Nucleotide Polymorphism
SSP	Swedish universities Scales of Personality
SSP-D	Detachment
SSP-E	Embitterment
SSP-SS	Stress Susceptibility
SSP-STA	Somatic Trait Anxiety

1 INTRODUCTION

Depressive disorders are a set of heterogeneous disorders whose common characteristics are sadness and lack of interest, but varying regarding the age at onset, the nature of other concurrent symptoms, the severity and duration of symptoms, the response to treatment and the probability of recurrence and chronicity (Belmaker and Agam, 2008; Shyn and Hamilton, 2010). The prevalence of depressive disorders is high with an estimated lifetime prevalence of 14.1% (95% Confidence Interval [95%CI] = 10.2 to 18.7) and an estimated one year prevalence of 7.5% (95%CI = 5.7 to 9.7) (Waraich et al., 2004). Depressive disorders have such high prevalence because their relative early age at onset, ranging between the late 20s and the early 40s (Kessler et al., 2007; Kessler et al., 2005); and due to the chronic course of the disease. Two factors lead to a chronic course: First, only around 40% of patients with depressive disorders receive adequate treatment in developed countries settings (Forsell, 2004; Wang et al., 2005; WHO World Mental Health Survey Consortium, 2004), but this figure is even lower for developing countries (Wang et al., 2007). Second, up to half of depression patients under treatment fail to experience adequate recovery despite treatment switches (Rush et al., 2006).

Disability due to the symptoms was stated as one of the diagnostic criteria since the publication of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association. and American Psychiatric Association. Task Force on DSM-IV., 1994); and disability itself is a problem leading to a high social burden. Consequently, depressive disorders are a serious public health problem not only due to the high prevalence, but also due to the burden associated with their disability (McKnight and Kashdan, 2009). Thus, the Global Burden of Disease Project has estimated that the burden of unipolar depression was 65.5 million disability-adjusted life years (DALYs) lost worldwide during 2004. Moreover, unipolar depression will be the main cause of the burden of disease worldwide by the year 2030 (World Health Organization, 2008).

Depression has a multifactorial causality pathway with several genetic, behavioral and environmental factors playing a putative causal role (aan het Rot et al., 2009; Belmaker and Agam, 2008; Kupfer et al., 2012). Although the heritability of depression has been estimated to be between 37% and 43% (Shyn and Hamilton, 2010), the genetic mechanisms are complex (polygenic) and only a single gene is not involved in the disorder (Levinson, 2006), which is a common fact in psychiatric and neurological disorders (International Schizophrenia Consortium, 2009). On the contrary, the variance of depressed heritability explained by individual genes is low, e.g. the variance in the familial risk of depressive mood accounted for a functional polymorphism in the serotonin transporter (*5-HTT*) gene, one of the most studied genes in genetic psychiatry, is only 1.8% (Gunthert et al., 2007). Genetic factors are mediated by the expression of implicated genes through several neurobiological, neuroanatomical, neurophysiological and psycho-pathological mechanisms (aan het Rot et al., 2009; Blom et al., 2007; Lee et al., 2010), thus, it is difficult to point to a specific mechanism in genetic linkage or genetic association studies (Mill and Petronis, 2007). Furthermore, the depression syndromal criteria have changed over time and no biological marker exists (Lesch,

2004), and thus, there is a higher heterogeneity regarding the outcome in psychiatric genetic studies in comparison with somatic diseases, e.g. diabetes (Caspi et al., 2010), leading to misclassification of such outcomes and diminishing the power for detecting associations (Hernandez et al., 2006; Susser, 2006).

The environment is on the other side of the coin: the current literature is consistent regarding the paramount role of social environmental factors in the genesis of depressive disorders (Hammen, 2005). Among the social environment, current evidence highlights childhood adversity (Clark et al., 2010; Korkeila et al., 2010; McLaughlin et al., 2010; Wiersma et al., 2009), stressful life events and life difficulties (Kendler and Gardner, 2010; Kendler et al., 1999; Mitchell et al., 2003; Monroe et al., 2007), occupational conditions (Bonde, 2008; Netterstrom et al., 2008; Stansfeld and Candy, 2006), socio-economic status (Muntaner et al., 2004; Vanroelen et al., 2010) and social support (Leskela et al., 2004; Wade and Kendler, 2000a) as predictors of the onset and the course of depressive disorders.

Finally, neither the individual's genetic factors act in a vacuum nor do the environmental factors affect persons equally. Instead, the environment plays a pivotal role in the causality pathway of depression, but, it is moderated by the individual's genetic makeup (Caspi and Moffitt, 2006; Hernandez et al., 2006). This fact increases the complexity of the research on depressive disorders, because plausible *gene x environment interactions* (GxE) must be taken into account when doing research on depression (Caspi et al., 2010).

Thus, the overarching aim of this thesis is to contribute to elucidate the interwoven effects of some of the environmental stressors and genetic factors on the occurrence and course of depressive disorders.

2 BACKGROUND

2.1 DEFINITIONS OF DEPRESSIVE DISORDERS

In this thesis, the definitions of mental disorders from the *Diagnostic and Statistical Manual IV Edition Text Revision* (DSM-IV-TR, 2000) of the *American Psychiatric Association* (APA) were used (American Psychiatric Association, 2000).

2.1.1 Major Depressive Disorder

Major Depressive Disorder (MDD), or Major Depression, is a syndrome characterized by the occurrence of one or more episodes consisting of 1) low mood and/or 2) an inability to experience interest and pleasure in nearly all activities, both lasting two weeks or more. The episode (i.e. major depressive episode) must be accompanied by four or more of the following groups of symptoms during two or more weeks: 1) changes in appetite or weight; 2) changes in sleep; 3) changes in psychomotor activity; 4) decreased energy; 5) feelings of worthlessness or guilt; 6) difficulty thinking, concentrating, or making decisions; or 7) recurrent thoughts of death or suicidal ideation, plans, or attempts. Depressive episodes must be accompanied by clinically significant distress or impairment in social, occupational, or other important areas of functioning (American Psychiatric Association, 2000). Depression is regarded mostly as a mood disorder but is often accompanied by cognitive deficits that highly correlate to motivational symptoms (American Psychiatric Association, 2000).

2.1.2 Dysthymia

The DSM-IV-TR defines *Dysthymia* in this manner: “The essential feature of Dysthymic Disorder is a chronically depressed mood that occurs for most of the day more days than not for at least 2 years. ... During periods of depressed mood, at least two of the following additional symptoms are present: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulty making decisions, and feelings of hopelessness. ... During the 2-year period, any symptom-free intervals last no longer than 2 months. The diagnosis of Dysthymic Disorder can be made only if the initial 2-year period of dysthymic symptoms is free of Major Depressive Episodes” (American Psychiatric Association, 2000).

Thus Dysthymia and Major Depression are differentiated based on severity, chronicity, and persistence criteria. In Major Depression, the depressed mood must be present for most of the day, nearly every day, for a period of at least 2 weeks, whereas Dysthymia must be present for more days than not over a period of at least 2 years. Additionally, the diagnosis of "double depression" is done when a superimposed major depressive episode occurs after the initial 2 years of dysthymia (American Psychiatric Association, 2000).

2.1.3 Minor Depression

Minor Depressive Disorder is a proposed research category in the DSM-IV-TR, and is defined as "... one or more periods of depressive symptoms that are identical to *Major Depressive Episodes* [MDE] in duration [lasting two or more weeks], but which involve fewer symptoms and less impairment. An episode involves either a sad or "depressed" mood or loss of interest or pleasure in nearly all activities. In total, at least two but less than five additional symptoms must be present. ... During the episode, these symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. ... There has never been a Major Depressive, Manic, Mixed, or Hypomanic Episode, and criteria are not met for Dysthymic or Cyclothymic Disorder." (American Psychiatric Association, 2000).

2.1.4 Mixed Anxiety-Depressive Disorder

This diagnosis is one of the criteria sets proposed as a research diagnosis in the DSM-IV-TR. The *Mixed Anxiety-Depressive Disorder* consists on a persistent or recurrent dysphoric mood lasting at least one month, accompanied by at least four of the following additional symptoms: concentration or memory difficulties, sleep disturbance, fatigue or low energy, irritability, worry, being easily moved to tears, hyper-vigilance, anticipating the worst, hopelessness or pessimism about the future, and low self-esteem or feelings of worthlessness. The symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. For doing this diagnosis, current or past occurrence of major depressive disorder, dysthymic disorder, panic disorder, or generalized anxiety disorder must be ruled out. Also, the current occurrence of any other anxiety or mood disorder in partial remission must be ruled out; and the symptoms are due to the direct physiological effects of a substance or a general medical condition (American Psychiatric Association, 2000).

2.1.5 Taxonomic Developments

The innovation of the DSM-III was to classify and define mental disorders according to a set of phenomenological characteristics, with clear inclusion criteria and hierarchical exclusion rules in order to avoid overlap among diagnosis (Watson et al., 2008). This taxonomic effort continues with the DSM-IV, and currently with the publication of the DSM-V in May 2013; where the APA is proposing that "dimensional assessments" be added to diagnostic evaluations of mental disorders. These would permit clinicians to evaluate the severity of symptoms, as well as take into account "cross-cutting" symptoms. Additionally it will include considerations of how gender, race and ethnicity may affect the diagnosis of mental illness (<http://www.dsm5.org>).

2.2 OCCURRENCE AND COURSE OF DEPRESSION

2.2.1 Phases over the Course of Depression

The symptoms of people chronically afflicted by depression merely wax and wane. But, the study of chronic depression has been complicated by varying definitions in the literature (Mondimore et al., 2007). Thus, it is necessary to define and operationalize the changing periods over the course of illness (Frank et al., 1991; Monroe and Harkness, 2011). Such conceptual system is explained here:

- **Remission:** It is defined as an initial and relatively brief period of significant improvement of symptoms after the occurrence of a MDE. Sometimes, the virtual absence of depressive symptoms is achieved. Current recommendations are for three consecutive weeks of sustained improvement to initiate remission; if maintained for four months, remission becomes recovery. After remission, the subject could fall into relapse or could achieve recovery (Monroe and Harkness, 2011).
- **Recovery:** It is defined as a sufficient period of sustained remission. Current recommendations are for sustained improvement during four months of remission. Sub-syndromal symptoms not meeting the criteria for MDE are permitted. After recovery, the subject could fall into recurrence (Monroe and Harkness, 2011).
- **Relapse:** It is defined as a return to the index MDE following the onset of remission but before fulfilling the criteria for recovery. Current recommendations are a return of symptoms meeting criteria for MDE after three weeks of improvement but before completing four months of sustained improvement. After relapse, the subject could achieve remission again. Relapse differs from recurrence with respect to time since remission and assumed differences in underlying vulnerability (Monroe and Harkness, 2011).
- **Recurrence:** It is defined as the development of a completely new episode of MDE after completing remission and attaining recovery. Current recommendations are for a return to MDE status after four months of symptom improvement (i.e. full remission). Sub-syndromal symptoms not meeting criteria for MDE are permitted. After recurrence, the subject could achieve remission again. Any new occurrence of a MDE in the same individual is conceptualized as a *recurrence* as opposed to a new MDE or a different illness (Monroe and Harkness, 2011).

2.2.2 Research Definitions for Occurrence and Recurrence

The literature is consistent regarding the chronic and recurrent nature of depression (Monroe and Harkness, 2011) (Judd and Akiskal, 2000). 60% of people who suffer a first lifetime episode of MDD will develop a second, 70% of those with a second episode will suffer a third, and 90% of those with three or more episodes will experience further recurrences (American Psychiatric Association, 2000; Solomon et al., 2000). In the research arena, it has been confusion and imprecision about the terminology describing depression recurrence and other related concepts. Thus, Monroe and Harkness have made an effort on clarifying some research terms (Monroe and Harkness, 2011):

- **First Lifetime Episode of Depression (FLED):** It is the first MDE in the person's life. The first lifetime MDE may not be the only lifetime episode of MDE, as subsequent recurrences may occur.
- **Single Lifetime Episode of Depression (SLED):** It is the only MDE in the person's life. The only lifetime episode of MDE means that there is never a recurrence. Of course, it is also the subject's FLED.
- **Index Episode of Depression:** It is the current or the explored MDE. It is a generic term that brought the participant into the research protocol or it is the episode identified during the follow-up. The index episode could be a FLED, a SLED, a fourth life-time recurrence, etc.
- **Non-recurrence:** It is the status when after a person develops at least one MDE and recovers; this person never experiences another MDE over the life course. In this case, the last MDE could be the subject's SLED or another MDE (e.g. the third life-time MDE).

2.2.3 Chronicity

In this doctoral thesis, the *chronicity of depressive disorders* is defined as the presence of any or both forms of depression: 1) a *chronic persistent course* and 2) a *recurrent episodic course*. The former is defined as depressive symptomatology lasting two years or more, which is differentiated in the DSM-IV-TR as Dysthymia when the levels or symptoms are mild, and as Chronic Major Depression when symptomatology fulfills the criteria for major depressive episodes (Klein and Santiago, 2003). The chronicity of persistent forms of depression after 10 years has been estimated to be 26% (Klein et al., 2006).

The recurrent episodic course of depression consists of a sequence of repetitive major depressive episodes lasting less than two years fulfilling the criteria for recovery between the episodes (Brodaty et al., 2001; Judd et al., 1998; Monroe and Harkness, 2012). The individual's course after the first episode is not homogeneous; recurrence has been reported to range from 40% to 85% (Hughes and Cohen, 2009).

There is a gray zone between the chronic persistent and the recurrent episodic trajectories, when symptoms no longer meet full diagnostic criteria, neither for major depression nor for dysthymia, but residual symptoms persist (Mondimore et al., 2007). The DMS-IV-TR codes it as “incomplete inter-episode recovery”. Furthermore, another form of chronic depression has been described in the DMS-IV-TR research categories: the “depressive personality disorder” defined as a pervasive pattern of depressive cognitions and behaviors beginning in the early adulthood (American Psychiatric Association, 2000).

2.3 DETERMINANTS OF DEPRESSION

2.3.1 Social Environment and Environmental Stressors

Social environment comprises a part of the general environment into which the life of people happens. The general environment also includes physical aspects, such as the weather and the geography, which are not considered in this thesis. The social environment comprises several aspects of people’s social life, such as the family, the friendship and the job. The social environment interacts with individuals and groups through the environmental stressors (Berkman and Kawachi, 2000; Hammen, 2005). The main environmental stressors considered in this thesis are the following:

2.3.1.1 The Psychosocial Work Environment

Adult people, who are employed, spent between a third and a quarter of their time at work; thus the psychosocial work environment has been a life-sphere extensively scrutinized as a risk factor for the development of mental disorders (de Lange et al., 2003; Stansfeld and Candy, 2006) and specifically, for depressive disorders (Bonde, 2008; Netterstrom et al., 2008; Wieclaw et al., 2008).

There are different conceptual models for describing the work environment, but the *Job Demands-Control-Support Model* (JDSCM) has been the most influential since its appearance in the late 1970s. The JDSCM involves two logical and easily understandable dimensions: (*psychological*) *demands* and *control* (or decision latitude). Job demands refer to task requirements and work load. Job control refers to individuals’ ability to control his/her work activities. The job control dimension has two sub-components: i) *skill discretion* concerns requirements to use skills and learn new things at work; ii) *decision authority* refers to the freedom to decide what and how should be done at work. Furthermore, Karasek emphasized that both, demands and control, determine the psychological strain at work; and job strain was defined as the combination of high demands and low control (Karasek, 1979). A third dimension was later added to the model: the social support at work. It is defined as the support received from colleagues and supervisors at work, which hypothetically buffers the effect of job strain situations on health outcomes (Johnson and Hall, 1988; Johnson et al., 1989). Thus, the whole model is called the *Job-Demands-Control-Support Model* (JDSCM).

The literature shows inconsistent results for the longitudinal relationships between JDCSM variables and depressive disorders, but two recent meta-analyses and a systematic review (Bonde, 2008; Netterstrom et al., 2008; Stansfeld and Candy, 2006) showed coherent results on high job demands and low occupational social support as risk factors for subsequent major depressive disorders or mental illness occurrence. In contrast, these reviews showed contradictory results regarding job control, or its components, as risk or protective factors for major depression. But, the findings about major depression in these reviews were based on small number of papers for each JDCSM dimension (between two and five papers).

2.3.1.2 Stressful Life Events

Stressful life events (SLEs) are a well-recognized risk factor for the occurrence of depressive episodes (Hammen, 2005; Risch et al., 2009; Tennant, 2002). The risk of developing a new depressive episode increases with both greater severity and greater number of SLEs, with the risk being greatest shortly after the occurrence of the event and diminishing thereafter (Hammen, 2005; Kendler et al., 1998; Tennant, 2002). SLEs additionally predict recurrences of MDD; however, with repeated episodes less stress may be required to trigger a new depressive episode, i.e. a sensitization to stressor occurs over time (Hammen, 2005; Kendler et al., 2000; Monroe and Harkness, 2005).

A moderate degree of causality for dependent SLEs (i.e. those likely influenced by the individual's behavior) onto depression has been demonstrated, although a large proportion of observed associations are non-causal (Kendler and Gardner, 2010). Indeed, previous studies have shown that genetic factors may increase the risk for exposure to certain stressors; thus such genes could be the common cause of both depression and SLEs (Kendler et al., 1999; Tennant, 2002; Zannas et al., 2012).

2.3.1.3 Social Support

Social support in different life spheres is important for individual's well-being (Harris and Craig, 2006; Sinokki et al., 2009). There are bidirectional relationships between social support and depressive disorders, but also personality has been pointed as the common liability factor explaining observed associations between personal support and depression (Kendler, 1997; Kendler et al., 2005; Wade and Kendler, 2000b). Low social integration, inadequate social support, and negative social interactions have been associated with the chronic course of depression (Holzel et al., 2010). Moreover, inadequate social support and marital status, which are risk factors for the first onset of depression, were not related with recurrence (Hardeveld et al., 2010).

2.3.1.4 Childhood Adversities

Childhood adversities are defined as stressors or difficulties happening before the person were 18 years old; such as death of a parent, familial hassles, parents' divorce, economic difficulties or child maltreatment. Childhood adversities have been identified as robust and strong determinants of occurrence of depression during the adulthood

(Clark et al., 2010; Kendler et al., 2004; Korkeila et al., 2010; McLaughlin et al., 2010; Perepletchikova and Kaufman, 2010; Wiersma et al., 2009). Thus, childhood adversities influence the risk of adulthood psychopathology by means of three processes: i) a stress-sensitization (i.e. kindling) mechanism increasing the vulnerability to adulthood life events, probably via epigenetic changes (Canli and Lesch, 2007; Mill and Petronis, 2007); ii) a exposure-mediating mechanism increasing the risk of exposure to stressful life events during adulthood; and iii) a morbidity-mediating mechanism determining adolescent and young adulthood psychopathology (i.e. personal history of mental disease) (Clark et al., 2010; Korkeila et al., 2010; McLaughlin et al., 2010). Moreover, the life trajectories of young persons from divorced families were previously shown to contain more stressful paths and more distress (Aro, 1994).

2.3.2 Genetics

Meta-analysis of twin studies rendered a significant additive genetic effect for depression with heritability of 37% (Sullivan et al., 2000). Heritability studies based on twins, extended-pedigree and adoption provided evidence in line with a moderate and multigenic heritability of depressive disorders (Camp and Cannon-Albright, 2005; Levinson, 2006). The monoamine hypothesis of depression, formulated by Schildkraut and Kety in 1967 (Shyn and Hamilton, 2010), posits that there is a deficiency in the *serotonin* (or 5-hydroxytryptamine, 5-HT) or the norepinephrine (or noradrenaline) neurotransmitters in the brain (Belmaker and Agam, 2008). Additionally, the *dopamine* (DA) is the neurotransmitter involved in mesocortical and mesolimbic dopaminergic systems, which have been most implicated as playing a role in reward (Morilak and Frazer, 2004). In this manner, genetic association studies of depression have focused on such neurotransmitter systems, rendering significant associations with variants of genes exemplified by those encoding the serotonin transporter [SERT or 5-HTT], the serotonin 2A receptor [5HTR2A], the tryptophan hydroxylase 1 [TPH1] (which is involved in serotonin synthesis), the catechol-O-methyltransferase [COMT] and the monoamine oxidase A [MAOA] (which are involved in dopamine catabolism), and the tyrosine hydroxylase [TH] (the limiting enzyme of dopamine synthesis) (Cusin et al., 2002; Levinson, 2006).

But also, variants of other genes, acting through other biological mechanisms, have been associated with depression: among others, the glucocorticoid receptor gene [*NR3C1*], the gene for glycogen synthase kinase-3 β , glutamatergic genes [e.g. *GRM3*, *GRIK4*], the brain-derived neurotrophic factor gene [*BDNF*], *FKBP5* (a regulator of cortisol binding to the glucocorticoid receptor) and *TREK1* (a potassium channel) (Kupfer et al., 2012).

In this thesis, we studied known functional variants in the genes encoding the catechol-O-methyltransferase (COMT) and the serotonin transporter (5-HTT) and explored their main (i.e. independent) and moderating effects on the occurrence of depression.

2.3.2.1 *COMT Gene*

The catechol-O-methyltransferase (COMT) is an enzyme which inactivates the catecholamines epinephrine, norepinephrine and dopamine. Dopamine (DA) plays a central role in the reward mesocortical-mesolimbic brain system. Rewards are stimuli that “elicit and reinforce approach behavior, inducing subjective feelings of pleasure and positive emotional states” (Morilak and Frazer, 2004). The reward mesolimbic brain system comprises the nucleus accumbens, the ventral striatum, the hippocampus and the amygdala and interconnects with the orbito-frontal and the medial prefrontal cortices, orbitofrontal cortex and prefrontal cortex (PFC), which get ascending dopamine projections from the ventral tegmental area (Schultz, 2007; Volkow et al., 2004). When dopamine is released into synaptic clefts in these areas, is removed by dopamine transporters (DAT) or catabolized by MAOA or COMT. DAT is active in the striatum but is less common in the prefrontal cortex, where MAOA and COMT are of more significance (Tunbridge et al., 2006).

The *COMT* gene contains the functional polymorphism Val¹⁵⁸Met, which is encoded by a G→A single nucleotide polymorphism (SNP) (rs4680); that is, the SNP results in a valine (val) to methionine (met) amino acid substitution. The Met-158 allele produces a heat-labile enzyme that is associated with a three- to four-fold reduction in degradation of dopamine in the synapse compared to the Val-158 allele (Lotta et al., 1995).

Research findings about the association between *COMT* Val¹⁵⁸Met and depressive disorders have not been consistent. Some studies reported that Met allele carriers had higher depression vulnerability (Mandelli et al., 2007; Ohara et al., 1998), others indicated that Val/Val genotype was associated with depression (Massat et al., 2005); and finally others reported non-significant results (Baekken et al., 2008; Cusin et al., 2002; Serretti et al., 2006; Wray et al., 2008).

2.3.2.2 *Serotonin Transporter Gene*

The serotonin (or 5-hydroxytryptamine, 5-HT) is a neurotransmitter involved in several behavioral and physiological processes, from food intake and reproductive activity to cognition and emotion. Serotonin modulates the medial prefrontal limbic network, which includes amygdala, anterior cingulate cortex and medial prefrontal cortex (Kupfer et al., 2012). A key regulatory protein in the 5-HT system is the serotonin transporter (5-HTT or SERT) which reuptakes the serotonin released into the synaptic cleft. The 5-HTT is encoded by a single gene located in the chromosome 17q: the serotonin transporter gene solute carrier family 6-member 4 or *SLC6A4* (Canli and Lesch, 2007; Hu et al., 2007). The *SLC6A4* transcriptional activity is controlled by a tandem repeated sequence located upstream (i.e. 5') of the gene, known as the 5-HTT-gene-linked polymorphic region (5-HTTLPR). This region consists of varying numbers of copies of a 20 to 23 base-pair (bp) imperfect repeat sequence, which generates several polymorphisms (Hu et al., 2006), but the most frequent is a 44 base-pair insertion/deletion polymorphism which generates two alleles: the *short* (“S”, 14 repeats) and the *long* (“L”, 16 repeats). The short-form allele reduces the transcriptional rate of the *SLC6A4*, thus S/S homozygous cells have lower 5-HTT activity than the L/L homozygous cells. Additionally, S/L heterozygous cells have an intermediate 5-HTT

activity compared with the homozygous genotypes (Greenberg et al., 2000; Lesch et al., 1996; Little et al., 1998).

The short-5-*HTTLPR* allele has been associated with the occurrence of depressive disorders, but such effect is weak (Clarke et al., 2010). Thus, the research interest has not been on the main effect of the gene, but it has been on the moderating effect of exposures to adversities (see 2.3.3 below).

Increasing the complexity of the 5-*HTT* genetics, an A→G single nucleotide polymorphism (SNP), rs25531, was identified in the *SLC6A4* promoter (Hu et al., 2006) located 18 bp 5' of the 5-*HTTLPR* insertion/deletion variation (Perroud et al., 2010). The G allele induces an AP2 transcription factor binding site and reduces the transcriptional activity of the long-5-*HTTLPR* allele to an activity similar to the short-5-*HTTLPR* allele (Hu et al., 2006; Kraft et al., 2005). Thus, the 5-*HTTLPR*/rs25531 mini-haplotype implies the functional division of individuals into three expression types: high expression type (diplotypes L_A/L_A), intermediate expression type (diplotypes L_A/L_G, S_A/L_A) and low expression type (diplotypes S_A/S_A, L_G/S_A, L_G/L_G and S_G/S_A). The S_G diplotype is very rare in Caucasians (Wendland et al., 2006).

2.3.3 Gene x Environment Interactions

Most depressive episodes are preceded by stressful life events, but only one in five persons become depressed after a severe environmental stressor (Conway et al., 2010). Thus, there are differences in the sensitivity to environmental stressors among individuals (Boyce and Ellis, 2005). The *diathesis-stress model* posits there are risk factors inherent to individuals (i.e. diathesis) which makes them more vulnerable to develop depressive responses to the environment (i.e. stress) (Monroe and Simons, 1991). It has been argued that such diathesis is explained by several personality (temperament) and genetic mechanisms (Belsky and Pluess, 2009). The latter has been operationalized as *Gene x Environment interactions* (GxE) (Hernandez et al., 2006; Kraft et al., 2007; Susser, 2006), and they have been initially demonstrated in the seminal paper of Caspi and colleagues which indicated that the 5-*HTTLPR* moderates the effects of childhood maltreatment and adulthood stressful life events on depression risk in young adults (Caspi et al., 2003). After, this pioneering article, several studies have been done with inconsistent findings, i.e. successful replications, partial-replications and non-replications (Clarke et al., 2010; Uher and McGuffin, 2008, 2010). Furthermore, two meta-analyses showed inconclusive results (Munafo et al., 2009; Risch et al., 2009); but a third one rendered strong evidence that 5-*HTTLPR* moderates the relationship between environmental stressors and depressive disorders (Karg et al., 2011).

2.3.4 Personality

The personality traits are related with depressive disorders in different degrees of certainty (Klein et al., 2011). In their seminal paper, Clark, Watson, and Mineka (Clark et al., 1994) have first described the association between depressive symptoms and high levels of *Neuroticism*, as well as low levels of *Extraversion*, in young subjects. Recent

meta-analyses confirmed a strong relationship of major depression with high Neuroticism and low *Conscientiousness*, reported only a modest and inconsistent relationship with low Extraversion, and no significant associations with *Agreeableness* and *Openness* to experience (Klein et al., 2011; Kotov et al., 2010). Moreover, these associations are independent of subject's age (Weber et al., 2012).

Although the relationship between the serotonin transporter gene polymorphism and neuroticism measures was initially reported two decades ago (Lesch et al., 1996); current meta-analytic studies indicated that the claimed effects of individual genes on personality, if they exist, are very small (Munafò and Flint, 2011).

2.3.5 Mental Health Comorbidity

It is infrequent that mental disorders occur alone (Cerdeira et al., 2008; Krueger and Markon, 2006). The chronic course of depression is consistently predicted by comorbidities with anxiety disorders, personality disorders and substance abuse (Fergusson et al., 2009; Fichter et al., 2010; Gaynes et al., 1999; Holzel et al., 2010; Kessler, 1999; Kessler et al., 2008; Rhebergen et al., 2011). Also, the co-occurrence of other mental health disorders is associated with higher levels of functional disability among subjects suffering depression (Ormel et al., 2004; Rhebergen et al., 2010).

2.3.6 Depression Characteristics

Taking into account the number and characteristics of depressive episodes over course of the illness, it has been argued that past depression is the best predictor of future depression (Judd et al., 1998; Judd et al., 2000; Kendler et al., 2001; Rudolph et al., 2009). The number of previous episodes and subclinical residual symptoms after recovery from the last depressive episode are consistent determinants of the onset of future episodes; while the evidence regarding the role of age at index episode, severity and duration of previous episodes, age at onset of depression, family history of depression and disability after episodes were inconclusive (Hardeveld et al., 2010). But, the number of previous depressive episodes is not consistently associated with a chronic course of the illness (Holzel et al., 2010).

3 OVERARCHING AIM

The overarching aim of this thesis is to elucidate the interwoven effects of some environmental stressors, individual's characteristics and genetic factors on the occurrence and the course of depressive disorders.

3.1 RESEARCH QUESTIONS

In order to point to the main aim of this doctoral thesis, three specific research questions were addressed by the thesis constituent studies:

1. Are the relationships between polymorphisms in *COMT* and *5-HTT* genes and depressive disorders explained by main effects, gene x environment interactions or both? (*COMT* gene in Study I and *5-HTT* gene in Study III).
2. What is the contributing role of specific dimensions of the Job-Demands-Control-Support Model on the occurrence of major depression over time? (Study II).
3. Is the course of depressive disorders determined by characteristics intrinsic to the disorder (e.g. severity, duration, etc.); or individual's characteristic (i.e. familial antecedents, personal background and personality) and the psychosocial environment could also explain depression course? (Study IV).

Each study corresponds with a published or submitted paper (see individual papers in the appendices).

4 MATERIALS AND METHODS

4.1 FRAMEWORK OF THE THESIS: THE PART STUDY

In this thesis, the subjects and the individual constituent studies (papers) derived from a population based study: *PART* (In Swedish: Psykisk hälsa, Arbete och RelaTioner), a longitudinal study of mental health, work and relations among adult people living in the Stockholm County, Sweden (Hällström et al., 2003). The PART was a panel study with three phases: wave 1 (W1) at 1998-2000, wave 2 (W2) at 2001-2003 and wave 3 (W3) at 2010. At each wave, subjects who agreed on participate, answered a self-responed questionnaire sent by mail (4.1.4 below). The ethical committee at the Karolinska Institutet, Stockholm, approved the study and informed consents were obtained from all participants. Only 11% of the PART individuals had a non-Swedish origin, and among them, the majority had a Nordic origin (Hällström et al., 2003). Figure 1 depicts a scheme of the PART study.

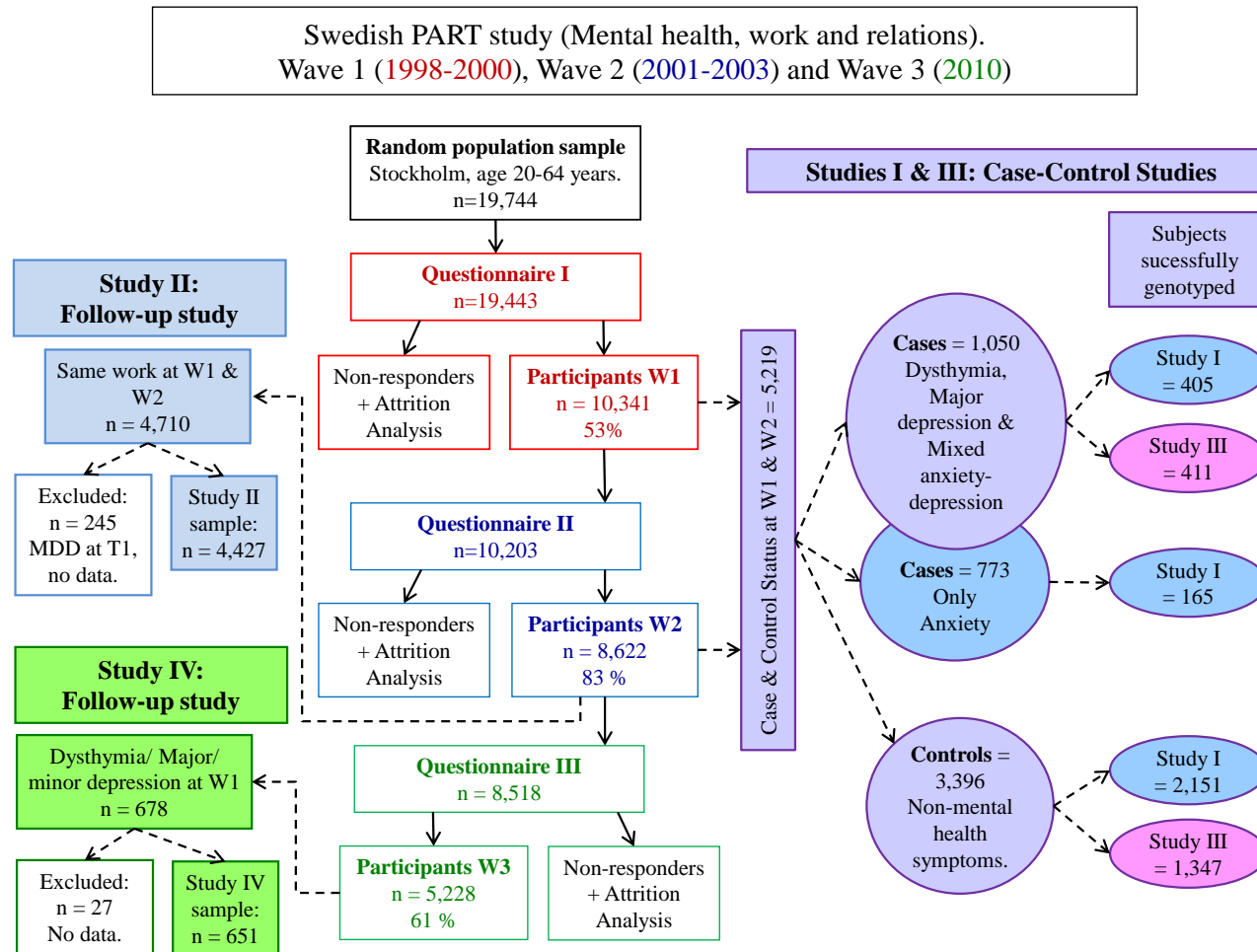
4.1.1 Wave 1

The data were collected between 1998 and 2000. The original PART study sample, from which all study sub-samples were drawn, included 19,744 adult individuals 20 to 64 years of age registered in the Stockholm county and randomly selected from the county council register; but only 19,457 were reached due to address problems. Among the latter, 10,443 individuals responded the questionnaire at wave 1 (53% of the intended sample). Non-response analysis was done by using available official registers. Participation was related to female gender, higher age, higher income and education, being born in the Nordic countries, and having no psychiatric diagnosis in the hospital discharge register or in the early retirement register. Associations among age, gender, income, country of origin, and in-patient hospital care due to psychiatric diagnosis were calculated for participants and non-participants separately, and results were similar between both groups (Lundberg et al., 2005).

4.1.2 Wave 2

The data were collected between 2001 and 2003. All participants from the first wave received a second, almost identical questionnaire three years after they had answered the first one. The participation rate at the follow-up phase (wave 2) was 83% (n= 8,622). Attrition in the second wave was associated with the same conditions as in the first wave, and associations between possible risk factors and depression, determined at wave 1, were the same in both wave 2-participants and wave 2-non-participants subsamples (Bergman et al., 2010). Additionally, participants diagnosed with major depression at wave 1 had higher probability of non-participation at wave 2 (OR = 1.6; 95% CI = 1.1.-2.4).

Figure 1. Design and Subjects of Individual Studies of the Thesis into the PART Study.



4.1.3 Wave 3

The data were collected during 2010. All participants from the second wave received a second, almost identical questionnaire seven to eight years after they had answered the second one. The participation rate at the third follow-up phase (wave 3) was 61% (n= 5,228). Non-participation in the third wave was associated with being a male, belonging to younger age groups, having lower education levels, being self-employed or unskilled worker and having alcohol binge drinking behaviour (Sydén et al, unpublished data).

4.1.4 Questionnaires and Instruments

The PART study participants received each wave a questionnaire including demographics, childhood adversities, financial status, social network, potential stressful life events (SLEs) during the last year, somatic illnesses, a scale on psychological well-being and screening instruments for psychiatric symptoms, harmful alcohol use, illicit drug use and social disability due to psychiatric or psychological symptoms. Specifically, the instruments are: the WHO (Ten) Well-Being Index (Bech et al., 1996), the Major Depression Inventory (MDI) (Bech and Wermuth, 1998), the Alcohol Use Disorder Identification Test (AUDIT) (Saunders et al., 1993), the Sheehan Patient-Rated (Panic) Anxiety Scale (Sheehan, 1983), the Yale-Brown Obsessive-Compulsive Scale (Goodman et al., 1989), symptoms of social phobia and agoraphobia according to Marks and Mathews (Marks and Mathews, 1979), eating disorders according to Beglin and Fairburn (Beglin and Fairburn, 1992), and the Brief Disability Questionnaire (BDQ) (Ormel et al., 1999). At wave 2, pathological anxiety symptoms were assessed according to the Hopkins Symptoms Checklist (SCL-90) (Derogatis et al., 1973) and the Swedish universities Scales of Personality (SSP) (Gustavsson et al., 2000) was including for assessing personality factors.

The instruments utilized for assessing the outcomes and the main putative predictors in this thesis are explained below (see 4.3 and 4.4) including the operationalization of such outcomes and predictors.

4.2 AIMS, DESIGNS AND SUBJECTS OF INDIVIDUAL STUDIES

The subjects of all individual studies constituting this thesis were drawn from the PART study, following the scheme depicted in the Figure 1. The aims, designs and subjects of each individual study of this doctoral thesis are explained in this section. Studied variables are listed according to the design of each study; but their definitions and operationalization are described in the measurements sections (see 4.3 and 4.4 below). Further details about the studied variables are explained in the Papers (see appendices).

4.2.1 Study I: Depression, COMT Gene and SLEs

Study I had two aims i) to investigate the associations between the Val¹⁵⁸Met polymorphism of the catechol-O-methyltransferase (*COMT*), childhood adversities, social support and recent negative life events on the risk of depression and anxiety occurrence; and ii) to establish the relationships between *COMT* Val¹⁵⁸Met genotype and motivational and mood symptoms among depressed subjects.

The design was a *nested case-control study* (Szklo and Nieto, 2007) within the initial PART cohort. Cases and controls were randomly selected from the pool of participants (see Figure 1), and they entered to the study after been successfully genotyped for the *COMT* Val¹⁵⁸Met polymorphism. Thus, the cases were i) 405 depressed individuals (major depression, dysthymic or mixed anxiety depression as defined by DSM-IV-TR) either in the first or the second wave; and ii) 165 individuals with an exclusive anxiety diagnosis (i.e. excluding depression comorbidity) either in the first or the second wave. Also, 2,151 healthy controls (i.e. individuals with no symptoms of psychopathology at both first and second waves) were included.

The variables utilized in the study were the following:

- **Outcomes:** i) Depression occurrence and anxiety occurrence as dichotomic variables; ii) Motivational and mood symptoms among those depressed as continuous variables.
- **Putative Predictors:** *COMT* Val¹⁵⁸Met genotype, family problems during childhood, financial problems during childhood, negative life events, and social support/social network score.
- **Confounders:** None.
- **Stratification Variables:** Sex, depression status.

4.2.2 Study II: Psychosocial Work Environment & Depression

Study II had two aims: i) to determine the longitudinal effects of job demands, skill discretion, decision authority, and social climate (support) at work on the occurrence of major depression (assessed by a diagnostic algorithm) among working men and women from the general population; and ii) to test the dose-response of the Job Demands-Control-Support Model (JD-CSM) components on risk of major depression over time.

The design was a *follow-up study*. For this study, only participants who were working at wave 1 (employed and self-employed) and who continued in the same job at wave 2 were selected, i.e. 4,710 subjects (55.3% of sample at wave 2), and among them 244 persons were excluded because they fulfilled the case criteria for major depression at wave 1 according to the MDI algorithm (Bech and Wermuth, 1998), i.e. 5% of the remaining sample. Additionally, one case was excluded because there was no information about his/her depressive status at wave 2. Finally, our study sample included 4,427 subjects (51% of sample at wave 2), 2,415 women and 2,012 men.

The variables utilized in the study were the following:

- **Outcomes:** Major depression/dysthymia occurrence as a dichotomic variable.
- **Putative Predictors:** Psychological job demands, inadequate job skill discretion, inadequate job decision authority and inadequate social climate at work.
- **Confounders:** Age, living without another adult, little help with household chores, small children at home, education level, income level, occupational groups, inadequate availability of social attachment (as a continuous score), depressive symptoms at baseline (wave 1) as a continuous score, and number of potentially negative life events at wave 2.
- **Stratification Variables:** Sex, occupational groups.

4.2.3 Study III: Depression, 5-HTT Gene & Loss/Separation

The aim of Study III was to examine the effects (main and interaction) of the 5-*HTTLPR*/rs25531 diplotype and loss/separations over the life, on the risk of depression occurrence.

This study had a *nested case-control design* (Szklo and Nieto, 2007) within the initial PART cohort where environmental exposures statuses were assessed concurrently in the moment of case definition, for both cases and controls. Cases and controls were randomly selected from the pool of participants (see Figure 1), and they entered to the study after been successfully genotyped for the 5-*HTTLPR*/rs25531 diplotype. Thus, the cases were 411 depressed individuals (major depression, dysthymic or mixed anxiety-depression as defined by DSM-IV-TR) either in the first or the second wave. Also, 1,347 healthy controls (i.e. individuals with no symptoms of psychopathology at both first and second waves) were included.

The variables utilized in the study were the following:

- **Outcomes:** Depression occurrence (major depression, dysthymic or mixed anxiety-depression) as a dichotomic variable.
- **Putative Predictors:** 5-*HTTLPR*/rs25531 diplotype, parental separation due to death or divorce, and divorce or separation from the partner the last 12 months.
- **Confounders:** Sex, age, lack of social attachment (as a single score), income level and educational level (the latter, only at wave 1).

- **Stratification Variables:** Sex.

4.2.4 Study IV: Chronic Course of Depression

The aim of Study IV was to analyze the interrelationships among personal characteristics and circumstances over different life periods with the chronicity of depression in a well-defined population-based sample.

This was a follow-up study over three waves of the PART study. The sample framework for the present study included data from 5,228 persons who had participated in all three waves (see Figure 1). They were the 50.5% of respondents at the first wave of PART. Among them, 5,122 (98%) had data about their index depressive status (Major depression, Dysthymia, minor depression or neither disorder) at wave 1; and of those 678, fulfilled the criteria for Major depression, Dysthymia or minor depression for entering to this follow-up study (see Figure 1). Among the latter, 4% were excluded due to missing data on childhood adversities in tier 1 (see variables below); thus finally the Study IV sample included 651 subjects.

Study variables were selected from all PART questionnaires taking into account those used in previous studies following the CDMF (Kendler et al., 2002, 2006a; Sjöholm et al., 2009). For the *structural equation modeling* (SEM) analyses (Byrne, 2012), the 27 variables were organized in six developmental tiers and one final outcome, according to the following framework:

- **Tier 1 variables:** Woman (exogenous), Familial Mental Disease (exogenous), Childhood Parental Loss (exogenous), Other Childhood Adversities (exogenous).
- **Tier 2 variables:** Age (exogenous), Low Educational Level, History of Mental Disease.
- **Tier 3 variables:** Somatic Trait Anxiety (STA), Stress Susceptibility (SS), Embitterment (E), Detachment (D).
- **Tier 4 variables:** Inadequate Personal Support, Alcohol Misuse, Depression Severity, Disability Level, Anxiety Disorders, Partner Loss, Other Negative Events.
- **Tier 5 variables:** Depression Severity, Disability Level, Anxiety Disorders, Chronic Diseases.
- **Tier 6 variables:** Marital Problems, Life Difficulties, Other Dependent Life Events, Independent Life Events.
- **Outcome variable:** Depression Status. It was assessed according to the MDI algorithm (Bech and Wermuth, 1998) and coded into the ordinal categories 0=no depression, 1=minor depression and 2=major depression/dysthymia.

Exogenous predictors were those variables not determined by any other variable in the SEM model. Otherwise, the variable was treated as *endogenous*, including the final outcome variable.

4.3 MEASUREMENT OF OUTCOME VARIABLES

4.3.1 Depressive Disorders

4.3.1.1 *Major Depression/Dysthymia*

Major Depression and/or Dysthymia status were assessed by means of the *Major Depression Inventory* (MDI) (Bech et al., 2001; Bech and Wermuth, 1998) following a diagnostic algorithm according to the DSM-IV-TR criteria. The MDI scale includes a list of symptoms from the major depression criteria in the DSM-IV-TR criteria, using six-point intensity Likert scales (from “not at all” to “all the time”). A question on duration of symptoms was added in the questionnaire and only those answering ≥ 2 weeks were included. Validity studies for the MDI has been performed in population based settings in Sweden (Forsell, 2005), and also in clinical settings in European countries (Bech et al., 2001; Cuijpers et al., 2007; Olsen et al., 2003). The sensitivity of MDI was 0.78 and the specificity was 0.78 in a study based on the PART first wave (Forsell, 2005).

Dysthymia was considered if the persons answered that the symptoms lasted ≥ 2 years. However, since these data might be unreliable the two diagnoses were collapsed; thus *Major Depression/ Dysthymia* diagnoses were established at all waves. Major Depression/Dysthymia was one of the outcomes in Studies I, III and IV; and it was the unique outcome in Study II.

4.3.1.2 *Minor Depression*

Minor depression status was assessed by means of the MDI (Bech and Wermuth, 1998) following a diagnostic algorithm according to the DSM-IV-TR criteria (American Psychiatric Association, 2000). Minor depression was part of the ordinal outcome variable in the Study IV: *Depression Status at Wave 3* (see 4.2 above); and it was established at waves 1 and 3.

4.3.1.3 *Mixed Anxiety-Depressive Disorder*

This diagnosis was established using questions from the MDI and the anxiety instruments (see 4.3.2 below); but ruling out the occurrence of major depressive disorder, dysthymic disorder, panic disorder, generalized anxiety disorder or any other anxiety or mood disorder in partial remission, following the DSM-IV-TR diagnostic criteria (American Psychiatric Association, 2000). Mixed Anxiety-Depressive Disorder was one of the outcomes in Studies I and III (see 4.2 above).

4.3.2 Anxiety Disorders

Anxiety disorders were assessed with a battery of instruments. At wave 1, occurrence of anxiety disorders was established if the respondent was positively screened by any of the following instruments: the Sheehan Patient-Rated (Panic) Anxiety Scale (Sheehan, 1983), the Yale-Brown Obsessive-Compulsive Scale (Goodman et al., 1989) or the Marks and Mathews' symptoms of social phobia and agoraphobia (Marks and Mathews, 1979). At wave 2, occurrence of anxiety disorders was assessed by a positive result in the Hopkins Symptoms Checklist (SCL-90) (Derogatis et al., 1973). The diagnosis of anxiety was established if the person fulfilled the criteria, covering the last four weeks, for obsessive-compulsive disorder, social phobia, general anxiety disorder, agoraphobia or panic syndrome according to this battery of instruments. Anxiety disorder was one of the outcomes in the Study I (see 4.2 above).

4.4 MEASUREMENT OF PREDICTOR VARIABLES

In Studies I, II and III, the putative predictor variables corresponded to the explored genetic and environmental determinants or to the main confounding variables for each study. In Study IV, only the exogenous variables were completely independent, i.e. not determined by other variables in the SEM Model (see 4.2 above).

4.4.1 DNA Collection and Genotyping

From the pool of cases and controls for Studies I and III (see Figure 1), 460 depressed subjects and 1,500 controls were selected randomly for genotyping of both *COMT* and *5-HTT*, but the success-rate varied between the genotyping protocols. For *COMT*, an additional set of 409 super-controls and 175 anxiety subjects were put for genotyping. In *COMT*, but not *5-HTT*, we regarded we should combine the super-controls with the controls. Thus, the final numbers of successfully genotyped subjects per each gene were: 1) for *COMT*, 405 depression cases, 165 anxiety cases and 2,151 controls; 2) for *5-HTT*, 411 depression cases and 1,347 controls.

In Study I, the genotype of each participant was determined regarding the *COMT* Val¹⁵⁸Met polymorphism. The rate of successive genotyping was 92.5% among the DNA samples from persons with depression or anxiety and controls. TaqMan SNP genotyping assay, rs4680 (Applied Bio systems, Foster City, CA), was used to detect the Val¹⁵⁸Met polymorphism using TaqMan genotyping master mix according to manufacturer's protocol. The SNP was analyzed on an ABI 7900 HT instrument according to the manufacturer's instruction (Applied Bio systems, Foster City, CA). Six negative controls were distributed in each 384 plate and 12.5% of the samples were re-genotyped to verify genotyping results.

In Study III, the genotype of each participant was determined regarding the *5-HTTLPR*/rs25531 dyplotype. For logistic reasons, genotyping was performed on 460 (95.0%) depression cases and 1,500 (80.0%) non-depressed individuals randomly

selected from the available DNA material. The genotyping process was successfully completed among 89.4% of cases (n=411) and among 89.8% of controls (n=1,347). The definite sample comprised 1,050 women (59.7%) and 708 men (40.3%).

4.4.2 Psychosocial Work Environment

The Swedish Demand-Control-Support-Questionnaire (DCSQ) (Sanne et al., 2005), a translation/adaptation of Karasek's demand-decision latitude questionnaire (Landsbergis et al., 2000; Theorell and Karasek, 1996), was used to assess psychological demands, skill discretion, and decision authority (Karasek and Theorell, 1990; Karasek, 1979).

There were five questions on job (psychological) demands and six on job control (four questions on skill discretion and two questions on decision authority). The questions on *psychological demands* concerned requirements to work very fast, to work very hard, to do an excessive amount of work, to have enough time to get the job done and to have conflicting demands at work. Cronbach's alpha for the job demands scale at wave 1 was 0.74. The four questions on skill discretion concerned requirements to learn new things, whether skills were required, whether creativity was required and whether the work was monotonous or variable. Cronbach's alpha for the skill discretion scale at wave 1 was 0.66. The two questions on decision authority concerned freedom to decide what should be done and how the job should be done. Cronbach's alpha for decision authority scale at wave 1 was 0.77. The last two scales were reversed for the analyses, thus they expressed *inadequate job skill discretion* and *inadequate job decision authority*. Cronbach's alpha for the job control scale at wave 1 was 0.73.

"Inadequate social climate at work" is a scale measuring social support at work, extracted from the DCSQ, which did not cover instrumental support at the time of the first PART data collection (Hällström et al., 2003) and was oriented towards the atmosphere at the worksite (Landsbergis et al., 2000; Theorell and Karasek, 1996). The social climate scale has six questions related to atmosphere at the work place, sense of fellowship, fellow co-worker's support, collegial atmosphere, and good relationship with superiors and workmates. The Likert scale (1 to 4 points) was used to get scores for the four response alternatives, with higher scores indicating lower social climate. Validity studies show that this scale explained 72% of the variance in a total index of social support originally containing 15 items (Ahlberg-Hultén et al., 1995) with an adequate solution in principal component analyses and a satisfactory internal consistency, i.e. Cronbach's alpha = 0.83 (Sanne et al., 2005). This scale showed a Cronbach's alpha of 0.86 at wave 1.

4.4.3 Adulthood Stressful Life Events

A list of 23 potentially negative stressful life events (e.g. divorce, death of a child, financial strain) was provided in the questionnaire (Hällström et al., 2003) and each respondent stated if they occurred or not during the last twelve months before filling the questionnaire at each wave. Most of these questions have been used in previous Swedish studies (e.g. (Theorell et al., 1975)). Thus, the occurrence of *stressful life*

events (SLE) was operationalized in different manners in each study of this doctoral thesis:

- In Study I, SLEs were dichotomized as the occurrence of any SLE concurrently with the assessment of depression status.
- In Study II, unemployment was excluded from the list, and the others SLEs were categorized as none, one, two, and three or more events.
- In Study III, only two objective events were selected from the SLE list. Thus, those persons who experienced the death of his/her partner or a negative experience of divorce/separation from the partner the last 12 months were categorized as having 'Separation from the partner' in the analyses.
- In Study IV, SLEs were categorized as dependent or independent according to their relation with the respondent. A *dependent life event* happened directly to the subject; and an *independent life event* happened to persons in the subject's network (i.e. family, friends) (Monroe et al., 2007). Those SLEs were divided in subgroups in the Study IV (see 4.2.4 above, and also Paper IV in appendices).

4.4.4 Childhood Adversities

Childhood adversities were assessed with questions about death of parents, divorce of parents, familial hassles and familial financial problems occurring during the subject's childhood (defined as before the age of 18 years). Questions about experiences of violence or child maltreatment were not included in the PART self-responded questionnaires due to ethical considerations. Death of any parent and divorce of parents were operationalized as a unique dichotomic predictor variable in Studies III and IV.

4.4.5 Social Support

Availability of attachment in the social network (AASN) was assessed with three questions from a Swedish modification of the Interview Schedule for Social Interaction (ISSI) (Henderson et al., 1980; Undén and Orth-Gomér, 1984); each question used a four-points Likert scale (1=completely true to 4=not at all) and they were added up in a single score; the higher the score the worse the social attachment. Cronbach's alpha for the inadequate availability of the social attachment scale at wave 1 was 0.75. Scores of AASN were used as a predictor variable in Studies I and II. Additionally, an individual question from this scale was utilized as an endogenous ordinal variable in Study IV, i.e. the degree of close person's support at wave 1.

4.4.6 Depression Severity

Depression severity was operationalized in two forms:

- In Study I, depressive symptoms at wave 1 were assessed by the Major Depression Inventory – MDI (Bech et al., 1997; Bech and Wermuth, 1998) as a continuous score ranging 0 to 50 points. This scale had a Cronbach's alpha of 0.92 at wave 1. This score was utilized as a confounder in Study I.

- In Study IV, depression severity was assessed aggregating the depressive symptoms in the MDI according to the DSM-IV-TR characterization and, finally, counting the number of DSM-IV-TR symptoms. In this manner depression severity was a discrete variable ranges 0 to 9 points. Depression severity was an endogenous (i.e. dependent) variable in the study IV, and it was assessed at waves 1 and 2.

4.4.7 Alcohol Use

Patterns of alcohol use in the participants were assessed with the Alcohol Use Disorder Identification Test (AUDIT), an instrument designed for assessing alcohol use in the general population (Saunders et al., 1993). The AUDIT rendered a continuous score (0 to 40 points), which was dichotomized following the Swedish cut-off points (≥ 8 points for men/ ≥ 6 points for women) (Kallmen et al., 2007), in order to indicate the occurrence of any alcohol misuse pattern: hazardous use, harmful use or abuse of alcohol. Alcohol misuse was established at wave 1 and utilized as a binary endogenous variable in Study IV.

4.4.8 Disability Level

The Role Disability Scale (RDS) of the Brief Disability Questionnaire (BDQ) (Ormel et al., 1999) was utilized for assessing the subject's disability levels. RDS score ranges 0 to 15 points, the higher the score the worse the disability. RDS was measured at waves 1 and 2. These measurements were ordinal endogenous variables in the Study IV.

4.4.9 Personality Facets

The *Swedish universities Scales of Personality* (SSP) is a personality instrument which measures several facets related with personality traits (Gustavsson et al., 2000). The PART questionnaire at wave 2 included four SSP-personality facets, which were coded as continuous variables (range 1 to 4) according to the SSP guidelines. Thus, the facets were:

- Somatic Trait Anxiety (SSP-STA)
- Stress Susceptibility (SSP-SS)
- Embitterment (SSP-E)
- Detachment (SSP-D)

Three personality traits (neuroticism, extraversion and aggressiveness), as latent factors, were mapped on the four scales (i.e. facets). The factor loadings of each trait were: *neuroticism* loaded on somatic trait anxiety (SSP-STA: 0.73), stress susceptibility (SSP-SS: 0.80) and embitterment (SSP-E: 0.64); *extraversion* loaded on detachment (SSP-D: -0.52); and *aggressiveness* loaded on SSP-D (0.40) and SSP-E (0.41) although its loadings were moderate. SSP-scales have shown temporal stability in both clinical

and community settings (Gustavsson et al., 2000). The four SSP facets were calculated at wave 2 and considered as continuous endogenous variables in the Study IV.

4.5 STATISTICAL ANALYSES OF INDIVIDUAL STUDIES

4.5.1 Study I: Depression, *COMT* Gene and SLEs

Significance of differences in gender and age between affected states and between genotype groups were tested using 2-sided Pearson chi-square test and Kruskal-Wallis test, respectively. Differences in genotype distribution between affected states were analyzed for each gender separately using 2-sided Pearson chi-square test, and using logistic regression with gender and age as covariates. Genotypic association analyses for depression and anxiety were performed as separate analyses. Difference in mean of mood and motivation symptoms scores between genotypes were tested using 2-tailed F-test. Depressed individuals were compared against healthy controls in logistic multiple regressions models considering risk factors of depression identified previously in the PART study (Sjöholm et al., 2009). The risk factors were entered in blocks. The analyses were performed using Intercooled STATA version 8.0 (StataCorp LP, College Station, Texas) and SPSS version 16 (SPSS Inc., Chicago, Illinois).

Interaction analysis between the *COMT* Val¹⁵⁸Met gene and risk factors used in the logistic regression model were addressed by using an additive interaction approach (Ahlbom and Alfredsson, 2005). There are three available indices to test additive interactions: 1) the relative excess risk due to interaction (RERI), 2) the proportion attributable to interaction (AP) and 3) the synergy index (S). RERI is the excess risk due to interaction relative to the risk without exposure. AP refers to the proportion attributable to disease that is due to interaction among individuals with both exposures. S is the excess risk from both exposures when there is an additive interaction, relative to the risk from both exposures without interaction. $RERI \neq 0$, $AP \neq 0$, or $S \neq 1$ are indicative of additive interaction (Rothman et al., 2008). Indices results over the null value indicate synergistic interactions; indices below the null value indicate antagonistic interactions (Szklo and Nieto, 2007). In this study, additive interaction indices were calculated using an Excel ® tool (available at <http://www.epinet.se>) (Andersson et al., 2005).

4.5.2 Study II: Psychosocial Work Environment & Depression

The JDSCM scales on job demands, inadequate job skill discretion, inadequate job decision authority, and inadequate work social climate were split by cut-off points defined by scale specific quartiles obtained from the current study sample, i.e. subjects without major depression at T1 according to the MDI algorithm and who had the same job at both waves. Thus, sample distribution quartiles, independently for each JDSCM variable, were used for defining the exposure groups (i.e. exposure categories grouping scores of JDSCM scales). Due to the limited number of scale points, the scales could not be divided into exact medians or quartiles. Median split exposure groups were defined merging the two lowest (Q1 and Q2) and the two highest (Q3 and Q4),

respectively. The JDCSM quartiles resulted in percentages different to the theoretical 25% in each one, given the empirical distribution of scales scores, e.g. for job demands a 12-point score was not only the 25th percentile but also the 35th percentile. There were not significant differences in cut-offs between women and men for the JDCSM dimensions, thus the same divisions were used for generating the exposure categories.

Nearly eleven per cent (10.64%) of the subjects' records had at least one variable with missing values; thus, the regression imputation method (Donders et al., 2006; Groves et al., 2009; Raghunathan, 2004) was used to complete the missing values in exposure variables and confounders before running the regression models. Initially, cross-tabulations and single-regression analyses were done to explore associations among the outcome variable and exposures and confounders using the crude data. Then, regression analyses followed a four models sequence: Model 0 was a single regression model for each JDCSM variable. Model 1 adjusted for all JDCSM variables (i.e., job demands, skill discretion, decision authority, and job social climate) and age. Model 2 included model 1 variables and additionally adjusted for living alone status, inadequate social availability (scale score), having little help with household chores, having small children at home and number of negative life events at wave 2. Model 3 included model 2 variables and additionally adjusted for education level, income level and occupational groups. Model 4 included model 3 variables and additionally adjusted for depressive symptoms score (MDI) at wave 1.

All described analyses were done for men's and women's subsamples, separately. Collinearity among co-variables in regression models were checked using variance inflation factors (VIFs); no collinearity was found. Finally, trends over quartiles of significant JDCSM variables were explored with the trend Wald's test and orthogonal polynomial contrasts for linear, quadratic and cubic trends (Szklo and Nieto, 2007). Analyses were done by using STATA 11.2 (StataCorp LP, College Station, Texas).

4.5.3 Study III: Depression, 5-HTT Gene and Loss/Separation

The Hardy-Weinberg equilibrium (HWE) was tested using Pearson's chi-square test. Crude associations between sex (women), parental separation, separation from partner, 5-HTTLPR/rs25531 diplotype, age, lack of social attachment, income level, educational level and depression were explored using simple logistic regression with depression as the outcome variable. Results were expressed as Odds Ratios (OR), which indicate the relative opportunity of obtaining the outcome (i.e. the ratio depressed versus non-depressed) comparing the categories of each variable with a reference category. Also, associations between the '5-HTT diplotype' and separation types (parental separation and separation from partner) were explored by simple logistic regressions.

Experiences of separations among subjects were organized into four mutually exclusive groups: A) those who experienced both childhood parental and previous year partner separations (the 'both separations' group), B) those who only experienced separation of, or death of, any or both parent (the 'only parental separation' group), C) those who only experienced separation/divorce from partner the previous year (the 'only separation from partner' group), and D) those who did not experienced any of

those separations (the ‘no separations’ group), which is the reference group. To explore the heterogeneity (modification) of separation effects on depression risk due to the *5-HTT* diplotype, multiple logistic regressions were run using separations (groups A, B, C and D) and the confounding variables, stratified by the *5-HTT* diplotype. Thus, adjusted OR for occurrence of depression were calculated for types of separation: B) ‘only parental separation’, C) ‘only separation from partner’ or A) ‘both types of separation’ vs. the ‘no-separation’ group (D) with regard to *5-HTT* diplotype stratum. In order to test different associations between sexes, stratified analyses were repeated, splitting the sample by sex.

Complementarily, gene-environment interactions (G x E) between the *5-HTT* diplotype groups and the types of separation undergone by each subject were scrutinized using multiplicative terms in multiple (adjusted) logistic regression models. Two models of interaction were addressed, with the following corresponding null hypotheses: 1) Additive model: the joint effect of the two factors (gene and environment) equals the sum of the effects of each factor, and 2) Multiplicative model: the joint effect of the factors equals the product of the effects of the factors. Thus, the multiplicative interaction appears as a multiplicative term in logistic regressions. OR interaction values higher than one (1) indicate synergistic effects and values lower than one indicate antagonistic effects between the risk factors (Kleinbaum and Klein, 2002). In this study, the additive interactions indices (see 4.5.1 above) were calculated by means of an Excel © tool (Zou, 2008), using the parameters yielded by previous logistic regressions. This tool was kindly provided by its author (Dr. G. Y. Zou). In order to test different G x E effects between sexes, additive and multiplicative interaction analyses were repeated, splitting the sample by sex.

Additionally, two-way interactions between combinational pairs of exposure variables (*5-HTT* diplotype, ‘parental separation’ and ‘divorce/separation from partner the last year’) were tested by means of hierarchical logistic regression models (adjusted for confounders) following this order: 1) The main effects model (only the exposure variables), 2) Models including only one interaction per time (three models), and 3) A model including all two-way interactions. The relative goodness of fit among models was established by the Likelihood-Ratio test (Kleinbaum and Klein, 2002), using the main effects model as the reference. For all performed logistic regression models, the Nagelkerke’s R² (also Cragg & Uhler’s R²) was calculated, indicating how much the regression model predicts the outcome, with values ranging from 0–nothing to 1–perfectly (Long, 1997). The statistical analyses were performed using IBM SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY, USA) and STATA® 11.2 (StataCorp, College Station, TX; USA). A p-value < 0.05 was considered to be statistically significant for the main effects; and a p-value < 0.10 was considered to be statistically significant for interaction terms and interaction indices, because the epidemiologic data have limited power to detect product (i.e. interaction) terms (Greenland, 1993).

Finally, given the small number of cases in the study sample (411 depressed subjects) and the small number of subjects with the low activity diplotype (n=430), the statistical power for obtaining a significant OR into each *5-HTT* diplotype stratum was calculated for each separation group (A, B and C) vs. no-separation group (D, the reference).

Also, the statistical power for obtaining a significant multiplicative interaction (OR of the G x E) was calculated for each separation group vs. the reference group. Power tests were performed using the QUANTO ® 1.2 software (<http://hydra.usc.edu/gxe/>) based on methods described by Gauderman and colleagues (Gauderman, 2002a, b; Kraft et al., 2007).

4.5.4 Study IV: Chronic Course of Depression

In order to explore the relationships among putative predictors, *structural equation modeling* (SEM) was used in the analyses. This technique allows to simultaneously estimate multiple causal paths (i.e. regression terms) among several variables using simultaneous multiple regression equations based on generalized linear models (Tu, 2009). Mplus© Version 4.2 software (Muthén and Muthén, 1998–2006) was selected for analyses, because it can deal with different types of outcomes; thus, in each regression equation the outcome variable could be binary, ordinal or continuous. We used a SEM approach named path analysis (Byrne, 2012), which only utilizes manifest variables, although Mplus© created a continuous latent variable for each binary and ordinal endogenous variable in the model (Muthén and Muthén, 1998–2006). This latent variable indicated the *liability* (i.e. the latent propensity) for obtaining a binary or ordinal outcome in each path, modeled with probit regressions; thus each probit coefficient should be interpreted as the probability change for obtaining such liability. Exogenous variables were those without explanatory terms (i.e. all variables in tier 1 and age in tier 2; see 4.2.4 above); thus the other 22 variables were endogenous, being Depressive Status (DS) the final outcome. Scores obtained directly from some instruments were recoded as ordinal variables with collapsed categories when the frequency of some categories was low (continuous variables were not skewed); thus the ordinal variables had up to 10 categories. The weighted least squares (WLS) estimator was used in analyses. Missing values in endogenous variables were dealt with the Expectation-Maximization (EM) algorithm (Muthén and Muthén, 1998–2006). We followed an exploratory SEM approach, starting with a saturated model where each variable explained the whole group of variables in all subsequent tiers (all paths) and residual correlations between all variables into the same tier. Second, non-significant ($p \geq 0.05$) paths and residual correlations were removed. Third, in order to improve model fit and its conceptual coherence, we performed specification searches (post-hoc) following an iterative process where subsequent models were re-specified and re-estimated according to the Lagrange Multiplier (LM) test results. Finally, the process stopped when the last LM was non-significant according to the family-wise Type I error, established using the adjusted Bonferroni approach. Model fit was assessed with three indices (Byrne, 2012): Comparative Fit Index (CFI), Tucker–Lewis Index (TLI), and Root Mean Square of Approximation (RMSEA). A good model fit is indicated when CFI and TLI are > 0.95 and RMSEA is < 0.05 . Linear and probit coefficients (paths) were expressed as standardized estimates: StdY for paths including exogenous variables and StdXY for other paths (see Figure 2).

4.6 ETHICAL CONSIDERATIONS

The PART (Psykisk hälsa, Arbete och RelaTioner) study was approved by the ethical committee at the Karolinska Institutet (Stockholm), registration numbers: 96-260, 97-313, 01-218, 03-201, 04-528 and 09-880. Informed consents were obtained from all participants. The subjects in the PART study, who agreed to participate in the first and subsequent waves, were all informed that they could withdraw their participation at any time. A brochure including information about mental health problems in general and a statement that anyone can have it during life accompanied the questionnaire. All persons who admitted that they had suicidal thoughts almost half of the time during the past two weeks were contacted and offered an interview with a psychiatrist. If the interviewers found that the participants had a need of care, he/she was given instructions how to contact appropriate health care. The interviewer then made a call to the participant to ensure that care went well. In two occasions the participants were followed directly to psychiatric emergency care. During the data collection, the participants had possibilities to contact the research staff that included a psychologist, a psychiatrist and psychiatric nurses. Open seminars were held where all the participants were invited. Preliminary results were presented and the participants were able to get in personal contact with the researchers. Some of the results have been presented in Swedish available on Internet. Most likely, persons that found the questions too sensitive to answer did not participate. Due to that the questionnaire was self-responded; questions about experiences of violence and sexual abuse during childhood were not included.

5 RESULTS

The doctoral thesis studies covered three main topics in relation with the risk of depression occurrence or recurrence: 1) Gene x Environment interactions, 2) Psychosocial work environment and 3) Risk factors for the chronicity of depression. The main results will be addressed here:

5.1 GENE X LIFE EVENTS INTERACTIONS

This thesis addresses polymorphism in two genes coding for: 1) The catechol-O-methyl-transferase enzyme (the *COMT* gene) and 2) the serotonin transporter protein (the *5-HTT* gene). In addition to the polymorphism, GxE were analyzed in relation to recent stressful life events, childhood problems and current social support.

5.1.1 *COMT* Gene Interactions

The *COMT* alleles were in *Hardy-Weinberg's equilibrium* (HWE) in controls and in subjects with only anxiety; but it was not HWE in subjects fulfilling the criteria for depression diagnosis. The *COMT* risk alleles, i.e. Met/Met (A/A) and Met/Val (A/G), had a main effect on depression risk according to multiple logistic regression results adjusted by age, childhood psychological strain, childhood financial problems, low social support and concurrent negative life events (see Paper I, Table 3, in appendices), but that effect was significant only among men (OR= 2.4; CI_{95%}= 1.3-4.6).

Table 1. Modification Effects of the *COMT* Gene Expression on the Odds Ratios for Depression Risk Factors

<i>COMT</i> Genotype	Men		Women	
	G/G	A/A or A/G	G/G	A/A or A/G
	n=122	n=704	n=225	n=985
	OR (CI _{95%})	OR (CI _{95%})	OR (CI _{95%})	OR (CI _{95%})
Increasing age (years)	1.0 (0.9-1.1)	0.9 (0.9-1.1)	1.0 (0.9-1.0)	1.0 (0.9-1.0)
Low social support	3.9 (1.1-14.5)	4.2 (2.4-7.1)	4.8 (2.0-11.6)	4.1 (2.7-6.0)
Family problems during childhood	1.2 (0.3-5.1)	1.9 (1.1-3.2)	1.5 (0.7-3.5)	2.1 (1.5-3.0)
Financial problems during childhood	1.5 (0.4-6.0)	2.5 (1.4-4.4)	1.2 (0.5-2.6)	1.3 (0.9-1.8)
Negative life events	N.C.	8.0 (2.8-22.7)	16.9 (2.2-129)	6.5 (3.5-12.4)

N.C.: Non-calculated because lack of controls.

When modification effects by the *COMT* genotype were explored (Table 1), they showed that *COMT* genotype modified the effect of family problems and financial problems during childhood, and concurrent negative life events. But, interaction analyses indicated that an additive interaction was found only between the *COMT* risk genotype and family problems during childhood, as shown by additive interaction

indices: RERI= 0.88; CI_{95%}= 0.09-1.66 and AP= 0.43; CI_{95%}= 0.03-0.82 (see Paper I, Table 4, in appendices). No other interactions were found between the *COMT* genotype and the depression risk factors in Table 1.

Additionally, the *COMT* risk genotype was related with an increased number of pathological motivational symptoms among men with depression diagnosis. No differences were found for mood symptoms in men and any kinds of symptoms in women, regarding different *COMT* genotypes (see Paper I, Table 5, in appendices).

5.1.2 Serotonin Transporter Gene Interactions

The 5-*HTTLPR* genotypes were in HWE in both persons fulfilling the criteria for depression and those that did not. In crude and adjusted logistic analyses, the 5-*HTTLPR*/rs25531 low activity diplotypes were not related with depression risk among women and men. Table 4 shows the effect modifications of the 5-*HTTLPR*/rs25531 diplotypes on the risk of depression occurrence by the separation categories. The “Only separation from partner” group was significantly related with the risk of depression among both low activity and high activity 5-*HTTLPR*/rs25531 groups; in both sexes sample and in each sub-sample split by sex. Moreover, in both sexes sample, the additive interaction indices were significant: RERI = 2.79 (90% CI=0.15-7.68) and S = 2.97 (90% CI=1.10-8.05). When interaction analyses were repeated in each sex sub-sample, a synergistic additive interaction was found for women (RERI = 2.48, 90% CI=0.07-7.17; S = 3.57, 90% CI=1.01-12.58); but it was not found for men.

Table 2. Influence of 5-*HTTLPR*/rs25531 diplotypes on the risk of being depressed given exposure to separations.

Diploype* (n)	Only parental separation. OR(95% CI)**	Only separation from partner. OR(95% CI)**	Both separations occurred. OR(95% CI)**
Low activity (430)	1.21 (0.60-2.42)	4.33 (1.85-10.16)	2.26 (0.79-6.49)
Female (267)	1.43 (0.63-3.15)	3.68 (1.42-9.55)	2.20 (0.65-7.49)
Male (163)	0.60 (0.10-3.60)	11.13 (1.33-92.90)	2.28 (0.25-20.84)
High activity (1,328)	1.62 (1.11-2.36)	2.34 (1.50-3.65)	3.48 (1.78-6.77)
Female (783)	1.38 (0.87-2.19)	1.98 (1.17-3.35)	2.87 (1.17-7.03)
Male (545)	2.29 (1.16-4.26)	4.19 (1.80-9.75)	4.55 (1.64-12.62)

Those in ‘Only parental separation’ column were not exposed to divorce/separation from partner.

Those in ‘Only separation from partner’ column were not exposed to parental separation.

OR: Odds Ratio; CI: Confidence Interval.

* Low activity diplotypes: (S_A/L_G, S_A/S_A, L_G/L_G, S_G/S_A); High activity diplotypes: (L_A/L_G, S_A/L_A, L_A/L_A).

** The OR reference category was the “No Separations” group. All ORs were adjusted for sex, age, lack of social attachment, income level and educational level.

Note: Adapted from Table 2 in Paper III: Fandiño-Losada, A., Wei, Y., Åberg, E., Sjöholm, L.K., Lavebratt, C., Forsell, Y., 2013. Influence of serotonin transporter promoter variation on the effects of separation from parent/partner on depression. *J Affect Disord* 144, 216-224.

5.2 PSYCHOSOCIAL WORK ENVIRONMENT

Logistic regression analyses showed different results regarding the relationship between Job-Demands-Control-Support-Model (JDCSM) components and the risk of depression occurrence at the three year follow-up. Firstly, when only JDCSM components were included in regression analysis, all inadequate social climate quartiles (low, high and highest), among women, and the highest quartile, among men, were significantly related with depression (see Tables 3 and 4, also see Paper II in appendices). Among men, high job demands quartile and high inadequate skill discretion quartile were protective factors against depression (see Table 4). Secondly, these figures changed when other confounders were added to regression models. In this manner, all inadequate social climate quartiles continued to be risk factors for depression among women in Models 1 and 3 (see Table 3. Model 2 only shown in Paper II; see appendices). On the other hand, among men, the highest and high quartiles of job demands and the high quartile of inadequate skill discretion resulted as protective factors against depression in the fully adjusted model; while the highest inadequate social climate quartile did not yield significant results (see Table 4).

In the Paper II (see appendices), the results were described by JDCSM quartiles for women, but men's results were collapsed in median split, due to the small number of cases into each JDCSM quartile. Paper II results were similar to those in Table 4, with high job demands and high inadequate skill discretion appearing as protective factors against depression at the three-year follow-up.

Table 3. Adjusted Multiple Logistic Regression Models for Major Depression at T2 among Women.

Outcome: Major Depression at T2	Model 1		Model 3		Model 4	
Quartiles Split of:	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Job Demands T1 ^a						
Lowest (5 to 12 points) ^b	1		1		1	
Low (13 points)	1.36	(0.77-2.40)	1.21	(0.67-2.20)	1.23	(0.67-2.26)
High (14 to 15 points)	1.21	(0.74-1.98)	0.99	(0.59-1.67)	0.94	(0.55-1.59)
Highest (16 to 20 points)	1.33	(0.83-2.13)	1.31	(0.79-2.15)	1.07	(0.64-1.79)
Inadequate Skill Discretion T1 ^a						
Lowest (4 to 6 points) ^b	1		1		1	
Low (7 points)	1.29	(0.78-2.14)	1.18	(0.69-2.02)	1.13	(0.65-1.95)
High (8 to 9 points)	0.86	(0.53-1.42)	0.63	(0.37-1.08)	0.65	(0.37-1.13)
Highest (10 to 16 points)	1.63[†]	(0.96-2.77)	1.12	(0.61-2.05)	1.12	(0.60-2.10)
Inadequate Decision Authority T1 ^a						
Lowest (2 points) ^b	1		1		1	
Low (3 points)	0.57[†]	(0.32-1.01)	0.61	(0.33-1.11)	0.63	(0.34-1.17)
High (4 points)	1.00	(0.62-1.62)	1.05	(0.62-1.76)	1.02	(0.60-1.76)
Highest (5 to 8 points)	0.79	(0.48-1.31)	0.75	(0.44-1.30)	0.74	(0.42-1.30)
Inadequate Job Social Climate T1 ^a						
Lowest (6 to 9 points) ^b	1		1		1	
Low (10 to 11 points)	2.35^{**}	(1.34-4.14)	2.08[*]	(1.15-3.75)	2.09[*]	(1.15-3.81)
High (12 to 13 points)	2.41^{**}	(1.40-4.16)	2.08[*]	(1.18-3.68)	1.85[*]	(1.03-3.31)
Highest (14 to 23 points)	3.84^{***}	(2.20-6.71)	2.78^{***}	(1.53-5.06)	2.06[*]	(1.10-3.83)

Model 1: Adjusted for each other JDCSM variables (i.e. job demands, skill discretion, decision authority, and job social climate) and age at T1.

Model 2: Shown in Paper II; see appendices.

Model 3: Model 1 and additionally adjusting for living alone status, inadequate social availability (scale score), having little help with home chores, and having small children at home at T1, Negative Life Events at T2 and education level, income level and occupational groups at T1.

Model 4: Model 3 and additionally adjusting for score of depressive symptoms (MDI) at T1.

[†] Significance level at p<0.10; ^{*} Significance level at p<0.05; ^{**} Significance level at p<0.01; ^{***}

Significance level at p<0.001; ^a Quartiles Split; ^b Reference Category; OR: Odds Ratio; CI: Confidence Interval.

Note: Adapted from Table 3 in Paper II: Fandiño-Losada, A., Forsell, Y., Lundberg, I., 2012. Demands, skill discretion, decision authority and social climate at work as determinants of major depression in a 3-year follow-up study. *Int Arch Occup Environ Health*. 2012 Jul 4. [Epub ahead of print] doi:

10.1007/s00420-012-0791-3.

Table 4. Adjusted Multiple Logistic Regression Models for Major Depression at T2 among Men.

Outcome: Major Depression at T2	Model 1		Model 3		Model 4	
Quartiles Split of:	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Job Demands T1 ^a						
Lowest (5 to 12 points) ^b	1		1		1	
Low (13 points)	0.59	(0.19-1.80)	0.54	(0.16-1.81)	0.52	(0.14-1.91)
High (14 to 15 points)	0.20*	(0.06-0.70)	0.16**	(0.04-0.61)	0.13**	(0.03-0.53)
Highest (16 to 20 points)	0.48	(0.19-1.25)	0.41[†]	(0.14-1.17)	0.29*	(0.09-0.92)
Inadequate Skill Discretion T1 ^a						
Lowest (4 to 6 points) ^b	1		1		1	
Low (7 points)	0.79	(0.29-2.11)	0.80	(0.27-2.39)	0.77	(0.24-2.53)
High (8 to 9 points)	0.21*	(0.06-0.76)	0.19*	(0.05-0.77)	0.12**	(0.02-0.59)
Highest (10 to 16 points)	1.05	(0.37-2.99)	0.77	(0.20-2.98)	0.82	(0.19-3.48)
Inadequate Decision Authority T1 ^a						
Lowest (2 points) ^b	1		1		1	
Low (3 points)	2.20	(0.80-6.06)	1.45	(0.49-4.35)	1.68	(0.54-5.26)
High (4 points)	1.22	(0.37-4.05)	0.84	(0.23-3.15)	0.75	(0.19-3.03)
Highest (5 to 8 points)	2.52[†]	(0.82-7.72)	1.74	(0.52-5.80)	1.29	(0.35-4.84)
Inadequate Job Social Climate T1 ^a						
Lowest (6 to 9 points) ^b	1		1		1	
Low (10 to 11 points)	1.25	(0.41-3.79)	1.44	(0.43-4.76)	1.21	(0.34-4.30)
High (12 to 13 points)	1.52	(0.51-4.48)	1.45	(0.43-4.89)	1.11	(0.31-4.01)
Highest (14 to 23 points)	4.22**	(1.49-11.96)	3.35[†]	(0.99-11.27)	1.60	(0.43-5.91)

Model 1: Adjusted for each other JDCSM variables (i.e. job demands, skill discretion, decision authority, and job social climate) and age at T1.

Model 2: Shown in Paper II for median-split analyses; see appendices.

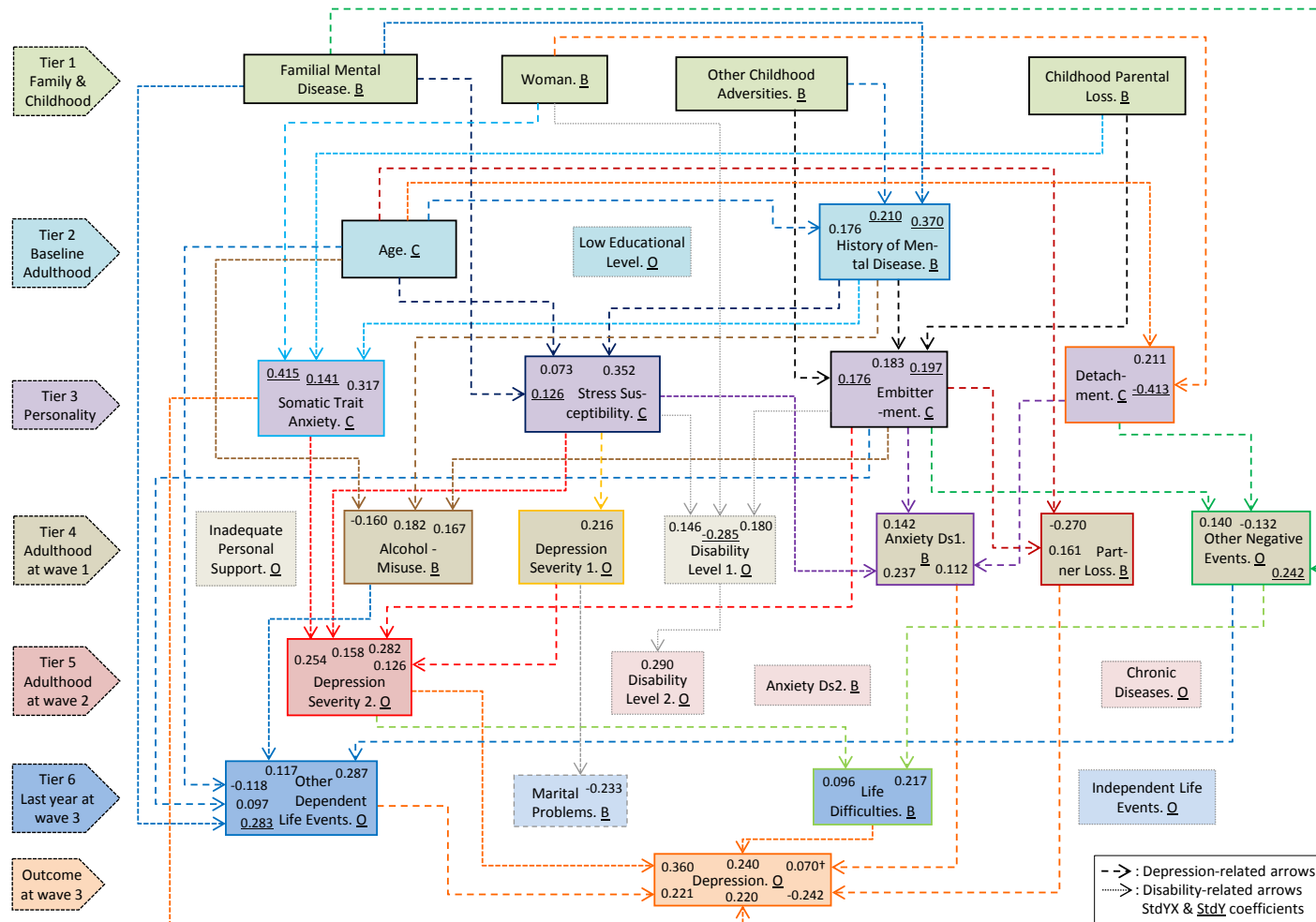
Model 3: Model 1 and additionally adjusting for living alone status, inadequate social availability (scale score), having little help with home chores, and having small children at home at T1, Negative Life Events at T2 and education level, income level and occupational groups at T1.

Model 4: Model 3 and additionally adjusting for score of depressive symptoms (MDI) at T1.

[†] Significance level at p<0.10; * Significance level at p<0.05; ** Significance level at p<0.01; ***

Significance level at p<0.001; ^a Quartiles Split; ^b Reference Category; OR: Odds Ratio; CI: Confidence Interval.

Figure 2. Interrelated explanatory paths for the liability of chronicity/ recurrence of depression.



[†] $p < 0.10$; B: Binary variable; O: Ordinal variable; C: Continuous variable; StdYX & StdY standardizations, see the text.

5.3 CHRONICITY OF DEPRESSION

The results showed that factors acting in different phases over the person's life span had direct and indirect effects on the liability of chronicity/recurrence of depression. Table 5 and Figure 1 summarize such findings, which are explained with further detail in Paper IV (see appendices). Figure 2 shows individual direct paths as colored arrows. Direct paths ending on the same endogenous variable have the same color. All depression related arrows finish on the outcome (*Depression Status at wave 3*), excepting the arrow on Marital Problems at wave 3. Disability-related arrows do not end on the outcome. Table 5 shows that depression severity in tier 5 was the strongest predictor of depression liability, but also it was a proximal determinant over the causal chain leading to depression (see Figure 2). Interestingly, the second strongest predictor of depression liability was Somatic Trait Anxiety (a personality facet) in tier 3, which was a distant determinant in the causal chain. Also, personality facets of Stress Susceptibility and Embitterment were significant determinants of depression liability. Moreover, Embitterment was the most connected endogenous variable over the depression-related paths (see Figure 2). Additionally, all the endogenous variables in the SEM model (i.e. woman, familial mental disease, parental loss, other childhood adversities and age) were significant predictors of depression liability at wave 3; being the familial mental disease the strongest determinant among variables in tier 1, the most distal tier in the causal chain (see Figure 2).

Table 5. Total, direct and indirect effects of the variables on the depression liability at wave 3.

Variable / Effects	Total Effects SPE	Direct Effects		Indirect Effects	
		SPE	%Tot.	Total Indirect SPE	%Tot.
Woman T1 ^a	0.134 ^{****}	--	--	0.134 ^{****}	100%
Familial Mental Disease T1 ^a	0.161 ^{****}	--	--	0.161 ^{****}	100%
Parental Loss T1 ^a	0.069 ^{**}	--	--	0.069 ^{**}	100%
Other Childhood Adversities T1 ^a	0.054 ^{**}	--	--	0.054 ^{**}	100%
Age T2	0.068 ^{***}	--	--	0.068 ^{***}	100%
History Mental Disease T2	0.158 ^{****}	--	--	0.158 ^{****}	100%
Somatic Trait Anxiety T3	0.317 ^{****}	0.220 ^{****}	69.4%	0.097 ^{****}	30.6%
Stress Susceptibility T3	0.087 ^{****}	--	--	0.087 ^{****}	100%
Embitterment T3	0.121 ^{****}	--	--	0.121 ^{****}	100%
Detachment T3	-0.007	--	--	-0.007	100%
Alcohol Misuse T4	0.026 [*]	--	--	0.026 [*]	100%
Depression Severity T4	0.048 ^{****}	--	--	0.048 ^{****}	100%
Anxiety T4	0.070 [†]	0.070 [†]	100%	--	--
Partner Loss T4	-0.242 ^{****}	-0.242 ^{****}	100%	--	--
Other Negative Life Events T4	0.116 ^{****}	--	--	0.116 ^{****}	100%
Depression Severity T5	0.383 ^{****}	0.360 ^{****}	94.0%	0.023 [*]	6.0%
Other Dependent Life Events T6	0.221 ^{****}	0.221 ^{****}	100%	--	--
Life Difficulties T6	0.240 ^{****}	0.240 ^{****}	100%	--	--

SPE: Standardized Parameter Estimates. %Tot.: Effect % with respect to total effects;

^a Standardized (StdY) parameter;

† p < 0.10; * p < 0.5; ** p < 0.1; *** p < 0.01; **** p < 0.001; -- Fix Parameter, not calculated.

6 DISCUSSION

The objective of this thesis was to study the role of some of the genetic and social environmental factors on the occurrence and prognosis of depressive disorders. Mental disorders are a very complex area of research because currently there are a lot of possible pathological and physiological mechanisms for such disorders, but a lack of consensus (Jasinska et al., 2012; Kupfer et al., 2012; Pezawas et al., 2005). Furthermore, the definitions of mental disorders have evolved over time and current definitions are closer to syndromes than to diseases (Krueger et al., 2005; Watson et al., 2008). Consequently, depressive disorders are a set of multiple disorders with common affective and behavioral manifestations (American Psychiatric Association, 2000). Despite an accurate definition of depressive disorders as an individual disease, the current literature is clear about the complex and multifactorial nature of depression (Belmaker and Agam, 2008; Kupfer et al., 2012) which includes both genetic and environmental factors and their causal interactions.

The results of this thesis demonstrate the important role of both genetic and social environmental factors on the occurrence and chronicity of depressive disorders, and how their effects interact changing the risk of depression occurrence among different people depending on their genetic setup.

6.1 GENE X ENVIRONMENT INTERACTIONS

In this thesis, the effects of two genetic polymorphisms on depression risk were explored conditional on the occurrence of environmental exposures, i.e. certain stressful life events over the life span and the degree of social support received. In this manner, we first scrutinized the interaction between the *COMT* gene and family problems during childhood, financial problems during childhood, current low social support and severe life events the year before the occurrence of depression in Study I (see Paper I in appendices). Then, we addressed the interaction between the serotonin transporter linked polymorphic region (*5-HTTLPR*) and separation from parents before the age of 18 years and/or partners in Study III (see Paper III in appendices).

The results showed that both genes moderated the effects of certain stressful life events on the risk of depressive disorders; while they did not moderate the effects of other stressful life events. Also, the causal relationships were not homogeneous comparing these genes. In this manner, the *COMT* gene showed both a main effect and an interaction effect with family problems during childhood. A main effect implied that the *COMT* gene had a role in depression causality independent of effects of the other explored risk factors (i.e. family problems during childhood, financial problems during childhood, low social support/network and recent negative life events) and also independent of its interaction with family problems during childhood. On the other hand, the reported interaction implied that the risky effect of family problems during childhood was moderated by the *COMT* gene, i.e. these childhood problems were a risk factor for depression occurrence only in persons with the A/A (met/met) or A/G (met/val) variants of the *COMT* gene. On the other hand, we found that *COMT* Val/Val genotype was associated with fewer motivational symptoms among depressed men.

In contrast with the *COMT* findings, the *5-HTTLPR* diplotype only showed an interaction effect, i.e. the diplotypes have no main effect on depression risk; but they moderated the risk of depression occurrence only after the exposition to adulthood partner separation, i.e. the vulnerability was higher among persons having a less functional *5-HTTLPR* diplotype makeup, then they had an increased risk of developing depression after a separation.

Comparing significant GxE in this thesis, the indices of the “*5-HTTLPR* x Separation from partner” interaction were higher (RERI=2.79; AP=0.54) than the “*COMT* x family problems during childhood” interaction indices (RERI=0.88; AP=0.43); which indicates that the moderation effect of genes on the risk of depression after exposure to environmental stressors was higher for the combination of the *5-HTTLPR* short allele and the recent occurrence of objective negative life events. There are several plausible explanations for this finding: First, distal (i.e. childhood-related) developmental factors have lower effects on the depression risk than proximal (i.e. adulthood-related) factors because the former must act over longer causal chains than the latter (Colman and Ataullahjan, 2010; Kendler et al., 2002, 2006a; Sjöholm et al., 2009). This fact was also demonstrated in the paper IV of this thesis, regarding distal and proximal factors on depression recurrence risk (see the appendices). Second, categorization of stressful life events into more refined dimensions could strengthen the magnitude and significance of GxE (Monroe and Reid, 2008); thus in the paper III, the utilization of objective stressful life events related with the depressogenic *loss dimension* (Kendler et al., 2003b) allowed to obtain stronger interaction indices. Finally, childhood adversities constitute vulnerability factors for depression per se (Korkeila et al., 2010; Salum et al., 2010), thus the exposure to childhood difficulties could interact with different gene polymorphism combinations (e.g. *5-HTTLPR*, *BDNF*, *MAOA*) generating heterogeneous liabilities to depressogenic effects of stressful life events (Conway et al., 2010; Kaufman et al., 2006; Perepletchikova and Kaufman, 2010). Such differential diathesis could be only discovered by studies addressing gene x gene (GxG) interactions (i.e. epistasis) in addition to GxE (Conway et al., 2010; Kaufman et al., 2006).

Our combined findings in papers I and III were different to results from a *case-only* study which concurrently has scrutinized interactions of *5-HTT* gene and *COMT* gene with stressful life events on the risk of mood disorders (Mandelli et al., 2007). Its results showed that the association between genetic makeup and risk of depression was higher for the *COMT* gene than for the *5-HTTLPR*. Furthermore, Mandelli and colleagues’ findings indicated an interaction between those two genes (i.e. epistasis) on the risk of depression. Although case-only designs are useful for discovering GxE interactions (Li and Conti, 2009), such designs have problems related with their ability for assessing main effects and testing additive interactions, and also they have problems with the assumption of independence between genetic and environmental factors (Hernandez et al., 2006); thus, the reported epistasis must be considered with caution. Adding to the current evidence on epistasis, a recent follow-up study explored the effects *5-HTTLPR* x *COMT* epistasis on the depression vulnerability in the face to life stress; finding evidence in line with *Gene x Gene x Environment* (GxGxE) three-way interactions: homozygous carriers of the long-*5-HTTLPR* allele were not resilient to

environmental stressors if they also carried a *COMT*-Met-158 allele. Surprisingly, the last allele did not potentiate the effect of the short-5-*HTTLPR* allele on depression risk after exposure to environmental stressors (Conway et al., 2010). Epistasis is a common phenomenon because patterns of Mendelian inheritance are infrequent in psychiatric genetics (Weinberg, 2009), instead the genetic determinants of psychiatric disorders are polygenic, involving thousands of common alleles of very small effects (Blom et al., 2007; International Schizophrenia Consortium, 2009).

Gene x Environment interaction is a conceptual construct (Hernandez et al., 2006; Susser, 2006), thus significant GxE should be contrasted with findings from molecular neurobiological and neurophysiological imaging studies in order to discovering the mechanistic substrate behind such interactions. In this manner, several studies have demonstrated that 5-*HTTLPR* and *COMT* genotypes determinate the neurophysiological responses to negative stimuli (Canli and Lesch, 2007; Kupfer et al., 2012). Such stimuli are the experimental surrogates of stressful life events, thus they allow approximations to neurobiological and neurophysiological mechanisms underlying the depression pathophysiology.

Thus, the *COMT*-Met-158 allele has been associated with increased stress hormone release and greater sensory and affective ratings of pain in response to physical and psychological stressors (Jabbi et al., 2007; Zubieta et al., 2003). Functional Magnetic Resonance Imaging (fMRI) studies consistently showed that the *COMT*-Met-158 variant is linked to increased activation in the amygdala and hippocampus following exposures to unpleasant and emotional visual stimuli (Kienast et al., 2008; Smolka et al., 2007; Smolka et al., 2005). Furthermore, a recent fMRI study found opposing gene-dose effects for fear versus happiness surrogate stimuli. Thus, activation in medial prefrontal, anterior cingulate, amygdala, basal ganglia and brainstem midbrain regions was increased with the number of Met-158 alleles for conscious fear, but activation in the same regions decreased for conscious perception of happiness (Williams et al., 2010).

On the other hand, the short allele of 5-*HTTLPR* is associated with higher activity in the anterior cingulate cortex (ACC) and higher amygdala activation after several fearful or negative stimuli and decreased connectivity between ACC and amygdala. Thus, the 5-*HTTLPR*-associated vulnerability to depression implies developmental changes in neural circuitries and their functional interactions which affect the regulation of neural systems related with emotional reactivity and fear extinction (Pezawas et al., 2005) (Canli and Lesch, 2007; Jasinska et al., 2012). Additionally, hippocampus and amygdala activation at rest correlated positively with life stress exposure in short-5-*HTTLPR* allele carriers, but correlated negatively with life stress in non-carriers (Canli et al., 2006). Furthermore, and refining the genotyping procedures, low and intermediate expression diplotypes of 5-*HTTLPR*-rs25531 were recently associated with increased amygdala reactivity to angry faces (Lonsdorf et al., 2011), a finding supporting the necessity of such diplotypes approaches in genetic studies (Murphy et al., 2013).

Finally, a mechanistic model has been proposed recently for the influence of the 5-*HTTLPR* polymorphism on the brain serotonin system. Such integrative model

indicates that the genetic variability in serotonin re-uptake activity during stressor-induced raphe-raphe interactions disrupt the balance in the amygdala – ventromedial prefrontal cortex (VMPFC) – dorsal raphe nucleus (DR) circuitry, which is the critical neural network underlying the reactivity to stressors and regulation of emotions. Moreover, exposure to uncontrollable stressors over time yields hypo-reactivity of regulation of emotion in the VMPFC and hyper-reactivity to stress in the amygdala in carriers of the short-5-*HTTLPR* alleles, which are functional characteristics of depression (Jasinska et al., 2012).

6.2 PSYCHOSOCIAL WORK ENVIRONMENT

In Study II, the findings regarding inadequate job social climate were in line with the current evidence and showed that a good social climate seemed protective against major depression among women; but our findings regarding job demands and skill discretion among men were opposite to recent reviews (Bonde, 2008; Netterstrom et al., 2008), i.e. high job demands appeared as a protective factor against major depression and skill discretion appeared as a risk factor. These findings were not expected, although the results were consistent in analyses with and without imputation. We have found one nested case-control study derived from the Danish Work Environment Cohort Study (DWECS) that showed a significant protective effect of high demands on depressive disorders among men, but the authors did not offer a plausible explanation for their findings (Wieclaw et al., 2008). Additionally, we found no association between high job demands and major depression among women, a finding in line with other researches (Clumeck et al., 2009; Virtanen et al., 2010) (Thielen et al., 2011). We lack explanations for these findings and further investigation is warranted.

On the other hand, we obtained contradictory findings regarding job control components (i.e., skill discretion and decision authority) when the results of adjusted models were compared between genders. Among women there were no associations with depression occurrence, but among men; inadequate skill discretion appeared as a protective factor in adjusted models. The current literature is inconclusive about such findings in women (Bonde, 2008; Netterstrom et al., 2008). On the other hand, similar results have been obtained among men before (Kawakami et al., 1995; Kondo et al., 2006). A possible explanation for these peculiar results is that using skills has become more of a demand when work intensity increases (Joensuu et al., 2010). Furthermore, we stratified the men's analyses by three major occupational groups (blue collar workers, white collar workers and other workers) in order to test the robustness of this protective effect among different occupational groups. Thus, the OR of low skill discretion remained significantly protective only in the blue collar strata (data not shown); however the ORs for low skill discretion in the other two strata were also below unity.

Finally, inadequate social climate at work appeared as a predictor of major depression only among women and it remained significant over different adjusted models. Our results confirm findings about inadequate social climate as a risk factor for depressive disorders in other longitudinal studies (Bonde, 2008; Sinokki et al., 2009), but our

gender-specific findings were opposite to those reported in the literature, i.e. low work social support as a stronger risk factor among men than among women (Griffin et al., 2002; Netterstrom et al., 2008; Shields, 2006). But, the limited number of men with major depression in our sample (only 31 subjects) should have implied a low power to detect significant relationships about this issue.

6.3 CHRONICITY OF DEPRESSION

It is tautological to affirm that the cause of depression is depression itself. Several studies have found that the main determinant of future depressive episodes is the occurrence of previous depressive episodes or their characteristics (Burcusa and Iacono, 2007; Hardeveld et al., 2010; Kendler et al., 2002; Rudolph et al., 2009; Spijker et al., 2004). But, the real conundrum is: What are the determinants of sub-classes of depressive disorders characterized by severe/long symptomatology and recurrent or chronic course? Thus, in this thesis we have addressed this question using a *structural equations modeling* (SEM) approach which allows scrutinizing putative causal relationships among several variables.

The results of Study IV demonstrated that risk and protective factors for the chronicity of depression acted through complex and interrelated causal pathways, which could be assembled in major conceptual pathways, following the approach proposed by Kendler and colleagues with the *Comprehensive Developmental Model Framework* (CDMF) for occurrence of major depressive episodes (Kendler et al., 2002, 2006a), which were replicated in a sub-sample of the Swedish PART study (Sjöholm et al., 2009). In this manner, as a conceptual starting point, each pathway was anchored in one or more personality factors, following studies proposing personality traits as the core of latent liabilities explaining co-occurrence and relationships among common mental disorders (Griffith et al., 2010; Kendler et al., 2006b; Krueger and Markon, 2006). Thus, we propose two major psychopathological pathways: the *internalizing pathway* and the *externalizing/adversity pathway*.

The internalizing pathway is anchored by three SSP-personality facets: SSP-STA, SSP-SS and SSP-E. Those facets comprised the Neuroticism Factor (i.e. trait) in the SSP (Gustavsson et al., 2000). This pathway was influenced by familial history of mental diseases and other childhood adversities, through personal history of mental disease, affecting the three neuroticism-related facets; and was also influenced by childhood parental loss. Additionally, being a woman, positively and directly predicted SSP-STA levels. This pathway continued flowing from the neuroticism-related facets through the clinical characteristics of the depressive disorder, i.e. its severity at waves 1 and 2, and also through comorbidity with anxiety disorders (see Figure 2, also Figure 1 of Paper IV in appendices).

The *externalizing/adversity pathway* is anchored by two personality facets from the SSP: embitterment and detachment. The latter is included in the Extraversion Factor of the SSP and embitterment receives a moderate load from the Aggressiveness Factor of SSP (Gustavsson et al., 2000). This pathway was influenced by familial history of mental diseases, other childhood adversities and age, through personal history of

mental disease, which positively predicted SSP-E; and also influenced by childhood parental loss. Additionally, being a woman, predicted SSP-D levels. The externalizing/adversity pathway continued flowing from the extraversion/aggressiveness-related facets through partner loss, other negative life events and alcohol misuse at wave 1 (see Figure 2, also Figure 2 of Paper IV in appendices).

Although there are several theories linking personality and depressive disorders, design and findings in Study IV only support the pathoplasticity and predisposition theories. The first theory posits that personality affects the course of depression (Klein et al., 2011). Thus, states over the course of depression were independently and directly predicted by all neuroticism-related facets in the SEM model (see Figure 2). The predisposition theory states that personality predicts the onset of depressive episodes, but other variables moderates or mediated this relationship (Klein et al., 2011). Thus, our results indicated that life events acted as mediators between personality and depression (see Figure 2).

Linking the findings in Study IV with the genetic Studies (I and II); *COMT* and *5-HTT* gene polymorphisms were originally described in relation with personality traits, instead of in relation with depressive disorders (Munafò and Flint, 2011). Also, the genetic control of exposures to adversity (both acute and chronic stressors) could be mediated by the genetic setup of personality (Kendler et al., 2003a; Middeldorp et al., 2008; Saudino et al., 1997). Thus, personality characteristics (i.e. affective temperaments) are proposed as the psychopathological link between genes and affective disorders, including depression (Gokturk et al., 2008; Lazary et al., 2009). Additionally, results in Paper IV were similar, although less significant, when minor depression diagnosis were removed from Study IV outcomes (data not shown); this finding is coherent with a reported association between the *5-HTTLPR* and subthreshold depressive symptoms (Gonda et al., 2005); both findings are in line with the affective spectrum theory, which posits that there are no natural boundaries between depressive forms at the personality (depressive temperament), dysthymic, major depressive, minor and subsyndromal depression levels (Judd and Akiskal, 2000).

6.4 METHODOLOGICAL CONSIDERATIONS

Individually, each study has its own strengths and limitations (see individual Papers in the appendices), but methodological considerations common to all studies will be described here.

6.4.1 Participation Rate and Studies Sample Size

In the whole PART study, the baseline non-participation rate was high and most likely persons severely affected by depression did not participate. However, an extensive non-response analysis was done using available official registers showing that the associations between age, gender, income, country of origin and inpatient hospital care due to psychiatric diagnosis were very similar among participants and non-participants at waves 1 and 2 (Lundberg et al., 2005). Additionally associations between putative risk factors and major depression, determined at wave 1, were the same in both the wave-2-participant and the wave 2-non-participant subsamples (Bergman et al., 2010).

The low participation rate diminished the available sample-sizes, which generated problems with the statistical power in all studies. In this manner, in Studies I and III, there were low numbers of depressed individuals per group when stratifying the cases according to sex, genotypes and/or environmental stressors. Additionally, the quest for GxE requires big sample sizes (Caspi et al., 2010; Hernandez et al., 2006), which was a limitation in this thesis. We found interactions at the standard 5% significance level (α) in Study I; but in Study III, we had to set a lower significance level (i.e. $\alpha = 10\%$) for interaction indices, due to our sample size problems. In this manner, we found an additive interaction between the 5-HTTLPR/rs25531 dyplotypes and partner's loss/separation on the risk of depression. Thus, further researches are warranted due to lower statistical confidence.

In study II, the occurrence of major depression was lower compared with other population studies because we have followed a sample of working individuals, which was plausibly comprised by individuals healthier in terms of their physical and mental health than those unemployed or not in the labor market (i.e. the healthy worker effect). Additionally, conclusions about the relationship between JDCSM variables and major depression in this study should be interpreted with caution because our sample included only subjects who remained in the same job over the two study waves. Subjects who were not included in this sample may have changed jobs or have become unemployed due to work stress problems (Haahr et al., 2007) or depressive disorders (Lerner et al., 2004). In addition, the number of depression cases available for analyses further diminished because some cases had missing data in predictor or confounding variables; thus, in order to address the problem of low power due to few cases, the regression imputation method (Donders et al., 2006; Groves et al., 2009; Raghunathan, 2004) was used to complete the missing values in exposure variables and confounders before running the regression models.

In Study IV, the numbers of subjects with major depression/dysthymia diagnosis at wave 1 (the index episode at baseline) and at wave 3 (the outcome at follow-up) were low in order to allowing a powerful SEM analysis (Byrne, 2012); thus we extended the definition of depressive disorders including the minor depression diagnosis (see 2.1.3 above) and operationalized it into an ordinal outcome variable: depression status (see 4.2.4 above). Considerations about diagnosis specificity are explained elsewhere (see 6.4.4 below). In order to test the robustness of this extended diagnosis assumption on the SEM model in Figure 2 (and Paper IV in appendices), we repeated the SEM analyses using only major depression/dysthymia both as the inclusion criteria and as the dichotomic (i.e. binary) outcome, which rendered a SEM model with a similar structure, but including fewer significant paths, due to the smaller sample size. Additionally, interactions between covariates are difficult to modeling with SEM analyses and require big sample sizes (Kendler et al., 2002, 2006a); but on the other hand interactions between associated variables indicate mediation (Kraemer et al., 2008) which is addressed by the SEM models approach (Byrne, 2012); thus we kept the simpler analysis given our sample size.

6.4.2 Self-responded Questionnaires and Instruments

Diagnoses of depression made using a self-responded instrument (the MDI) could be a limitation; but the scale showed high reliability when it was validated, at the first data collection of PART study, with interviews performed by psychiatrists using the Schedules for Clinical Assessment in Neuropsychiatry instrument (Forsell, 2005).

On the other hand, self-responded questionnaires could lead to common method bias, due to, among other things, memory problems, answering styles and mood states (Podsakoff et al., 2012). Additionally, population studies rely on self-responded questionnaires about stressful life events could misclassify some mild events as severe and vice-versa, biasing the research results (Monroe and Reid, 2008). We tried to minimize such bias in several manners: In Study II, we ruled out subjects with a diagnosis of major depression/dysthymia at baseline (wave 1), and additionally the exposures (i.e. JDCSM variables at the first wave) and the outcome (major depression/dysthymia at the second wave) were measured in different moments, in order to diminish the effects of depressive mood on the answers. Furthermore, analyses were adjusted for the level of residual depressive symptoms at wave 1.

In Study III: we have focused on objective dependent life events, i.e. losses and separations. Exact definitions of SLEs are probably less biased by memory or mood issues (Monroe and Reid, 2008). Additionally, adulthood losses and separations were scrutinized only for the span of 12 months before each wave assessment, diminishing the possibility of memory problems. However, there is no reason to believe that there is much error in recording major objective losses such as those explored in Study III (Barraclough and Bunch, 1973). Nonetheless, the answers about childhood adversities could be biased due to memory; but the reliability in data on childhood conditions was supported by comparative analysis between data collected in different waves: only 14% of those 2,633 persons reporting problems during childhood in the first wave did not do so in the second wave, 3 years later (Forsell and Lundberg, unpublished material).

In Study IV, we minimized the common method bias organizing variables from different waves into serial developmental tiers, then causal paths were established only between variables located in different tiers, for avoiding the concurrent measurements of cause and outcome; furthermore, the associations between variables in the same tier were modeled as correlations.

6.4.3 Waves of a Panel Study

A panel study is a kind of longitudinal study where serial surveys are applied to the same group of people (i.e. the panel) at specific moments over time (i.e. the waves) (Groves et al., 2009). To perform follow-up analyses using waves of a panel study has some disadvantages. In Study II, we have no incidence estimates given that our population was examined twice over a three-year lag (Szklo and Nieto, 2007). Thereby, we could have lost incident cases appearing and disappearing between the two data collection times (wave 1 and 2). This fact could reduce the study power, but it would hardly affect our point prevalence estimates and the exposure-outcome relationships.

In Study IV, it was not possible to discern between relapses and chronic course of depression over different study waves, because the questionnaires measured the point prevalence of depression at each wave assessment. These different outcomes could be predicted by different factors, e.g. stressful life events during the follow-up did not predict relapses; but they might predict chronicity of depression (Kivela et al., 2000a, b).

6.4.4 Specificity of Diagnosis

In Studies I and III, the depression group and the anxiety group each consisted of several diagnoses. This is a double edged sword: The true associations between depression and specific genotypes (*COMT* and *5-HTT*) could actually have been between a specific diagnostic subgroup and the studied genotype. On the other hand, the lack of significant main effects for the anxiety outcome in Study I and for *5-HTTLPR/rs25531* diplotypes in Study III could have been the result of the inclusion of different diagnoses into each study outcome, leading to misclassification problems of an accurate target for the genetic studies (Levinson, 2006; Shyn and Hamilton, 2010; Szklo and Nieto, 2007).

In Study IV, we utilized an extended definition of depression which included minor depression, dysthymia and major depression. Minor depression is a research diagnosis in the DSM-IV-TR (American Psychiatric Association, 2000) and it makes part of the controversy about the dimensional continuum of depressive disorders over their symptomatic severity spectrum (Judd and Akiskal, 2000; Kendler and Gardner, 1998). But, the literature shows a high predictive value of minor depression on the illness course (Forsell, 2007; Judd et al., 1998; Rapaport and Judd, 1998), thus, it could be considered as part of the depressive disorders continuum.

6.4.5 Strengths

The main strength of this doctoral thesis is that it is based on material and data from a carefully designed and implemented follow-up research: the PART study (Hällström et al., 2003). This study has involved different but complementary research disciplines: genetics, occupational health, psychiatry, psychology, public health and epidemiology. In this manner, the PART study allowed to address multiple determinants of depressive disorders at the same time, i.e. genetic factors, social environments and behavioral issues, gaining in the understanding of this complex illness.

On the other hand, it is difficult to summarize other strengths common to all studies, because we have utilized different study designs in an attempt to take advantage of design: Studies I and III relied on case-control studies drawn from an ethnically homogeneous population, with sample sizes big enough to obtain genetic main effects (Hernandez et al., 2006); although these samples had problems with the statistical power necessary for discovering GxE (Caspi et al., 2010). Additionally, Study III included two polymorphisms in the promoter region of the *5-HTT* gene, *5-HTTLPR* and *rs25531*, both influencing the transcriptional rate of this gene. Thus, this approach

diminished the misclassification of the 5-HTT activity due to several polymorphisms in this gene (Hernandez et al., 2006; Murphy et al., 2013; Szklo and Nieto, 2007).

In Study II, we utilized a sample of subjects working in the same job at both waves (first and second); thus, it allowed having an assessment of psychosocial work exposure variables which should be more stable (over three years) and more accurate compared to other follow-up studies, where working conditions should have changed over the follow-up (Bonde, 2008; Netterstrom et al., 2008; Stansfeld and Candy, 2006). Additionally, we have assessed concurrently all dimensions in the psychosocial work model proposed by Karasek and Theorell's developments (Johnson and Hall, 1988; Karasek et al., 1998; Karasek and Theorell, 1990; Karasek, 1979)). Our approach allowed an individual assessment of each psychosocial work environment dimension, yielding independent conclusions about demands, decision authority, skill discretion, and social climate at work.

Finally, Study IV has many strengths: First, it has a population-based sample and it is known from previous studies that half of persons with major depression remain untreated, allowing to study risk and protective factors in a semi-naturalistic manner (McKnight and Kashdan, 2009). Second, the ten-year follow up allowed capturing the long term course of the disease and its determinants.(Monroe and Harkness, 2011) Finally, SEM is a statistical technique which allows to scrutinize complex causal relationship among multiple variables (Byrne, 2012; Tu, 2009), thus in this study it was possible to propose pathways for the chronicity of depression following a developmental approach.(Colman and Ataullahjan, 2010; Kendler et al., 2002, 2006a; Sjöholm et al., 2009), although variables from other life course phases (e.g. adolescence) (Colman and Ataullahjan, 2010; Jonsson et al., 2010; MacCabe et al., 2010) should be included in explanatory models of future researches.

6.5 FUTURE STUDIES

The neurobiology and neurophysiology of depressive disorders is complex and the current understanding of the disease core mechanisms is far to be comprehensive (aan het Rot et al., 2009). It is necessary to have a better understanding of neurobiological and pathophysiological substrates of depression in order to focus on better targets for genetic associations studies (Kraft et al., 2007; Levinson, 2006; Munafo, 2012; Munafo et al., 2008; Murcray et al., 2011). Currently, there is increasing evidence linking certain gene polymorphisms to specific functional mechanisms in the brain (Canli and Lesch, 2007; Froelich-Fabre et al., 2004).

These biological and physiological mechanisms constitute intermediate phenotypes or endophenotypes for depressive disorders (Hasler et al., 2004; Levinson, 2006; Shyn and Hamilton, 2010). An endophenotype is a measurable molecular, anatomical or physiological characteristic associated with a specific disease and that plausibly acts over the pathophysiological path of such disease (Gottesman and Gould, 2003). Thus, future studies should focus not only on the discovery of additional intermediate phenotypes for depressive disorders, but also in utilization of depression

endophenotypes as the target of *Genetic Wide-Association Studies* (GWAS) and *Genetic Linkage-Association studies*, in order to improving the power of such studies, due to less heterogeneous outcomes in the analyses (Munafo, 2012; Shyn and Hamilton, 2010).

Also, the quest for Gene x Environment interactions must improve the validity and the reliability of measures of environmental stressors. Small studies with accurate measurements of life events are more powerful than bigger studies with unreliable assessments of stressors (Monroe and Reid, 2008); thus it is better to focus on studies using interviews or dairies for assessing life events and to increase efforts in describing the temporal sequence of environmental stressors in relation to the moment of depression diagnosis.

Chronic stressors play an important role as risk factors for depression, and among them, work conditions are a source of environmental strain for employed people (Siegrist, 2008). Current literature reviews are based on small numbers of longitudinal studies (Bonde, 2008; Netterstrom et al., 2008), thus more follow-up studies are justified. Our findings strongly suggested that skill discretion and decision authority should be addressed separately in future studies about the psychosocial work environment; some recent studies utilized this approach (Grynderup et al., 2012) but others did not (Stansfeld et al., 2012). Furthermore, work conditions should be explored using simultaneous exposures defined in other models, i.e. the effort-reward imbalance model (Siegrist et al., 2004) and the work-to-family conflicts model (Frone, 2000), because complementary work models could address different aspects of the work environment (Siegrist, 2008). Also, other methodological approaches should be explored, such as the assessment of aggregated work-unit measures (Grynderup et al., 2012) or utilization of instrumental variables (Kivimaki et al., 2010). On the other hand, the degree of domestic work demands, availability of leisure-time and levels of physical activity are relevant out-of-work factors which interact with psychosocial work characteristics on modifying the risk of mental disorders (Håkansson and Ahlborg, 2010; Jonsdottir et al., 2010); thus they should be controlled in future occupational studies.

Although previous studies have proposed a developmental causal model for the onset of depressive episodes; to our knowledge, the Paper IV is the first study which describes a causal model for the chronicity of depression. This model should be tested in future SEM studies. Also, this model should be complemented with more developmental determinants from childhood and adolescence, with utilization of the complete set of scales in personality instruments (Klein et al., 2011; Kotov et al., 2010), such as the Swedish universities Scales of Personality (SSP) (Gustavsson et al., 2000) or the Big Five traits (Clark et al., 1994). Also, it is warranted to test the role of genetic polymorphisms on depression chronicity (Zannas et al.).

7 CONCLUSIONS

Depressive disorders are a set of heterogeneous mental illnesses, and their pathophysiology is complex with multiple genetic, behavioral and environmental putative determinants. The effort in this thesis consisted in putting some pieces, of a big puzzle, together.

Our findings demonstrated the existence of GxE interactions which involve the *COMT* and the *serotonin transporter* genes. Gene x Environment interactions are conceptual constructs; thus positive findings about such interactions should be triangulated with discoveries about neurobiological and neurophysiological mechanisms in animals and humans, in order to build a comprehensive model of depression pathophysiology.

Regarding the psychosocial work environment, the results showed a strong relationship between inadequate social climate and major depression among women, while there were no certain effects for the remaining exposure variables. Among men, the findings were controversial, high job demands and inadequate skill discretion appeared as protective factor against depression. Thus, more studies following worker employed in the same job are warranted in order to replicate or reject our findings.

The path analysis (SEM) model for the chronicity of depression revealed complex and intertwined psychopathological pathways leading to its chronicity, which could be assembled in two main mechanisms anchored on personality traits: an internalizing pathway comprising of a depression course sub-path and an anxiety-related sub-path; and an externalized/adversity pathway comprising of an alcohol misuse sub-path and a life events-related sub-path. These pathways were similar to mechanisms proposed in previous studies about the onset of depressive episodes and emphasize the role of personality in the onset and course of depression.

Finally, it is necessary to develop integrative models from different disciplines (e.g. genetics, neurosciences and epidemiology) in order to elucidate the complex mechanisms behind the depressive disorders and their course.

8 ACKNOWLEDGEMENTS

It is very difficult to thank all the people who helped me during my doctoral studies in this short space, but this is my best attempt to do it. Hopefully, I have not forgotten anyone:

First, thanks to my supervisors Yvonne Forsell, Catharina Lavebratt and Ingvar Lundberg for letting me being part of the PART study. For me it was an honor to have participated in this research. Thank you very much for all your teachings on psychiatry, mental health, genetics, public health, and epidemiology. Also, I want to thank my supervisor Shrikant Bangdiwala: thanks for your support and teachings on biostatistics.

I would like to thank Peter Allebeck, Maria Hasselberg and Lucie Laflamme for helping me during the difficult moments of my PhD, and then continue the support afterwards. Thank you very much for contacting me with Yvonne and the research team of the PART study.

I want to thank Christina Dalman and all staff of the Section of Epidemiology and Public Health Intervention Research (EPHIR) for welcoming me to the section. Thank you very much for all shared coffee breaks (“fika”) and lunches. Especially thanks to Henrik Dal, Hanna Hultin, Andreas Sundin, Antonio Ponce de León, Michael Lundberg, Peeter Fredlund, Pia Johansson, Eija Airaksinen, Jatte Möller, Imre Janszky and Cecilia Magnusson, for your advice and recommendations about my articles. Henrik, Hanna, and Andreas, thank you very much for teaching me to play Innebandy. Thanks to Ewa Andersson for maintain an excellent work environment in EPHIR section. I also would like to thank Yabin, Philippe, Louise and Elin, my colleagues at the Department of Molecular Medicine and Surgery, for sharing your knowledge about genetics.

Thanks to my fellow doctoral students in EPHIR for sharing academic sections and some celebrations: Charlotte, Mina, Selma, Åsa, Jenny, Kyriaki, Tord, Mats and Dheeraj. I also thank my EPHIR office-mates for sharing good moments: Charisse, Bojing and Zhengmin. Thank you very much to the Innebandy group of Norrbacka for the good games. I also would like to thank the staff of the Section of Social Medicine for warm welcome to Sweden. I thank my colleagues of Norrbacka 6th floor for sharing the fika-time: Lovisa, Sara, Elisabeth and Lily. Edison, thank you very much for your help, it was great to find another Colombian in the Department of Public Health Sciences (PHS): The best wishes for your career.

I would like to thank my fellow doctoral students in other sections of the Department of Public Health Sciences: Francisco, Hassan, Kristian, Diddy, Antonio, Koustuv, Davoud, Omid, Anna-Clara, Patric, Anna, Teresia and all others. It was a nice experience to share this academic time with you. Thanks to Örjan Sundin and Leif Svanström for your support and hospitality.

Thanks to my “Swedish parents”, Gunmaria and Melvyn, for having “adopted” me for a long time. And also I would like to thank Jamilette and Per, and Fernando and Victoria for letting me being part of your families all this time. You are in my heart!!

I would like to thank my friends of the "Colombian plus" team for being like my family in Stockholm: Daniel, Diego M., Tatiana, Diego B., Yvonne, David, Caroline, M. Camilo, Mario, Germán, Roberto, Sandra, Camilo C., Natalja, Lenis, Kurt, Catalina, Niklas and Andrés. The weekend in Göteborg for the U2 concert was amazing!! To whom had shared our apartment in Gärdet: thanks for tolerate me. Dear friends, thank you for supporting me during the difficulties and for sharing the good moments. Despite being away now, I know that our friendship is just at the beginning. Javier, thanks for being friendship “airbridge” between Colombia and Sweden. Also, thanks to Magda, Anastasia, Gabor, Juan, Martina, Jorge, Irene, Niky and Nathalie for sharing your leisure-time.

Thank you very much to my teachers, and now colleagues, in the School of Public Health at the Universidad del Valle: María Isabel Gutiérrez, Fabián Méndez, Olga Lucía Gómez, Julio César Mateus and Luis Alberto Tafur; your teachings during the Master of Epidemiology gave me a solid foundation for the PhD studies. I would like to thank my colleagues of the CISALVA Institute and the School of Public Health for your support, patience, and for taking over my duties when I had to travel to Stockholm. Also, I thank Jairo Osorno, my undergraduate professor, for your help with the English review in this thesis book. I would like to thank the sources of my student allowances: The COLFUTURO Foundation (Colombia), the ERACOL program of the European Union, the Universidad del Valle (Colombia) and the Karolinska Institute.

Lorena thanks for your support and patience during this last phase of my PhD. Also, I would like to thank my great Fandiño family for your confidence in me.

And finally, and the most important, I would thank my beloved Losada family for your continued support. Doris, my mom, Elssy and Elizabeth, my aunts, thanks for always being there when I need you. To my uncles Guillermo and Vicente, thanks for your support and confidence in me. Uncle Clovis, you are gone, thanks for our visit to Normandy. Thanks to my brothers Fernando, Humberto and Julián, and my cousins, Ana, Carolina, Jennifer, and Johanna, for your constant support. Thanks to Khalaff, Jusef, Samuel, and Tomás, the children of the family, for being an inspiration to move forward.

I dedicate this doctoral thesis to my beloved ones who are gone: My father Napoleón, my cousin Armando and my grandmother Ana.

Carlos Andrés Fandiño-Losada.
Stockholm, April 2013.

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