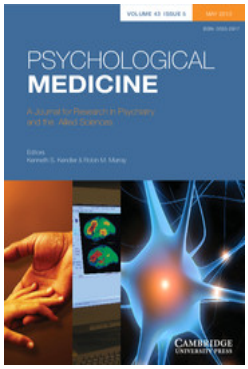

Longitudinal course of depressive symptoms in adulthood: linear stochastic differential equation modeling

T. Rosenström, M. Jokela, M. Hintsanen, L. Pulkki-Råback, N. Hutri-Kähönen and L. Keltikangas-Järvinen

Psychological Medicine / Volume 43 / Issue 05 / May 2013, pp 933 - 944
DOI: 10.1017/S0033291712002000, Published online: 30 August 2012

Psychological Medicine (2013), **43**, 933–944. © Cambridge University Press 2012
doi:10.1017/S0033291712002000

ORIGINAL ARTICLE

Longitudinal course of depressive symptoms in adulthood: linear stochastic differential equation modeling

T. Rosenström[1]*, M. Jokela[1], M. Hintsanen[1,2], L. Pulkki-Råback[1], N. Hutri-Kähönen[3] and L. Keltikangas-Järvinen[1]

[1] *IBS, Unit of Personality, Work and Health Psychology, University of Helsinki, Finland*
[2] *Helsinki Collegium for Advanced Studies, University of Helsinki, Finland*
[3] *Department of Pediatrics, Tampere University and Tampere University Hospital, Finland*

Background. Although many studies have addressed the topic of stability *versus* change in depressive symptoms, few have further decomposed the change to continuous accumulation *versus* non-systematic state fluctuations or measurement errors. This further step requires a longitudinal follow-up and an appropriate stochastic model; it would, for example, evaluate the hypothesis that women accumulate more susceptibility events than men.

Method. A linear stochastic differential equation model was estimated for a 16-year longitudinal course of depressive symptoms in the Young Finns community sample of 3596 participants (1832 women, 1764 men). This model enabled us to decompose the variance in depression symptoms into a stable trait, cumulative effects and state/error fluctuations.

Results. Women showed higher mean levels and higher variance of depressive symptoms than men. In men, the stable trait accounted for the majority [61%, 90% confidence interval (CI) 48.9–69.2] of the total variance, followed by cumulative effects (23%, 90% CI 9.9–41.7) and state/error fluctuations (16%, 90% CI 5.6–23.2). In women, the cumulative sources were more important than among men and accounted for 44% (90% CI 23.6–58.9) of the variance, followed by stable individual differences (32%, 90% CI 18.5–54.2) and state fluctuations (24%, 90% CI 19.1–27.3).

Conclusions. The results are consistent with previous observations that women suffer more depression than men, and have more variance in depressive symptoms. We also found that continuously accumulating effects are a significant contributor to between-individual differences in depression, especially for women. Although the accumulating effects are often confounded with non-systematic state fluctuations, the latter are unlikely to exceed 27% of the total variance of depressive symptoms.

Received 14 February 2012; Revised 20 July 2012; Accepted 24 July 2012; First published online 30 August 2012

Key words: Adult development, community sample, continuous-time model, depressive symptoms, gender differences, longitudinal study, stochastic differential equation, time trajectories, unipolar depression.

Introduction

In 2002, unipolar depressive disorders ranked fourth among the leading causes of disability-adjusted years of life, and they are projected to be ranked second by 2030 (Murray & Lopez, 1997; Mathers & Loncar, 2006). Lifetime prevalence of depression has been estimated to be approximately 16% (Kessler *et al*. 2003), with high variability between countries (Weissman *et al*. 1996). Depression can lead to various social role impairments (Kessler *et al*. 2003) and has a recurrence rate of up to 85% (Mueller *et al*. 1999). However, depressive disorders are heterogeneous phenomena in the population. There seems to be a heritable part of depression that is related to personality (Kendler *et al*. 2006). The heritability estimate for major depression varies from 31% to 42% in general population studies (Sullivan *et al*. 2000; Bienvenu *et al*. 2011). Twin studies have attributed 58–67% of the variance in depression to individual-specific environmental effects and measurement error (Sullivan *et al*. 2000).

Genetic research has dealt mainly with the presence of depression and not with its course over time. Although there is a genetic component in depression, its expression may be contingent on environment

* Address for correspondence: T. Rosenström, IBS, Unit of Personality, Work and Health Psychology, University of Helsinki (Siltavuorenpenger 1 A), PO Box 9, 00014, Helsinki, Finland.
(Email: tom.rosenstrom@helsinki.fi)

(Caspi *et al*. 2010). There are several different environmental exposures that can alter the course of depressive symptoms (Jokela *et al*. 2011; Cramer *et al*. 2012). For instance, traumatic events in early childhood may heighten the risk of persistent depression in adulthood (Brown & Harris, 2008). However, the dynamic nature of the time course of depressive symptoms in non-clinical community samples remains poorly understood.

The aim of this study was to estimate the extent to which variation in depressive symptoms in adulthood reflects (1) stable trait-like differences between different individuals, (2) the effects of protective and risk factors accumulating over time, and (3) random and non-systematic state fluctuations or measurement error. Longitudinal datasets with repeated measurements from the same individuals enable the estimation of a model that describes the course of individual time trajectories of depressive symptoms in the population. By constructing such a model, the hypothesis that women encounter more factors than men that together 'push and pull' the depressive symptoms over time can be assessed (Hyde *et al*. 2008), thereby resulting in a more continuous time course than for men. Push and pull by so many factors that all cannot be observed is reminiscent of the movement of a particle bouncing due to collision with countless unobserved atoms; a process frequently modeled by a continuous time random process known as Brownian motion (Øksendal, 2003; Klenke, 2008).

At least one study has estimated a similar model for children and adolescents followed for 3 years, at half-yearly intervals. Using a structural equation model (Bollen, 1989; Kenny & Zautra, 1995), children and adolescent depression was successfully decomposed into three components similar to those described above (i.e. trait, accumulating influences and fully random state variation) (Cole & Martin, 2005). The second component, time accumulation, was described with an autoregressive process; it is distinct from the static decompositions usually seen in genetic and measurement-related studies, as it adds an element of time evolution to the model. Importantly, an autoregressive process can contain randomness and thereby model different trajectories for different observed individuals instead of just group-level time evolution.

Unfortunately, the results from discrete-time autoregressive models cannot be readily compared across studies with different longitudinal time intervals (Bartlett, 1946; Oud & Delsing, 2010). To avoid misleading inferences, a transition to continuous-time modeling would be preferable, assuming that the underlying dynamics is continuous. Depressive symptoms seem to vary continuously in the population, ranging from subclinical symptoms to severe depression (Solomon *et al*. 2001; Hankin *et al*. 2005; Jokela *et al*. 2011), and we assume that some of them also develop relatively continuously in time. Continuity, however, does not necessarily imply determinism or fixed time trajectories among study participants: Brownian motion is a random process modeling a time trajectory of an agent or object that is perturbed continuously by many small influences; it typically yields the random part of a stochastic differential equation (Øksendal, 2003).

In this study, a linear stochastic differential equation model (Oud & Jansen, 2000; Oud & Delsing, 2010) was estimated for the time evolution of the continuous part of a depression score using data from a prospective population study (Raitakari *et al*. 2008). A stochastic differential equation model can describe fairly rugged depression paths, or trajectories, despite their continuity; in addition to this continuous part, a stable trait part, a state or measurement error part and relative shares of these three parts in explaining the total population variance are estimated from the data (Oud & Delsing, 2010). The state part cannot be differentiated from possible measurement error, and it captures those changes in depression score that do not provide further statistical information over a single measurement point and the population (i.e. trait) variation staying constant across time for any given individual. Parameters of the total model are retrieved from a structural equation model (Oud & Delsing, 2010), allowing a direct comparison of results across studies with different time intervals between measurements.

Method

Participants and measures

Participants were derived from the ongoing prospective Young Finns study that began in 1980 (Raitakari *et al*. 2008). The original sample consists of 3596 healthy Finnish children and adolescents derived from six birth cohorts (1832 women, 1764 men). To select a broadly sociodemographically representative sample, Finland was divided into five areas according to locations of university cities with a medical school (Helsinki, Kuopio, Oulu, Tampere, and Turku). In each area, urban and rural boys and girls were randomly selected on the basis of their unique personal social security number. All participants gave written informed consent and the study was approved by local ethics committees. The sample has been followed subsequently in seven data collection waves in 1983, 1986, 1989, 1992, 1997, 2001 and 2007–2008. A detailed description of the cohort

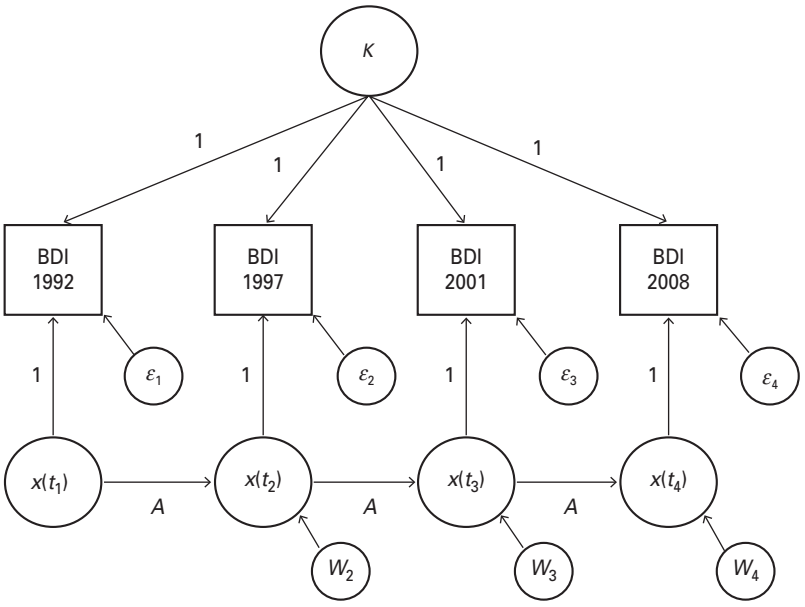

Fig. 1. Path analysis model yielding the discrete time equivalent for the exact discrete model (EDM). See text for meaning of symbols.

can be found in an earlier publication (Raitakari *et al*. 2008).

Four follow-up examinations contained a modified version of the Beck Depression Inventory (BDI) (reported, for example, by Elovainio *et al*. 2006), those from years 1992 ($n=2246$), 1997 ($n=2062$), 2001 ($n=2062$) and 2008 ($n=2032$). A total of 1057 participants had complete data whereas 535 had no depression data at all. However, even the participants without depression data were included in many analyses so as to include the variation due to missing data by using the bootstrap method; such observations do not contribute to the full information likelihood functions. At the initial time point in 1992, the ages of the participants in respective cohorts were 15, 18, 21, 24, 27 and 30 years, with approximately equal frequencies. The time series spans a total of 16 years, with unequal sampling intervals of 5, 4 and 7 years.

Depressive symptoms were measured using a modified version of the BDI, in which the second mildest symptom statement of each item of the original BDI is presented as a five-point scale ranging from 'not at all' to 'very much'. The sum score measure of depression, derived from all 21 items, is a value between 21 and 105. Although there is no natural scaling for the depression measure, BDI-II (Beck *et al*. 1996) is often interpreted with values ranging from 0 to 63. Hence, we rescaled the depression score to vary between values 0 and 63 with an affine transformation. Because items in the modified BDI describe milder symptoms than those in BDI-II, the distribution of the modified BDI is different from BDI-II, with higher mean levels. The two measures are highly correlated, however, as assessed from the same participants in the follow-up of 2008 where BDI-II was measured ($r=0.775$). Of all participants who reported a full set of BDI-II items ($n=2015$), 89.2% had a sum score of $\leqslant 13$ and only 1.2% were in the 'severe' category (score $\geqslant 29$).

Statistical model

The model that we applied in the current study corresponds to a continuous version of the autoregressive latent trait–state model (Kenny & Zautra, 1995; Cole & Martin, 2005), shown in path analysis form in Fig. 1 (Bollen, 1989). The difference is that a time-continuous process $x(t)$ is modeled instead of the four discrete successive latent variables that correspond to theoretically arbitrary measurement times t_1, t_2, t_3 and t_4 (here, the years 1992, 1997, 2001 and 2008). The applied model is more widely known as the linear stochastic differential equation model (Øksendal, 2003; Oud & Delsing, 2010), but it is estimated here using a structural equation model with appropriate nonlinear constraints (Oud & Delsing, 2010). This model has also been referred to as the exact discrete model (EDM) because it is in exact equivalence with the underlying continuous time process (Oud & Delsing, 2010).

For technical reasons, continuity is rarely modeled in practice, although it has long been recognized that the discrete approximation is problematic (Bartlett, 1946). For example, when fitting a

non-random autoregressive model specified simply by $x(t_i) = A_d x(t_{i-1})$, then

$$\frac{x(t_i) - x(t_{i-1})}{t_i - t_{i-1}} = \frac{A_d - 1}{t_i - t_{i-1}} x(t_{i-1}) \quad (1)$$

approximates to the continuous differential equation $dx/dt = Ax$ but depends nonlinearly on the measurement time interval. Discrete approximation for the true A is $(A_d - 1)/(t_i - t_{i-1})$, not A_d. Therefore, the opposite finding may seem apparent, even though the true underlying autoregression function in continuous time was larger in one study with longer measurement intervals than in another study with shorter intervals. The problems of discrete models for underlying continuous latent processes are discussed elsewhere in more detail (Oud & Delsing, 2010). Instead, the linear stochastic differential equation model is described in the following text.

Let us denote the depression score at time t as $x(t)$. Using existing notation (Oud & Delsing, 2010), the description of the time evolution that is fitted to the data is of the form:

$$\frac{dx(t)}{dt} = Ax(t) + b + k + G\frac{dW(t)}{dt}. \quad (2)$$

According to the model, the instantaneous time evolution of depressive symptoms depends linearly (with the scalar coefficient A) on (i) the level of depressive symptoms, (ii) the population mean level through the scalar b, (iii) the individual long-term mean level (trait) through the population random variable κ, and (iv) the standard (Wiener/Brownian) random process $dW(t)/dt$, scaled with the scalar G. Although involving randomness, the process W is continuous in time, describing the cumulative sources of variation. In addition, each observation of the process x, or measurement of a single individual's depression score at time t_i of measurement i, is modeled as:

$$y(t_i) = x(t_i) + \varepsilon_i, \quad (3)$$

where ε_i is a normally distributed error term. $\mathrm{Cov}(\varepsilon_i) = \Theta$ for all i, reflecting both measurement error and state fluctuations that are independent of the linear time evolution of equation (2). Hence, ε_i is independent of ε_j whenever $i \neq j$. Table 1 summarizes the parameters of the process and their interpretations. The parameters are assumed to be the same for the whole sample of individuals included in the model estimation.

The solution of the stochastic differential equation (2) is

$$x(t) = e^{A(t-t_0)}x(t_0) + A^{-1}(e^{A(t-t_0)} - 1)(b + k) + \int_{t_0}^{t} e^{A(t-s)} G\,dW(s), \quad (4)$$

where t_0 is the time of initial measurement; time can be rescaled so that t_0 is zero without a loss in generality

Table 1. *Interpretation of the model parameters*

Parameter	Interpretation
$\mu_{x(0)}$	Population mean at the initial measurement
A	Drift coefficient, related to the autoregression coefficient
b	Defines the long-term population average: $\lim_{t\to\infty} E[x(t)] = -b/A$, if stable
Φ_κ	Trait variance in the population
$\Phi_{x(0)}$	Latent population variance at the initial measurement
$\Phi_{\kappa,x(0)}$	Covariance between initial measurement and trait component
G^2	Defines the magnitude of cumulative sources of variance
Θ	State and measurement error variance

(Øksendal, 2003; Oud & Delsing, 2010). The last term on the right side of equation (4) is an instance of an Itô integral (Øksendal, 2003; Klenke, 2008). From equation (4) and the rules of Itô integration, a formula can be derived for the variance of $x(t)$. The variance is the sum of three terms that relate to initial depression value:

$$e^{2A(t-t_0)}\Phi_{x(0)} + 2e^{A(t-t_0)}A^{-1}(e^{A(t-t_0)} - 1)\Phi_{k,x(0)}, \quad (5)$$

trait variation:

$$A^{-2}(e^{A(t-t_0)} - 1)^2\Phi_k, \quad (6)$$

and variance due to cumulative effect:

$$(2A)^{-1}(e^{2A(t-t_0)} - 1)G^2. \quad (7)$$

In a stable process that does not increase or decrease without bounds, A is negative, implying that all variance components are positive at all times. The initial value of the contribution to variance [i.e. formula (5)] vanishes as time passes (i.e. the terms that depend on $x(0)$: shorthand for $x(t_0)$ in subindices). In the infinite time limit, the stable trait variance is $A^{-2}\Phi_\kappa$, and variance due to cumulative effects is $(2A)^{-1}G^2$. Variance due to the state/measurement error, Θ, relates to differences between the latent process of equation (4) and its measurement; Θ never depends on time. In the results section, the three-component variance decomposition of the measured depression score is presented for the infinite time limit. This is one way to interpret the course of depression without confounding due to variation in initial measurements, but we also present the decomposition at $t - t_0 = 82.4$; that is, after the modeled cumulative effects have accumulated for approximately the length of life expectation in high-income countries, as projected for the year 2030 (Mathers & Loncar, 2006). The proportion of variance attributed to cumulative effects is plotted as a function

of time in Fig. 3. In these time-specific calculations, the variance terms that depend on $x(0)$ are simply excluded.

The EDM was estimated using OpenMx structural equation modeling software (Boker *et al*. 2011). The structural model and its nonlinear constraints were formulated as instructed in the literature (Oud & Delsing, 2010). The model was estimated with the full information maximum likelihood (FIML) approach that has been found successful in the modeling of missing data (Muthén *et al*. 1987), even in the case of non-normal data (Enders, 2001). Structural equation models were evaluated using the likelihood ratio test and Akaike's (AIC) and Bayesian (BIC) information criteria (Bollen, 1989; Kass & Raftery, 1995). A model that attains a lower value than the competing models is preferred according to AIC and BIC. Differences between sample skewness and that of normal distribution are assessed with the D'Agostino test for skewness, and differences in kurtosis with the Anscombe–Glynn test, as implemented in the Moments package, version 0.12, by Lukasz Komsta (http://cran.r-project.org/web/packages/moments/moments.pdf). Bootstrapping with 1000 bootstrap resamples of original data was used to derive percentile confidence intervals (CIs) for the EDM parameters (Efron & Tibshirani, 1993).

Latent trait modeling

Latent trait measurement modeling is often applied to increase measurement precision. We chose to model the time trajectories of the sum score, however, for the following three reasons. First, recent evidence supports the view that depression represents a causal network of symptoms rather than the view that the symptoms reflect a common latent cause (Cramer *et al*. 2012). Enforcing of the latent trait model with time-invariant loadings to data from a causal network would inflate the error/state component of the model: if one symptom for an individual is truly elevated between two measurement times but another symptom is not, then the model would tend to interpret the change as a random fluctuation (as the underlying latent variable change is expected to reflect all symptoms according to their loadings). Hence, modeling of the sum score was deemed as being consistent with clinical practice and with existing theoretical models, whether based on the latent trait or causal network. Second, efficient missing data handling would be difficult, as estimation should be based on the polychoric correlation matrix among the Likert-scaled items. Third, in a latent trait formulation, the state/error variance is a high-dimensional construct (dimension per item or symptom), complicating comparison with trait and cumulative variance parts of the model. In addition, the additional burden of estimation due to introducing several latent trait loadings and unique-variance terms might outweigh the gains in precision achieved from measurement modeling.

The two first arguments against latent trait modeling constitute a partially testable hypothesis whereas various solutions exist for the third. Therefore, we conducted the following supporting latent trait analysis. An empirical polychoric correlation matrix (Ekström, 2009) was computed for depressive symptoms over all follow-ups, and a latent-trait formulation of the EDM was estimated using the matrix; that is, loadings of the unidimensional latent process $x(t)$ onto each depressive symptom, and the unique variances of the symptoms, were estimated along with the other model parameters (Oud & Delsing, 2010). The amount of observations required by OpenMx was set to a minimum over all two-variable margins among all 84 observed variables (21 symptoms $\times$ 4 follow-ups). The median of unique variances represented the state/error variance. Infinite-time limits of trait, cumulative and state variances and their variability over the bootstrap samples were examined.

Results

Although depression measurements for the four time points (years 1992, 1997, 2001 and 2008) were not normally distributed, deviations from normal distribution kurtosis were barely detectable ($p = 0.089$, 0.330, 0.038 and 0.040 respectively). Sample kurtosis varied between 2.893 and 3.241. Sample skewness varied between -0.6221 and -0.6169, with all p values $< 2.2 \times 10^{-16}$. The magnitudes of these deviations from normality, however, are far below the values typically examined when bias due to non-normality is assessed for the FIML estimates in a structural equation context (Enders, 2001). Hence, it seems safe to proceed without non-normality corrections that would add complexity for the present modeling aims.

In previous research, more stability in depression has been shown in adolescents than in children whereas greater cumulative effects have been found in children (Cole & Martin, 2005). Thus, we first tested whether or not all six cohorts could be treated together. A likelihood ratio test was performed for a model with equal means and covariances for all cohorts *versus* the 'saturated/unrestricted model' with means and covariances varying freely across cohorts. This constitutes a test for the equality of mean and covariance structures between cohorts, with appropriate handling of the missing data achieved using the full information estimation. The difference between cohorts was almost significant ($\chi^2 = 89.395$,

Table 2. *Estimated sample means and covariance for men and women*

	Women ($n=1832$)				Men ($n=1764$)			
Year	1992	1997	2001	2008	1992	1997	2001	2008
n_{missing}	592	594	635	633	758	940	899	931
Mean	19.48	19.15	18.10	17.66	16.62	16.51	15.34	16.09
Variance/covariance matrix[a]								
1992	91.55	–	–	–	84.31	–	–	–
1997	57.18	111.84	–	–	62.28	105.62	–	–
2001	56.32	74.92	124.79	–	49.77	69.00	98.05	–
2008	53.24	60.64	77.87	120.85	49.41	64.53	71.70	105.08

[a] Values on the diagonal are variances, other values are covariances among measurements. Only 177 women and 358 men lacked data each year.

$df_{\text{difference}}=70$, $p=0.059$), but BIC and AIC supported treating them as one set of data rather than as separate cohorts (-19051.17 *v.* $-18\,567.43$ and $32\,850.23$ *v.* $32\,900.84$). Minor differences among cohorts might inflate the trait component of the EDM. We therefore performed the same test after removing the mean levels of all depression measurements for each cohort because the EDM is not needed to assess such a simple difference. This retains the time variation but removes overall mean differences among cohorts. After this adjustment it is safer to conclude that all cohorts can be analyzed together ($\chi^2=85.863$, $df_{\text{difference}}=70$, $p=0.096$). Again, BIC ($-19\,010.18$ *v.* $-18\,522.92$) and AIC ($32\,891.22$ *v.* $32\,945.35$) supported this choice.

After the removal of the cohort means, we assessed whether it was possible to fit a single model combining men and women. The data suggested that solutions would be different for men and women, regardless of excluding the overall mean levels of sexes ($p<1.362\times10^{-11}$ with or without). Thus, all further results are given separately for men and women. This solution was also favored by AIC ($43\,299.11$ *v.* $43\,352.82$) and previous literature on depression (Nolen-Hoeksema & Girgus, 1994; Hankin *et al*. 1998; Hyde *et al*. 2008), but not by BIC (-8515.67 *v.* -8548.58), which penalizes more heavily from excess parameters (Kass & Raftery, 1995). Table 2 gives the FIML estimates of the saturated models. In practice, these correspond to sample means and covariance with less bias due to missing values than for the usual estimates of these quantities.

Because cohort-wise differences in the time average of depression inflate the stable trait variance in the final EDM estimates, we removed these small differences before fitting the EDM for men and women. OpenMx's full information estimation algorithm did not converge successfully for the saturated (i.e. unrestricted/null) model when using the dummy variable required for the EDM's structural equation formulation (Oud & Delsing, 2010). This precluded proper nesting of EDM within the fully unrestricted missing-data model, which is necessary for the likelihood ratio test of model fit (Bollen, 1989). However, according to BIC and AIC, EDM supersedes the unrestricted model that was estimated without the EDM dummy variable for women ($EDM_{BIC}=-11\,754.06$ *v.* $unrestricted_{BIC}=-1323.357$; $EDM_{AIC}=25\,173.11$ *v.* $unrestricted_{AIC}=25\,470.62$). The situation was similar for men ($EDM_{BIC}=-11\,379.91$ *v.* $unrestricted_{BIC}=-1421.58$; $EDM_{AIC}=17\,551.79$ *v.* $unrestricted_{AIC}=17\,818.76$). Thus, from the model parsimony point of view, EDM seems to fit to the data in the absolute sense; evidence against the null model was very strong (Kass & Raftery, 1995). We then turned to individual parameter estimates.

Table 3 gives the parameter estimates separately for men and women. Bootstrap distributions of parameters were fairly skewed, with heavy tails (probably due to nonlinear constraints that are needed in estimation of the EDM, and may even cause occasional failures in estimation). Hence, we present 90% CIs rather than the usual 95%. For the same reason, the less accurate but more robust percentile interval was used instead of the 'bias corrected and accelerated' interval, where the 'acceleration' estimates involve cubes of all deviations (Efron & Tibshirani, 1993). The parameter estimates allow calculation of the variance decomposition for the measured stochastic process, y [see equations (3), (6) and (7)]. Fig. 2 illustrates the estimated relative proportions of variance for stable trait, cumulative sources and state/error; it shows the proportional long run (infinite time) asymptotes of the respective components. Limiting values are more informative about the underlying population values because the data contain no information about how participants have arrived at the depression value observed at the initial measurement. For women, 32.2% of the variance (90% CI 18.5–54.2) was explained by

Table 3. *Estimated parameters for the linear stochastic differential equation model*

	Parameters for women			Parameters for men		
Parameter	Median	Lower CI	Upper CI	Median	Lower CI	Upper CI
$\mu_{x(0)}$	19.58026	19.17612	20.01371	16.65854	16.19383	17.09344
A	−0.06815	−0.13083	−0.04087	−0.17208	−0.27006	−0.07731
B	1.13487	0.65124	2.30060	2.70028	1.20430	4.27701
Φ_{κ}	0.18501	0.04972	1.26513	1.99846	0.40256	4.90009
$\Phi_{x(0)}$	62.03237	54.85961	69.81074	68.07483	59.01264	79.80700
$\Phi_{\kappa,x(0)}$	3.35781	1.75147	6.91873	8.44254	3.52242	13.61257
G^2	7.31223	4.88665	10.65357	8.15841	3.13279	17.28937
Θ	29.80552	23.69877	34.92791	17.44748	5.91849	25.80175

The lower confidence interval (CI) is the 5th bootstrap percentile from 1000 resamples and the upper CI is the 95th percentile. As in Table 1, the symbols refer to the population mean at the initial measurement ($\mu_{x(0)}$), the drift coefficient (A), long-term population average (b), trait variance in the population (Φ_{κ}), latent population variance at the initial measurement ($\Phi_{x(0)}$), covariance between the initial measurement and the trait component ($\Phi_{\kappa,x(0)}$), defining parameter for the cumulative sources of variance (G^2), and the state and measurement error variance (Θ). The numbers are reported with a high precision to facilitate possible (nonlinear) calculations in future studies.

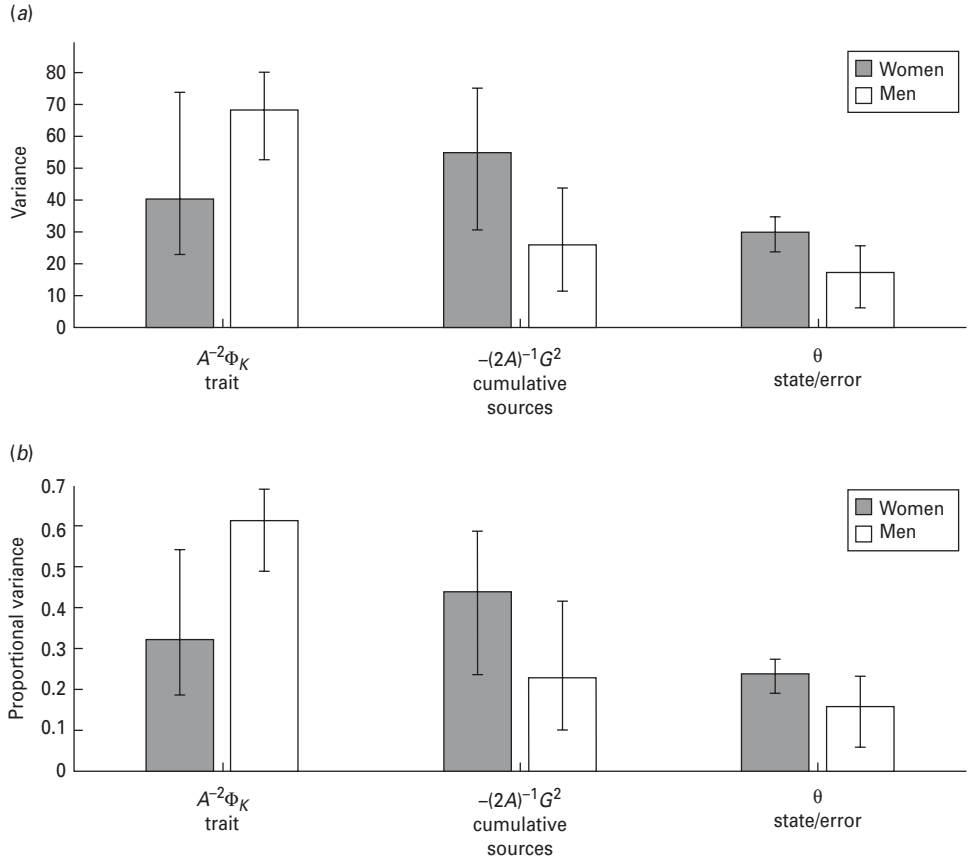

Fig. 2. (*a*) Model-derived time limits of the three sources of variance: trait, cumulative effects and state/measurement error. The infinite time limit is taken because otherwise these quantities depend on the initial measurement, and we wanted to compare them generally. Error bars show 90% bootstrap percentile confidence intervals (CIs). (*b*) Relative proportions of variance among the three model components, with 90% CIs derived from bootstrap replications of the corresponding proportions.

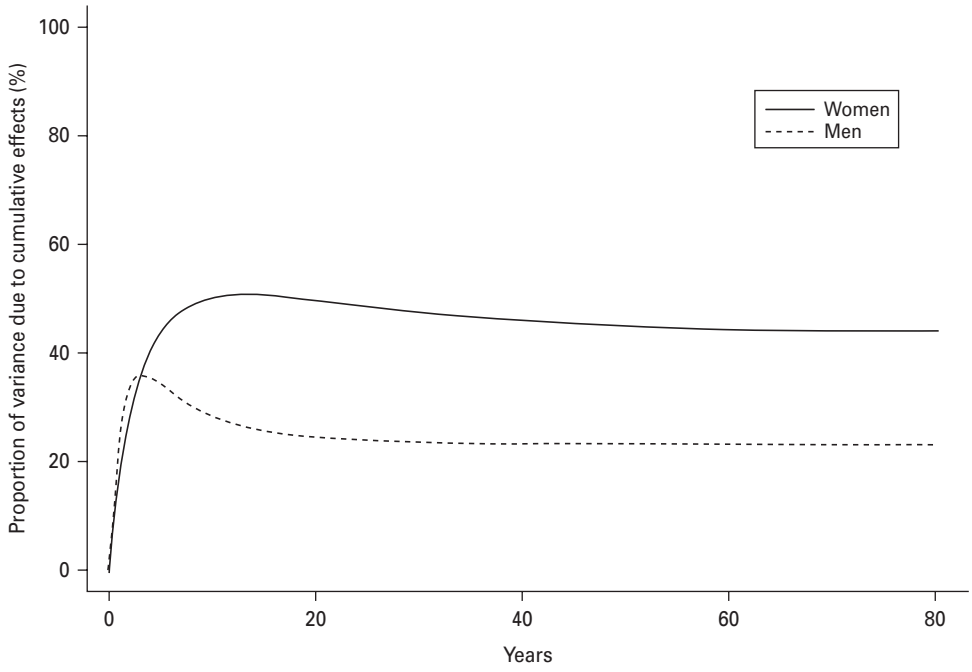

Fig. 3. Proportion of variance due to cumulative effects (%) as opposed to trait and state effects, plotted as a function of time (years).

the stable trait-like component, 43.9% (90% CI 23.6–58.9) by sources that accumulate in time and 23.9% (90% CI 19.1–27.3) by state fluctuation or measurement error. For men, 61.4% (90% CI 48.9–69.2) of variance was due to the stable trait, 23.0% (90% CI 9.9–41.7) to cumulative sources and 15.6% (90% CI 5.6–23.2) to state fluctuations. Precise decomposition between trait and cumulative sources was more difficult to obtain than the state variance, as shown by the CIs.

It is reasonable to ask whether the infinite time approximation corresponds well to variance shares observed in realistic time intervals. Therefore, we report proportional values for variance due to trait, cumulative effects and state, when an amount of time equal to life expectation in high-income countries has passed [i.e. variance decomposition for $x(82.4+t_0)$]. Variance terms dependent on the initial measurement point were excluded from the comparison. For women, 31.8% (90% CI 17.7–54.2) of the remaining variance share was attributed to the stable trait, 43.9% (90% CI 23.6–59.6) to the cumulative effects and 23.5% (90% CI 19.1–27.6) to the state effects. For men, 62.3% (90% CI 48.8–69.2) of the variance was attributed to the stable trait, 23.2% (90% CI 10.0–41.7) to the cumulative effects and 15.8% (90% CI 5.5–23.2) to the state effects. These values correspond very closely to observations in the infinite time limit. Fig. 3 shows how the proportion of variance attributed to cumulative effects first grows as time passes, and then settles near to an asymptote in about 20–40 years.

Finally, we tested the latent common cause formulation of the model, estimated from polychoric correlations. Because of frequent algorithmic failures and a high proportion of large deviations, bootstrap estimates would have varied considerably more than for the sum score, precluding reasonable CI estimates. Medians of 1000 bootstrap resamples for men and women were computed for a qualitative comparison between the latent trait model and the full information modeling of the sum score. The relative variance shares among the trait (17.1% for women, 20.7% for men), cumulative (43.5% for women, 37.5% for men) and state components (39.4% for women, 41.8% for men) replicated the gender tendencies for the sum score with the exception that the state/error component was considerably inflated; recall that the inflation of the error component was expected if the common cause assumption was wrong.

Discussion

This study examined the longitudinal course of depressive symptoms in adulthood, using the Young Finns follow-up data (Raitakari *et al*. 2008). Initially, 15- to 30-year-old participants were followed for 16 years. Four successive measurements were made, with 5-, 4- and 7-year intervals between them. The observed population variance of the course of

depressive symptoms was decomposed into the three main sources: (1) individual differences in stable trait-like depression that may be caused by genetic differences, or by early experiences that determined time-constant levels of depressive symptoms for individuals; (2) individual differences that derive from a continuously accumulating trajectory of small changes, such as negative (or protective) cycles of deteriorating (or improving) mental health that influence the course of depression; and (3) differences due to state fluctuation or measurement error without continuity over time. In men, the stable trait accounted for the majority (61%) of the total variance, followed by cumulative effects (23%) and state fluctuations (16%) (Fig. 2). In women, the cumulative sources were more important than among men and accounted for 44% of the variance, followed by stable individual differences (32%) and state fluctuations (24%). In addition to the differences in the longitudinal course, women had a higher mean level and higher variance of depressive symptoms than men, in all follow-ups (Table 2).

The present data are in agreement with the previous observations that women have higher mean levels and higher variance of depressive symptoms than men (Nolen-Hoeksema & Girgus, 1994; Hankin *et al*. 1998; Hyde *et al*. 2008). The gender difference emerges by ages 13–15 years, that is before the first follow-up in the present data. One model explains the gender difference with women's greater biological (e.g. pubertal hormones), affective (temperamental) and cognitive (e.g. objectified body consciousness) vulnerabilities, which combine with a larger amount of environmental triggers (e.g. role pressures) than for men (Hyde *et al*. 2008). The model emphasizes the role of interactions between many vulnerability factors and stressors in the emerging gender differences. Naturally, women may also continue to have more vulnerability–stressor interactions than men after puberty. Herein, the observed gender differences in the relative contributions of the estimated variance components suggest that men's level of depressive symptoms at a given time point is more a result of stable individual differences; whereas in women, time-dependent accumulating effects are more significant. Therefore, depressive symptoms of women are expected to change more than those of men in adulthood.

Previous studies have rarely decomposed the non-stable variance in depression into a state/error component *versus* a component that develops continuously over time. Here, it was estimated that $<27\%$ of variance is due to state-like fluctuations or measurement error. The rest is accounted for by autoregressive trajectories of depressive symptoms that accumulate over time differently for different participants, or by trait-like depression that stays constant for an individual, with between-individual variation in that constant. The latter share of the between-individual variance is either constitutional or has stabilized before adulthood. The cumulative part must be due to changes in the individual or in the environment that have occurred during the follow-up period of 16 years. Genetic effects can potentially enter the cumulative part only through gene–environment interactions (Brown & Harris, 2008; Caspi *et al*. 2010), preprogrammed lagged effects or epigenetic effects (Zhang & Meaney, 2010), but not as solid constitutional genetic effects. The cumulative proportion of intra-individual variation is not a measurement error, yet keeps changing in time.

In the current research literature on depression, the cumulative source of variation is the least well known among the three components accounting for the longitudinal course of depressive symptoms. Recall that we modeled an individual's time accumulating depression level using integration with respect to Brownian motion (also called the Wiener process). Brownian motion is a random process that is most frequently used to model a time trajectory of an agent or object that is continuously perturbed by many small outside influences (Øksendal, 2003). For example, it is a model for a very small particle immersed in fluid and undergoing movement due to countless tiny collisions with the surrounding moving atoms. Instead of moving atoms, we model effects due to many small external and internal occurrences affecting depression and adding up in time. The fact that women were estimated to have more such occurrences is in line with the multiple pathways model that aims to explain the gender differences in depression (Hyde *et al*. 2008). The time accumulation in a depression score might also reflect 'kindling' or a stress sensitization mechanism (Monroe & Harkness, 2005). A Brownian motion-based model is compatible with the concepts of multi- and equifinality (Cicchetti & Rogosh, 1996) because same starting value of depression can develop to different outcomes at a later time; and different initial values can converge. In effect, unobserved influences may or may not cancel each other out as time passes.

The model of time accumulation that was applied here is closely related to an autoregressive time-series approach that was used in a prior study of children and adolescent depression, along with the trait and state components (Cole & Martin, 2005). However, the present continuous-time model can be more readily compared with studies with different depression assessment-time intervals than the discrete-time autoregressive models (Oud & Jansen, 2000; Oud & Delsing, 2010). Using the parameter estimates in

Table 3, various calculations become possible for depression trajectories, including the expected number of level crossings, and the mean and variance trajectories (Øksendal, 2003; Klenke, 2008).

The findings of the present investigation also touch upon the issue of the theoretical underpinnings of depression. Attempts at modeling in terms of a time-evolving unidimensional latent common cause for depressive symptoms led to high variability of estimates. Nonetheless, and despite the very different technical implementation compared to sum score modeling, the most robust achievable (bootstrap median) estimates replicated the basic finding that the cumulative component plays a greater role for women than for men. In addition, the state/error part of the model was inflated relative to sum score modeling. Difficulties in estimation, and especially the inflation of error terms, are expected consequences if the underlying assumption of unidimensional common cause for symptoms is wrong (see Method). Therefore, although the evaluation of the common cause assumption was not the primary research question here, these observed phenomena are in line with recent evidence indicating that depressive symptoms reflect a causal network rather than unidimensional common cause (Cramer *et al*. 2012). Although problems due to the erroneous unidimensionality assumption are likely to be more prominent in longitudinal modeling, a sensitive cross-sectional measurement-theoretical analysis using a good data set revealed as many as six dimensions in a set of depressive symptom items (Uher *et al*. 2008). If the sum score derives from symptoms forming a causal network, it is pushed and pulled by several separate contributions; in that case, Brownian movement seems an especially fitting model.

Limitations

More measurement points would facilitate better precision for the parameter estimates than that obtained here. Less uncertainty in parameters would directly translate to less uncertainty in the model-derived variance decomposition. Unfortunately, the present estimates had a high variance. The bootstrap estimates can be considered conservative, however, in the sense that they incorporate both the sampling variability and the variability due to algorithmic convergence issues; OpenMx cannot compute the usual sampling theory estimates when nonlinear constraints required by the stochastic differential equation model are used in estimation.

In addition to variability issues, information was not available regarding who (if any) of the participants had received treatment for depression. The participants were drawn from the general population of Finland. In that general population, the prevalence of antidepressant use was estimated to be 5.3% in the year 2000 (Sihvo *et al*. 2008), and rose steadily to 8.9% between 2000 and 2008 (Pulkki-Råback *et al*. 2012). Nevertheless, not all users of antidepressants are depressed (Sihvo *et al*. 2008), and antidepressants seem to have a clear effect only for the severe cases of depression (Kirsch *et al*. 2008). Severe cases were scarcely present in our data as only 1.2% had a BDI-II score in the severe category ($\geqslant$29) in 2008. Therefore, treatment effects may impact the observed time trajectories only slightly.

Conclusions

A large proportion of the individual differences seen in male depressive symptoms are stable through the 16 years of adulthood studied here. They are less stable for women, who show more depression and larger variations in depression than men. For both genders, there is a distinctive part of the between-individual variance that exists due to different time trajectories. When only the presence of depression is modeled, the share of the state fluctuations and measurement error in the total depression variance is often estimated as being large (up to 67%): by contrast, it is unlikely to exceed 27% of the total variance when the longitudinal course of depressive symptoms is taken into account.

Acknowledgments

The Young Finns Study has received financial support from the Academy of Finland, the Social Insurance Institution of Finland, Kuopio, Tampere and Turku University Hospital Medical Funds, the Juho Vainio Foundation, Paavo Nurmi Foundation, Finnish Foundation of Cardiovascular Research and Finnish Cultural Foundation, Sigrid Juselius Foundation, Tampere Tuberculosis Foundation, and Emil Aaltonen Foundation. Expert technical assistance in data management by I. Lisinen and V. Aalto is gratefully acknowledged. Financial support has also been received from the Emil Aaltonen Foundation (M.H.), Ella and Georg Ehrnrooth Foundation (M.H.), Signe and Ane Gyllenberg Foundation (M.H. and L.K.J.), Niilo Helander Foundation (M.H.), the Academy of Finland [project numbers 123621 (L.P.R.) and 258711 (L.K.J.)], Research Foundation of the University of Helsinki (T.R.), and Oskar Öflund Foundation (T.R.).

Declaration of Interest

None.

References

Bartlett MS (1946). On the theoretical specification and sampling properties of autocorrelated time-series. *Supplement to the Journal of the Royal Statistical Society* **8**, 27–41.

Beck AT, Steer RA, Brown GK (1996). *Manual for the Beck Depression Inventory-II*. Psychological Corporation: San Antonio, TX.

Bienvenu OJ, Davydow DS, Kendler KS (2011). Psychiatric 'diseases' versus behavioral disorders and degree of genetic influence. *Psychological Medicine* **41**, 33–40.

Boker S, Neale M, Maes H, Wilde M, Spiegel M, Brick T, Spies J, Estabrook R, Kenny S, Bates T, Mehta P, Fox J (2011). OpenMx: an open source extended structural equation modeling framework. *Psychometrika* **76**, 306–317.

Bollen KA (1989). *Structural Equations with Latent Variables*. John Wiley & Sons, Inc.: New York.

Brown GW, Harris TO (2008). Depression and the serotonin transporter 5-HTTLPR polymorphism: a review and a hypothesis concerning gene–environment interaction. *Journal of Affective Disorders* **111**, 1–12.

Caspi A, Hariri AR, Holmes A, Uher R, Moffitt TE (2010). Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. *American Journal of Psychiatry* **167**, 509–527.

Cicchetti D, Rogosh FA (1996). Equifinality and multifinality in developmental psychopathology. *Development and Psychopathology* **8**, 597–600.

Cole DA, Martin NC (2005). The longitudinal structure of the Children's Depression Inventory: testing a latent trait-state model. *Psychological Assessment* **17**, 144–155.

Cramer AOJ, Borsboom D, Aggen SH, Kendler KS (2012). The pathoplasticity of dysphoric episodes: differential impact of stressful life events on the pattern of depressive symptom inter-correlations. *Psychological Medicine* **42**, 957–965.

Efron B, Tibshirani RJ (1993). *An Introduction to the Bootstrap*. Chapman & Hall/CRC: Boca Raton.

Ekström J (2009). An empirical polychoric correlation. Ph.D. thesis (http://escholarship.org/uc/item/2tw0b313). Accessed 17 April 2012.

Elovainio M, Keltikangas-Järvinen L, Pulkki-Råback L, Kivimäki M, Puttonen S, Räsänen L, Mansikkaniemi K, Viikari L, Raitakari OT (2006). Depressive symptoms and C-reactive protein: the Cardiovascular Risk in Young Finns Study. *Psychological Medicine* **36**, 797–805.

Enders CK (2001). The impact of nonnormality on full information maximum-likelihood estimation for structural equation models with missing data. *Psychological Methods* **6**, 352–370.

Hankin BL, Abramson LY, Moffitt TE, Silva PA, McGee R, Angell KE (1998). Development of depression from preadolescence to young adulthood: emerging gender differences in a 10-year longitudinal study. *Journal of Abnormal Psychology* **107**, 128–140.

Hankin BL, Fraley RC, Lahey BB, Waldman ID (2005). Is depression best viewed as a continuum or discrete category? A taxometric analysis of childhood and adolescent depression in a population-based sample. *Journal of Abnormal Psychology* **114**, 96–108.

Hyde JS, Mezulis AH, Abramson LY (2008). The ABCs of depression: integrating affective, biological, and cognitive models to explain the emergence of the gender difference in depression. *Psychological Review* **115**, 291–313.

Jokela M, Singh-Manoux A, Shipley MJ, Ferrie JE, Gimeno D, Akbaraly TN, Head J, Elovainio M, Marmot MG, Kivimäki M (2011). Natural course of recurrent psychological distress in adulthood. *Journal of Affective Disorders* **130**, 454–461.

Kass RE, Raftery AE (1995). Bayes factors. *Journal of the American Statistical Association* **90**, 773–795.

Kendler KS, Gatz M, Gardner CO, Pedersen NL (2006). Personality and major depression: a Swedish longitudinal population-based twin study. *Archives of General Psychiatry* **63**, 1113–1120.

Kenny DA, Zautra A (1995). The trait-state-error model for multiwave data. *Journal of Consulting and Clinical Psychology* **63**, 52–59.

Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS (2003). The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *Journal of the American Medical Association* **289**, 3095–3105.

Klenke A (2008). *Probability Theory: A Comprehensive Course*. Springer-Verlag: London.

Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT (2008). Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Medicine* **5**, e45.

Mathers CD, Loncar D (2006). Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Medicine* **3**, e442.

Monroe SM, Harkness KL (2005). Life stress, the 'kindling' hypothesis, and the recurrence of depression: considerations from a life stress perspective. *Psychological Review* **112**, 417–445.

Mueller TI, Leon AC, Keller MB, Solomon DA, Endicott J, Coryell W, Warshaw M, Maser JD (1999). Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. *American Journal of Psychiatry* **156**, 1000–1006.

Murray CJL, Lopez AD (1997). Alternative projections of mortality and disability by cause 1990–2020: global burden of disease study. *Lancet* **349**, 1498–1504.

Muthén B, Kaplan D, Hollis M (1987). On structural equation modeling with data that are not missing completely at random. *Psychometrika* **52**, 431–462.

Nolen-Hoeksema S, Girgus JS (1994). The emergence of gender differences in depression during adolescence. *Psychological Bulletin* **115**, 424–443.

Øksendal BK (2003). *Stochastic Differential Equations: An Introduction with Applications*. Springer-Verlag: Berlin.

Oud JHL, Delsing MJMH (2010). Continuous time modeling of panel data by means of SEM. In *Longitudinal Research with Latent Variables* (ed. K. Montfort, J. Oud and A. Satorra), pp. 201–244. Springer-Verlag: Berlin.

Oud JHL, Jansen RARG (2000). Continuous time state space modeling of panel data by means of SEM. *Psychometrika* **65**, 199–215.

Pulkki-Råback L, Kivimäki M, Ahola K, Joutsenniemi K, Elovainio M, Rossi H, Puttonen S, Koskinen S, Isometsä E, Lönnqvist J, Virtanen M (2012). Living alone and antidepressant medication use: a prospective study in a working-age population. *BMC Public Health*, **12**, 236.

Raitakari OT, Juonala M, Rönnemaa T, Keltikangas-Järvinen L, Räsänen L, Pietikäinen M, Hutri-Kähönen N, Taittonen L, Jokinen E, Marniemi J, Jula A, Telama R, Kähönen M, Lehtimäki T, Åkerblom HK, Viikari JSA (2008). Cohort profile: the Cardiovascular Risk in Young Finns study. *International Journal of Epidemiology* **37**, 1220–1226.

Sihvo S, Isometsä E, Kiviruusu O, Hämäläinen J, Suvisaari J, Perälä J, Pirkola S, Saarni S, Lönnqvist J (2008). Antidepressant utilisation patterns and determinants of short-term and non-psychiatric use in the Finnish general adult population. *Journal of Affective Disorders* **110**, 94–105.

Solomon A, Haaga DAF, Arnow BA (2001). Is clinical depression distinct from subthreshold depressive symptoms? A review of the continuity issue in depression research. *Journal of Nervous and Mental Disease* **189**, 498–506.

Sullivan PF, Neale MC, Kendler KS (2000). Genetic epidemiology of major depression: review and meta-analysis. *American Journal of Psychiatry* **157**, 1552–1562.

Uher R, Farmer A, Maier W, Rietschel M, Hauser J, Marusic A, Mors O, Elkin A, Williamson RJ, Schmael C, Henigsberg J, Perez J, Mendlewicz J, Janzing JGE, Zobel A, Skibinska M, Kozel D, Stamp AS, Bajs M, Placentino A, Barreto M, McGuffin P, Aitchison KJ (2008). Measuring depression: comparison and integration of three scales in the GENDEP study. *Psychological Medicine* **38**, 289–300.

Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu HG, Joyce PR, Karam EG, Lee CK, Leelouch J, Lépine JP, Newman SC, Rubio-Stibec M, Wells JE, Wickramaratne PJ, Wittchen H, Yeh EK (1996). Cross-national epidemiology of major depression and bipolar disorder. *Journal of the American Medical Association* **276**, 293–299.

Zhang T, Meaney MJ (2010). Epigenetics and the environmental regulation of the genome and its function. *Annual Review of Psychology* **61**, 439–466.