Data supplement for Frank et al., Association Between Systemic Inflammation and Individual Symptoms of Depression: A Pooled Analysis of 15 Population-Based Cohort Studies. Am J Psychiatry (doi: 10.1176/appi.ajp.2021.20121776)

## CONTENTS

## Appendix 1: Description of the Included Cohort Studies With Individual-Participant Data

**Costa Rican Longevity and Healthy Aging Study (CRELES)(1)**
The Costa Rican Longevity and Healthy Aging Study (CRELES) is a nationally representative, longitudinal survey which was established in 2005 to explore the health and lifecourse experiences of 2,827 Costa Rican adults aged ≥60 years. Baseline household interviews were conducted between 2004 and 2006, with two-year follow-up interviews in 2007 and 2009. CRELES has collected data on variety of biological, psychological, and sociological measures to assess the causes and consequences of health-related outcomes. Plasma C-reactive protein (CRP) was collected at baseline (2005) from fasting blood samples. Depressive symptoms were measured at baseline and two years later, using the Geriatric Depression Scale.(2) Written informed consent was obtained prior to the study. Ethical approval was granted by the Ethical Science Committee of the University of Costa Rica (http://ccp.ucr.ac.cr/creles).

**English Longitudinal Study of Ageing (ELSA)(3)**
The English Longitudinal Study of Ageing (ELSA) is an ongoing, nationally representative, longitudinal, population study of adults aged ≥50 years living in England. ELSA was established in 2002. Since then, participants have been followed up biannually. Thus far, there have been 9 waves of data collection in ELSA. For the present study, baseline levels of plasma CRP were measured at wave 6 (2012/13) from fasting blood samples. Depressive symptoms were ascertained at baseline and wave 8 (2016/17), using the 8-item version of the Centre for Epidemiological Studies Depression Scale.(4) Written informed consent was obtained at each data collection wave. Ethical approval was obtained from the London Multi-Centre Research Ethics Committee (https://www.elsa-project.ac.uk).

**Midlife in the United States (MIDUS)(5)**
The Midlife in the United States (MIDUS) study is a nationally representative, longitudinal survey of health and well-being of non-institutionalised, English-speaking adults aged 25 - 74 years in the United States. Participant selection was based on random digit dialling conducted between 1995 and 1996. The total original sample (n=7108) includes the main respondents (n=3487), their siblings (n=950), an oversample from five metropolitan areas in the United States (n=757), and a twin subsample (n=1914). The collection of psychosocial data was primarily based on telephone interviews and questionnaires distributed via email to study participants. A follow-up study of the cohort was conducted between 2004-2009 (MIDUS II), which included the *Biomarker Project*. Biological and neurological data of 1,255 respondents was collected from two distinct subsamples: the longitudinal survey sample of 1,054 participants, and the Milwaukee sample of 201 participants who participated in the baseline MIDUS Milwaukee study initiated in 2005. In the present multi-cohort study, we included individuals with complete data on two inflammatory markers (interleukin-6 [IL-6] or CRP), covariates, and depressive symptoms. Serum CRP and IL-6 measures were obtained from fasting blood samples. Depressive symptoms were assessed using the 20-item CES-D(4) questionnaire (http://www.midus.wisc.edu).

**Whitehall II(6)**
The Whitehall II study is a prospective cohort study comprising 10,308 men and woman aged 35 to 55 years, who were recruited from 20 London-based civil service departments in 1985. To date, there have been 11 phases of data collection. Since 1985, data has been collected every two to five years, using a wide range of self-report measures and clinical assessments to explore social, psychological, biological and behavioural factors determinants of health, illness, and social inequalities. In the present analyses, we used measures of fasting serum CRP and IL-6 at wave 7 (2002/04, baseline). Depressive symptoms were assessed at baseline and three years later (2007/2009) using the 20-item version of the CES-D.(4) Written informed consent from participants was obtained at each wave of data collection. Ethical approval has been granted by the University College London Medical School Committee on the Ethics of Human Research (https://www.ucl.ac.uk/iehc/research/epidemiology-public-health/research).

**Understanding Society (UKHLS)(7)**
Understanding Society, the UK Household Longitudinal Study (UKHLS), is a large-scale prospective cohort study that has followed people from over 40,000 households throughout the UK. It captures a representative sample of people of all age ages and ethnicities. UKHLS was launched in 2009, building on and including data from the British Household Panel Survey (BHPS). To date, there have been 8 waves of data collection. UKHLS has collected a variety of biopsychosocial measures, including information about participants' social and economic circumstances, psychological well-being, attitudes and beliefs, physical illness, and genetics. Psychosocial data and general health information were collected via annual face-to-face interviews and a self-completion online survey. Biomedical data

(e.g., weight, height, blood samples) were collected during the nurse health assessments. Serum levels of CRP were measured at wave 2 (2010-12, baseline) from non-fasting blood samples. Depressive symptoms were ascertained at wave 2 and 3 (2011-13), using the 12-item General Health Questionnaire (GHQ-12).(8) Written informed consent was obtained at each wave of data collection. UKHLS has been granted ethical approval by the University of Essex Ethics Committee; approval for the nurse health assessment was granted by the National Research Ethics Service approved the nurse health assessment (https://www.understandingsociety.ac.uk).

**National Health and Nutrition Survey (NHANES) – 2005/06, 2007/08, 2009/10, 2015/16, and 2017/18(9)**
The National Health and Nutrition Examination Survey (NHANES) is a series of studies designed to ascertain nationally representative information on health and the nutritional status of children and adults in the United States. NHANES was initially established by the National Centre for Health Statistics (NCHS) in the 1960s, and became continuous in 1999, collecting data from a nationally representative sample of approximately 5000 people each year. For the present analyses, we focused on 5 independent NHANES cohorts with complete data on CRP, covariates, and depressive symptoms from 2005/06, 2007/08, 2009/10, 2015/16, and 2017/18. In each cohort, measures on systemic inflammation were based on serum high-sensitivity CRP collected from participants' fasting blood samples. Depressive symptoms were measured using 9 items of the Patient Health Questionnaire (PHQ-9).(10) Written informed consent was provided prior to each study. Ethical approval was granted by the NCHS Research Ethics Review Board (ERB) (https://wwwn.cdc.gov/Nchs/Nhanes/2009-2010/CRP_F.htm).

**Social Environment and Biomarkers of Aging Study (SEBAS)(11)**
The Social Environment and Biomarkers of Ageing Study (SEBAS) is a nationally representative, longitudinal survey of both middle-aged and older adults living in Taiwan. The first wave of data collection was conducted in 2000 and participants were followed up in 2006. SEBAS provides a rich variety of social, environmental, psychological and biological data. Baseline measures of systemic inflammation included fasting serum samples of CRP and IL-6. Depressive symptoms were assessed at baseline and six years later, using a 10-item version of the CES-D.(4) SEBAS was approved by ethical committees in Taiwan, at Georgetown University, and at Princeton University. Written informed consent was obtained prior to the study. More information about the Social Environment and Biomarkers of Aging Study can be found at the Georgetown University Centre for Populations and Health website (https://cph.georgetown.edu/research/taiwan/).

**Health and Retirement Study (HRS)(12)**
The Health and Retirement Study (HRS) is a nationally representative, longitudinal, biannual, population-based cohort study of approximately 20,000 people aged ≥51 years in the United States. HRS was launched in 1992 by the University of Michigan and is funded by the National Institute on Aging. Since then, HRS has collected information about income, work, assets, pension plans, health insurance, disability, physical health and functioning, mental health, cognitive functioning, and health care expenditures (https://hrs.isr.umich.edu/about). CRP levels (dried blood spots) were collected after face-to-face interviews and subsequently analysed using an enzyme-linked immunosorbent assay. The 20-item version of the CES-D(4) to assess depressive symptoms. Participants provided written informed consent prior to the study, and ethical approval was granted by the University of Michigan Institutional Review Board.

**The Irish Longitudinal Study of Ageing (TILDA)(13)**
The Irish Longitudinal Study of Ageing (TILDA) is a prospective cohort study exploring the economic, social, age-, and health-related experiences of community-dwelling adults aged ≥50 years in the Republic of Ireland. The first wave of data collection was conducted between October 2009 and July 2011 in a representative sample of 8,175 adults. Sampling was based on a three-stage selection process using the Geodirectory (i.e., an extensive list of all addresses registered in Ireland) as a sampling frame. First, subdivisions of electoral districts stratified by socio-economic status, age, and geographical location were used as the primary sampling unit. Second, a random probability sample of 40 addresses was selected from within each cluster, resulting in an initial sample of 25,600 addresses. The third stage involved asking all adults aged ≥50 years of selected households to participate. Participants completed a computer assisted personal interview (CAPI) and a self-administered questionnaire and were then invited to attend one of two test centres for the collection of physical samples and bio-medical measures. High-sensitivity CRP was measured in non-fasting blood plasma using a third-generation particle enhanced immunoturbidimetric assay. Depressive symptoms were assessed using the 20-item version of the CES-D.(4) All participants provided written informed consent prior to the study. Ethical approval was granted by the Research Ethics Committee of Trinity College Dublin (https://tilda.tcd.ie).

**The National Social Life, Health, and Aging Project (NSHAP)(14)**
The National Social Life, Health, and Aging Project (NSHAP) is a nationally representative, longitudinal cohort study of community-dwelling older adults in the United States. NSHAP aims to examine the interactions among and relationships between physical health and illness, mental health, medication use, health behaviours, cognitive functioning, social relationships, and sexuality. Thus far, there have been three waves of data collection. The first wave of NSHAP was conducted between 2005 and 2006 by NORC and Principal Investigators at the University of Chicago, completing more than 3,000 interviews with a sample of adults born between 1920 and 1947 (aged 57 to 85 at the time of Wave 1 interview). Approximately 3,400 interviews were conducted for wave 1 with wave 2 respondents, wave 1 non-interviewed respondents, and their spouses or cohabiting romantic partners between 2010 and 2011. Wave 3 was conducted from September 2015 to November 2016, including 2,409 wave 2 respondents, and a refresher cohort consisting of adults born between 1948 and 1965 together with their spouses or romantic partners. A total 4,777 respondents were interviewed in Wave 3. Data on high-sensitivity CRP was derived from dried blood spots collected at participants' homes during the interview. Depressive symptoms were ascertained from the 11 items of the CES-D.(4) All participants gave their written informed consent prior to participation in the study. The study protocol was approved by NORC, the Institutional Review Boards of the University of Chicago, and the University of Arizona.

**The Mexican Health and Aging Study (MHAS)(15)**
The Mexican Health and Aging Study (MHAS) is a nationally representative, longitudinal cohort study of adults aged ≥50 years living in both urban and rural areas in Mexico. MHAS was designed to explore health and ageing-related biopsychosocial mechanisms and outcomes. To date, five waves of data collection have been conducted; a baseline wave of adults born in 1951 or earlier was conducted in 2001 with follow-up interviews held in 2003, 2012, 2015, and 2018. Data on biomarkers were collected from 2012 onwards, including serum levels of high-sensitivity CRP obtained from dried blood spots. Depressive symptoms were ascertained from 9-items of the CES-D.(4) All participants provided written informed consent prior to each wave of data collection. Ethical approval for MHAS study protocols and instruments were granted by the Institutional Review Board or Ethics Committee of the University of Texas Medical Branch, the Instituto Nacional de Estadistica y Geografia (INEGI) in Mexico, and the Instituto Nacional de Salud Publica (INSP) in Mexico (http://www.mhasweb.org).

**FIGURE S1. Selection of studies for individual-participant pooled analysis of the association between systemic inflammation and individual symptoms of depression**

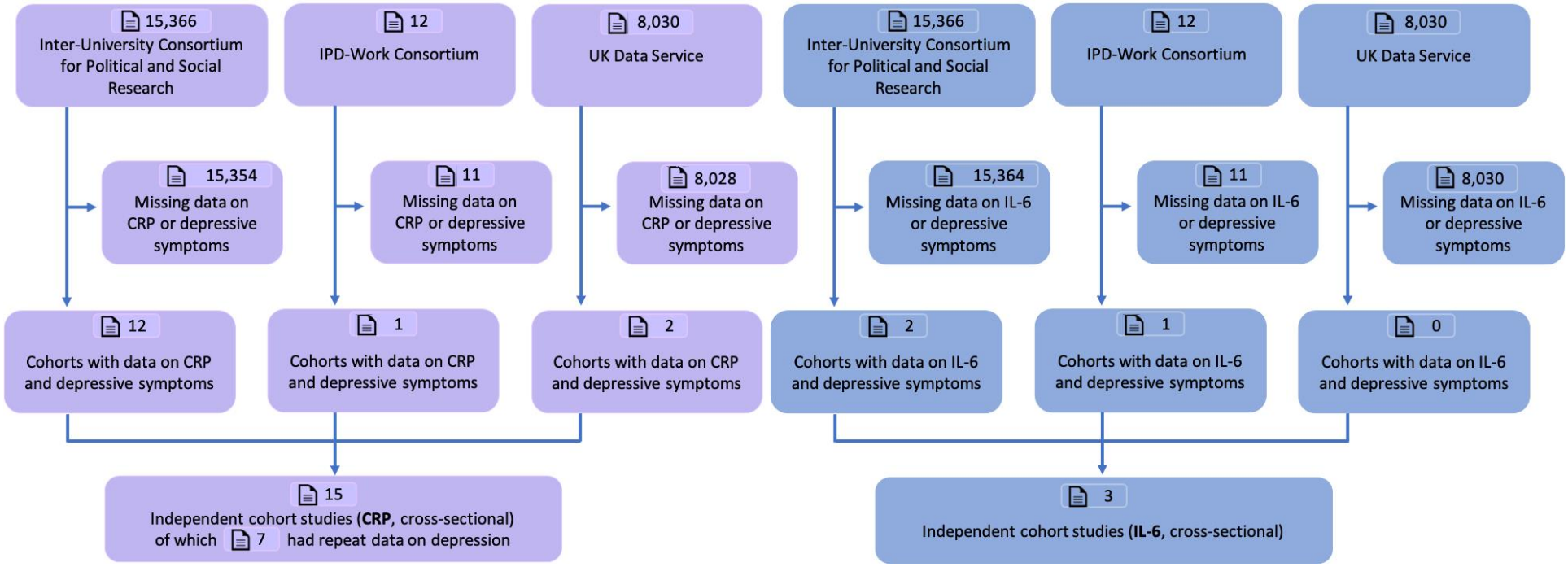

**TABLE S1. Method of exposure (C-reactive protein) and outcome (depressive symptoms) ascertainment**

| Study | Method of CRP ascertainment | Time interval blood collection and measurement of depressive symptoms at baseline | Method of depression symptoms ascertainment | Cut-off depression measures | Prevalence |
|---|---|---|---|---|---|
| **SEBAS** | Serum (fasting) | 24 days (mean lag) | Centre for Epidemiological Studies Depression Scale | ≥ 10 | 17.61% |
| **MHAS** | Dried blood spot | Same day | Centre for Epidemiological Studies Depression Scale | ≥ 4 | 36.65% |
| **MIDUS** | Serum (fasting) | 1 day | Centre for Epidemiological Studies Depression Scale | ≥ 16 | 13.17% |
| **CRELES** | Plasma (fasting) | Same day | Geriatric Depression Scale | ≥ 10 | 9.95% |
| **NSHAP** | Dried blood spots | Same day | Centre for Epidemiological Studies Depression Scale | ≥ 9 | 24.07% |
| **NHANES 2005** | Serum (fasting) | Same day | Depression Screener Questionnaire | ≥ 10 | 6.10% |
| **NHANES 2007** | Serum (fasting) | Same day | Depression Screener Questionnaire | ≥ 10 | 9.53% |
| **NHANES 2009** | Serum (fasting) | Same day | Depression Screener Questionnaire | ≥ 10 | 9.42% |
| **NHANES 2015** | Serum (fasting) | Same day | Depression Screener Questionnaire | ≥ 10 | 8.14% |
| **NHANES 2017** | Serum (fasting) | Same day | Depression Screener Questionnaire | ≥ 10 | 8.65% |
| **Whitehall II** | Serum (fasting) | 14 days (mean lag) | Centre for Epidemiological Studies Depression Scale (20-item version) | ≥ 16 | 15.10% |
| **TILDA** | Plasma (non-fasting) | ≥ 1 week | Centre for Epidemiological Studies Depression Scale | ≥ 16 | 8.23% |
| **ELSA** | Plasma (fasting) | 2 -6 weeks | Centre for Epidemiological Studies Depression Scale (8-item version) | ≥ 4 | 11.31% |
| **UKHLS** | Serum (non-fasting) | 5 months | General Health Questionnaire | ≥ 4 | 16.90% |
| **HRS** | Dried blood spots | No date | Centre for Epidemiological Studies Depression Scale | ≥ 4 | 14.56% |
| **Total** | | | | | **13.96%** |

**TABLE S2. Method of exposure ascertainment (interleukin-6)**

| Study | Method of IL-6 ascertainment | Time of blood collection | Fasting status | Analytical method |
|---|---|---|---|---|
| SEBAS | Serum | Morning | Fasting | High-sensitivity enzyme-linked immunosorbent assay (ELISA) |
| MIDUS | Serum | Morning | Fasting | High-sensitivity enzyme-linked immunosorbent assay (ELISA) |
| WHII | Serum | Morning | Fasting | High-sensitivity enzyme-linked immunosorbent assay (ELISA) |

## TABLE S3. Study-specific measures of adverse childhood experiences (ACEs)

| | Cohorts | MHAS | ELSA | CRELES | WHII | HRS | NSHAP | MIDUS |
|---|---|---|---|---|---|---|---|---|
| Adverse childhood experiences | 1 | Serious health problems | Ever lived in children's home or with foster parents | Poverty | Hospitalization for four or more weeks | Physical abuse by a parent | Family life happy growing up | Emotional abuse |
| | 2 | Lived with grandparents | Separation from mother for ≥6 months at age ≤16 years | Health Problems | Parental divorce | Parents' drinking/drug use caused problems | Family well off from age 6-16 | Physical abuse |
| | 3 | Had typhoid fever | Victim of serious physical attack/assault at age ≤16 years | Tuberculosis | Unintentional parental unemployment | Repeating a school year | Lived with both parents from age 6-16 | Sexgual abuse |
| | 4 | Had blow to head | Victim of sexual assault at age ≤16 years | Rheumatic fever | Parental mental illness/problematic alcohol consumption | | Health status from age 6-16 | Emotional neglect |
| | 5 | Had tuberculosis | Physically abusive parents at age <16 years | Poliomyelitis | Physical abuse by someone close | | Experienced violent event from age 6-16 | Physical neglegt |
| | 6 | Had rheumatic fever | Parents with substance abuse/mental health problems at age <16 years | Malaria | Exposure to frequent parental arguments or fights | | Witnessed violent event from age 6-16 | |
| | 7 | Had polio | Parents argued or fought very often at age <16 years | Asthma | Orphanage/children's home | | | |
| | 8 | Health compared to other children | Serious illness <16 years | No bathroom | | | | |
| | 9 | Had no toilet inside home | Loss of parent <16 years | No shoes | | | | |
| | 10 | Went hungry to bed | Foster care <16 years | No electircity | | | | |
| | 11 | No shoes | | | | | | |
| | 12 | Dropped out of school | | | | | | |
| | 13 | Family slept in same room where food prepared | | | | | | |
| | 14 | Family received financial assistance | | | | | | |

## Appendix 2. Study Characteristics

## TABLE S4. Study characteristics

| Study | Baseline (year) | Country | Number of participants | Number (%) of women | Mean age at baseline (years) | Geometric mean CRP (mg/L) [mean (CI)] | Method of depression symptoms ascertainment | Number of symptoms by domain (physical/cognitive/emotional/self-perception/self-harm) ** |
|---|---|---|---|---|---|---|---|---|
| **CRP COHORTS** | | | | | | | | |
| SEBAS | 2000 | Taiwan | 602 | 263 (43.7%) | 65.9 | 0.74 (0.57 - 0.97) | Centre for Epidemiological Studies Depression Scale | 4/1/1/0/0 |
| MHAS * | 2012 | Mexico | 865 | 527 (60.9%) | 54.8 | 0.96 (0.90 - 1.03) | Centre for Epidemiological Studies Depression Scale | 3/0/5/0/0 |
| MIDUS | 2004-2009 | USA | 949 | 509 (53.6%) | 45.8 | 0.74 (0.67 - 0.80) | Centre for Epidemiological Studies Depression Scale | 5/4/7/4/0 |
| CRELES | 2005 | Costa Rica | 1186 | 662 (55.8%) | 71.9 | 1.27 (1.24 - 1.30) | Geriatric Depression Scale | 1/1/2/0/0 |
| NSHAP * | 2005-2006 | USA | 1807 | 934 (51.7%) | 69.3 | 0.82 (0.77 - 0.87) | Centre for Epidemiological Studies Depression Scale | 4/1/5/1/0 |
| NHANES 2005 | 2005-2006 | USA | 3933 | 2037 (51.8%) | 47.9 | 1.10 (1.07 - 1.14) | Depression Screener Questionnaire | 4/2/1/1/1 |
| Whitehall II * | 2002-2004 | UK | 4133 | 1123 (27.2%) | 60.8 | 0.64 (0.62 - 0.67) | Centre for Epidemiological Studies Depression Scale | 5/4/7/4/0 |
| NHANES 2017 | 2017-2018 | USA | 4325 | 2206 (51.0%) | 51.2 | 0.87 (0.84 - 0.90) | Depression Screener Questionnaire | 4/2/1/1/1 |
| NHANES 2015 | 2015-2016 | USA | 4497 | 2309 (51.4%) | 49.7 | 1.03 (1.00 - 1.06) | Depression Screener Questionnaire | 4/2/1/1/1 |
| TILDA * | 2009-2011 | Ireland | 4704 | 2590 (55.1%) | 62.1 | 0.73 (0.70 - 0.76) | Centre for Epidemiological Studies Depression Scale | 5/4/7/4/0 |
| NHANES 2007 | 2007-2008 | USA | 4751 | 2404 (50.6%) | 50.4 | 1.02 (1.00 - 1.05) | Depression Screener Questionnaire | 4/2/1/1/1 |
| NHANES 2009 | 2009-2010 | USA | 4914 | 2474 (50.4%) | 49.3 | 1.00 (0.97 - 1.02) | Depression Screener Questionnaire | 4/2/1/1/1 |
| ELSA * | 2012-2013 | UK | 5490 | 3027 (55.1%) | 66.8 | 0.78 (0.76 - 0.80) | Centre for Epidemiological Studies Depression Scale | 3/0/5/0/0 |
| UKHLS * | 2010-2012 | UK | 5615 | 3121 (55.6%) | 53 | 0.81 (0.79 - 0.84) | General Health Questionnaire | 1/1/3/0/0 |
| HRS * | 2006-2008 | USA | 8580 | 5040 (58.7%) | 68.3 | 0.90 (0.88 - 0.92) | Centre for Epidemiological Studies Depression Scale | 3/1/5/0/0 |
| **Total** | | | **56351** | **29226 (51.5%)** | **57.8 (12.0)** | **0.89 (0.85 - 0.94)** | | |

*Continues…*

***Table S4* (*continued*)**

| Study | Baseline (year) | Country | Number of participants | Number (%) of women | Mean age at baseline (years) | Geometric mean CRP (pg/mL) [mean (CI)] | Method of depression symptoms ascertainment | Number of symptoms by domain (physical/cognitive/emotional/self-perception/self-harm) ** |
|---|---|---|---|---|---|---|---|---|
| **IL-6 COHORTS** | | | | | | | | |
| SEBAS | 2000 | Taiwan | 600 | 261 (43.5%) | 66 | 1.01 (0.96 - 1.06) | Centre for Epidemiological Studies Depression Scale | 4/1/1/0/0 |
| MIDUS | 2004-2009 | USA | 953 | 511 (53.6%) | 45.8 | 0.65 (0.61 - 0.70) | Centre for Epidemiological Studies Depression Scale | 5/4/7/4/0 |
| Whitehall II | 2002-2004 | UK | 3820 | 1005 (26.3%) | 60.6 | 0.55 (0.54 - 0.57) | Centre for Epidemiological Studies Depression Scale | 5/4/7/4/0 |
| **Total** | | | **5373** | **1777 (41.1%)** | **57.5** | **0.74 (0.70 - 0.78)** | | |

* Studies with repeated measures of depression symptoms

** Physical symptoms / Cognitive symptoms / Emotional symptoms / Symptoms of self-perception / Self-harm symptoms

**TABLE S5. Study characteristics of individuals with high CRP and high levels of the identified symptoms versus other study members**

| | High CRP (≥ 3mg/L) & high levels of identified symptoms (top tertile) | Others | p-value |
|---|---|---|---|
| | **N = 3,587** | **N= 52,764** | |
| **Age** | 59.66 (15.3) | 57.53 (16.1) | < 0.001 |
| **Sex** | | | < 0.001 |
| *Men* | 33.65% | 49.12% | |
| *Women* | 66.35% | 50.88% | |
| **Education** | | | < 0.001 |
| *None/Elementary* | 27.43% | 20.56% | |
| *Secondary* | 47.87% | 43.53% | |
| *Tertiary* | 24.70% | 35.91% | |
| **Smoking** | | | < 0.001 |
| *Yes* | 32.14% | 28.11% | |
| *No* | 67.86% | 71.89% | |
| **Physically inactive** | | | < 0.001 |
| *Yes* | 58.91% | 34.54% | |
| *No* | 41.09% | 65.46% | |
| **Alcohol** | | | < 0.001 |
| *None/low* | 61.40% | 39.26% | |
| *Moderate* | 31.89% | 48.92% | |
| *High* | 6.71% | 11.82% | |
| **Body mass index** | 32.37 (7.8) | 28.27 (5.8) | < 0.001 |
| **Systolic blood pressure** | 129.70 (20.23) | 128.83 (19.3) | 0.001 |
| **Diastolic blood pressure** | 75.24 (13.6) | 74.48 (12.7) | < 0.001 |
| **Diabetes** | | | < 0.001 |
| *Yes* | 24.78% | 10.93% | |
| *No* | 75.22% | 89.07% | |
| **Cancer** | | | < 0.001 |
| *Yes* | 14.08% | 9.46% | |
| *No* | 85.92% | 90.54% | |
| **CHD** | | | < 0.001 |
| *Yes* | 18.34% | 7.63% | |
| *No* | 81.66% | 92.37% | |
| **Stroke** | | | < 0.001 |
| *Yes* | 7.75% | 3.50% | |
| *No* | 92.25% | 96.50% | |

Note: Number (percentage) and mean (standard deviation).

**TABLE S6. Study characteristics of individuals with high CRP and high levels of the identified symptoms versus other study members among people with overall elevated levels of depressive symptoms**

| | High CRP (≥ 3mg/L) & high levels of identified symptoms (top tertile) | Others | p-value |
|---|---|---|---|
| | **N = 1,963** | **N= 4,851** | |
| **Age** | 58.26 (14.74) | 57.70 (15.15) | 0.162 |
| **Sex** | | | < 0.001 |
| *Men* | 30.92% | 39.72% | |
| *Women* | 69.08% | 60.28% | |
| **Education** | | | 0.271 |
| *None/Elementary* | 31.89% | 30.10% | |
| *Secondary* | 44.22% | 44.60% | |
| *Tertiary* | 23.89% | 25.30% | |
| **Smoking** | | | 0.702 |
| *Yes* | 36.12% | 36.61% | |
| *No* | 63.88% | 63.39% | |
| **Physically inactive** | | | < 0.001 |
| *Yes* | 61.49% | 42.75% | |
| *No* | 38.51% | 57.25% | |
| **Alcohol** | | | < 0.001 |
| *None/low* | 62.21% | 44.84% | |
| *Moderate* | 30.21% | 40.34% | |
| *High* | 7.58% | 14.82% | |
| **Body mass index** | 32.58 (8.08) | 28.14 (5.88) | < 0.001 |
| **Systolic blood pressure** | 129.16 (20.1) | 128.11 (19.27) | 0.043 |
| **Diastolic blood pressure** | 75.75 ( 13.25) | 75.27 (12.31) | 0.157 |
| **Diabetes** | | | < 0.001 |
| *Yes* | 25.06% | 13.75% | |
| *No* | 74.94% | 86.25% | |
| **Cancer** | | | < 0.001 |
| *Yes* | 12.53% | 9.48% | |
| *No* | 87.47% | 90.52% | |
| **CHD** | | | < 0.001 |
| *Yes* | 16.96% | 10.37% | |
| *No* | 83.04% | 89.63% | |
| **Stroke** | | | 0.002 |
| *Yes* | 8.00% | 5.92% | |
| *No* | 92.00% | 94.08% | |

Note: Number (percentage) and mean (standard deviation).

## Appendix 3. Study Specific Estimates for Random-Effect Meta-Analyses of C-Reactive Protein and Individual Depression

### FIGURE S2a. Random-effects meta-analysis of the cross-sectional association between C-reactive protein and individual depression symptoms (adjusted for age & sex)

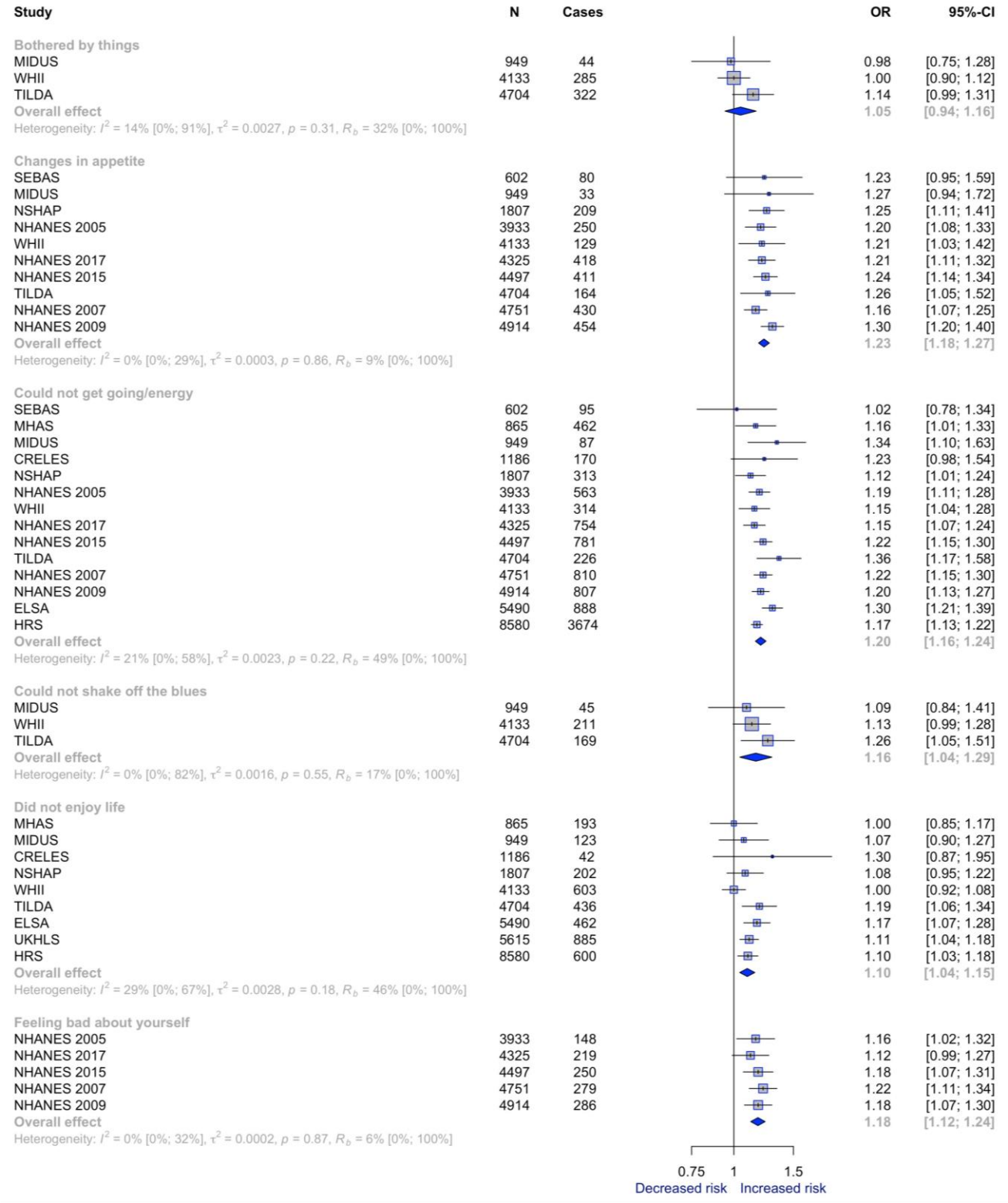


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***Figure S2a (continued)***

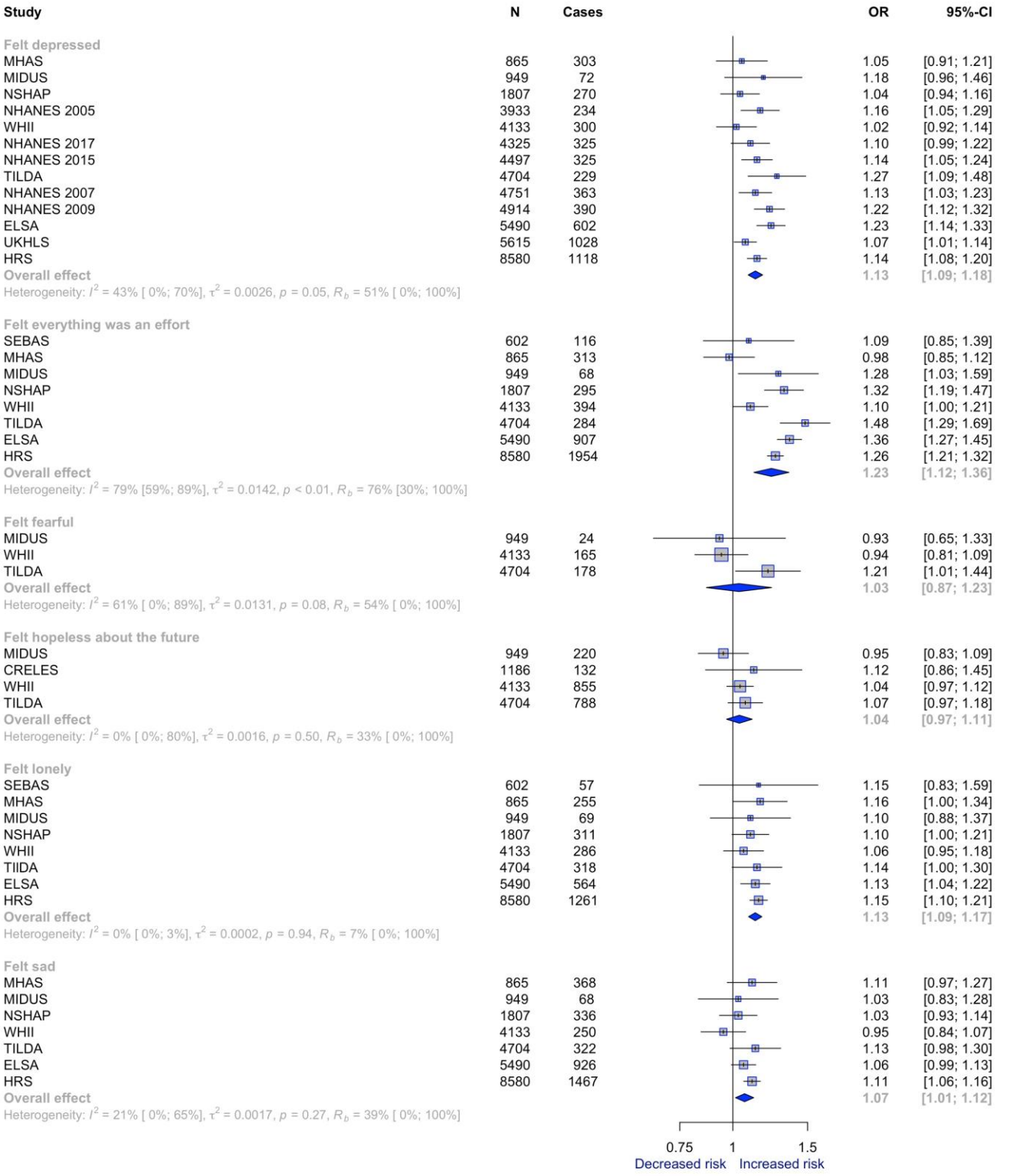


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***Figure S2a (continued)***

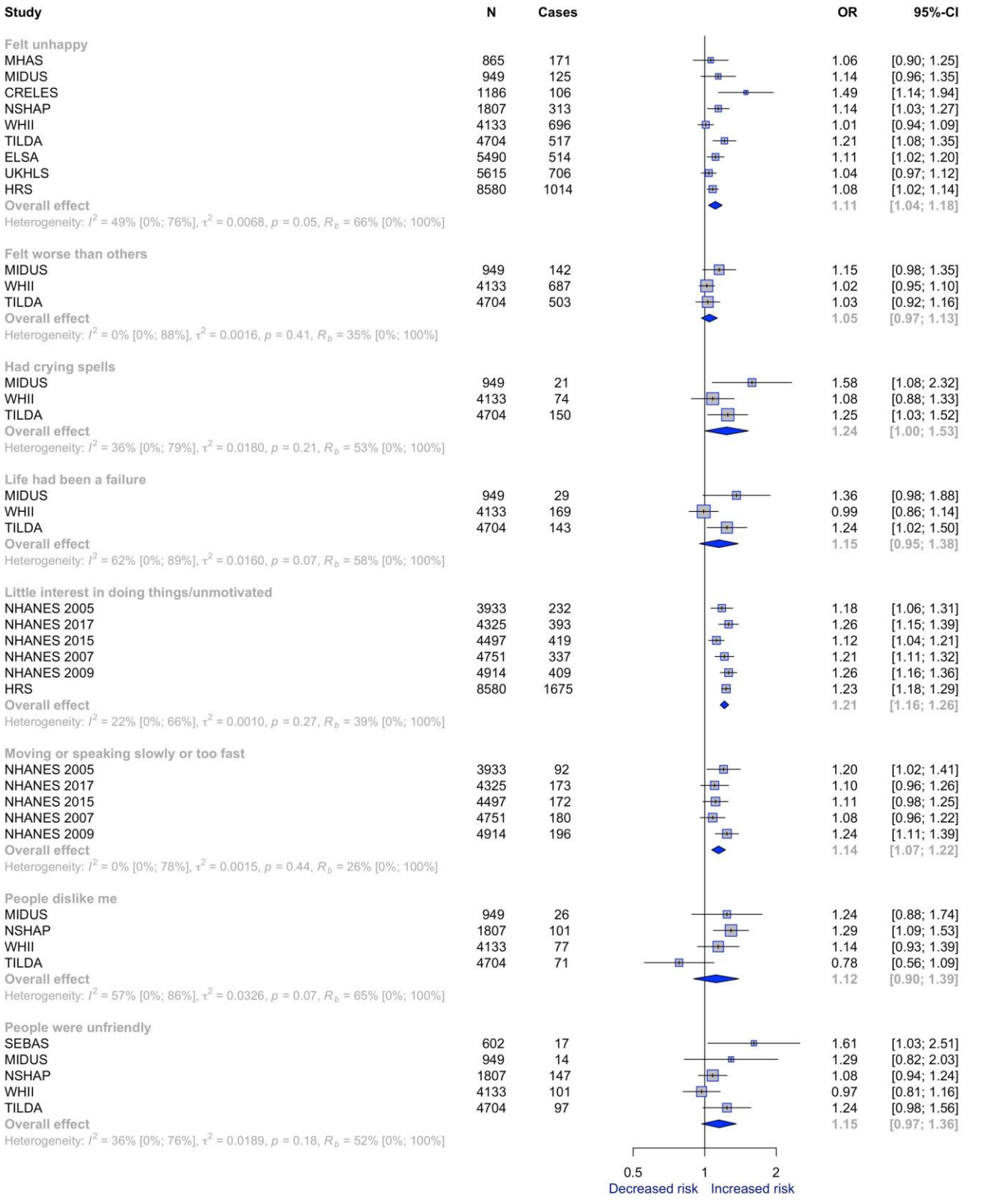


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***Figure S2a (continued)***

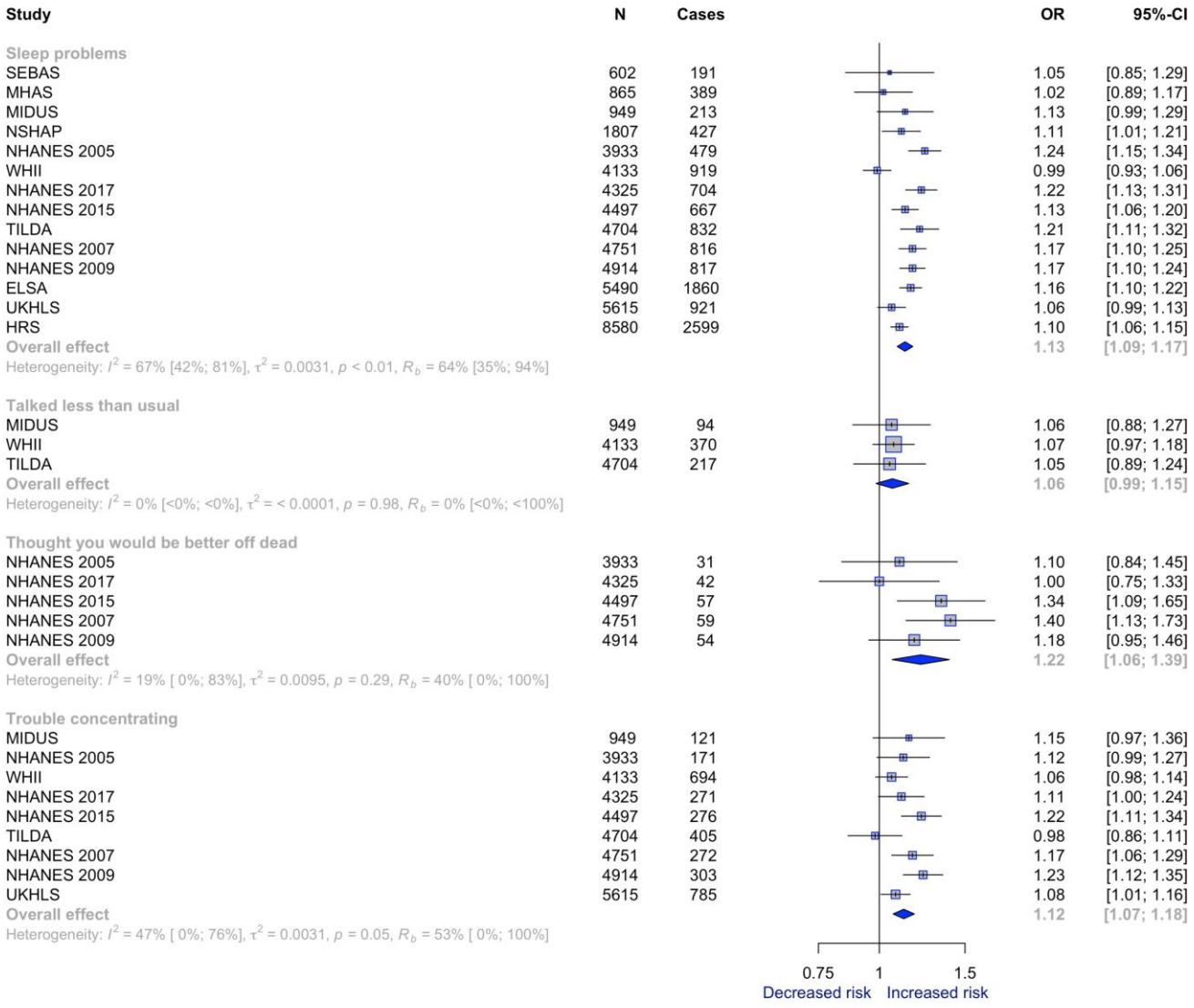
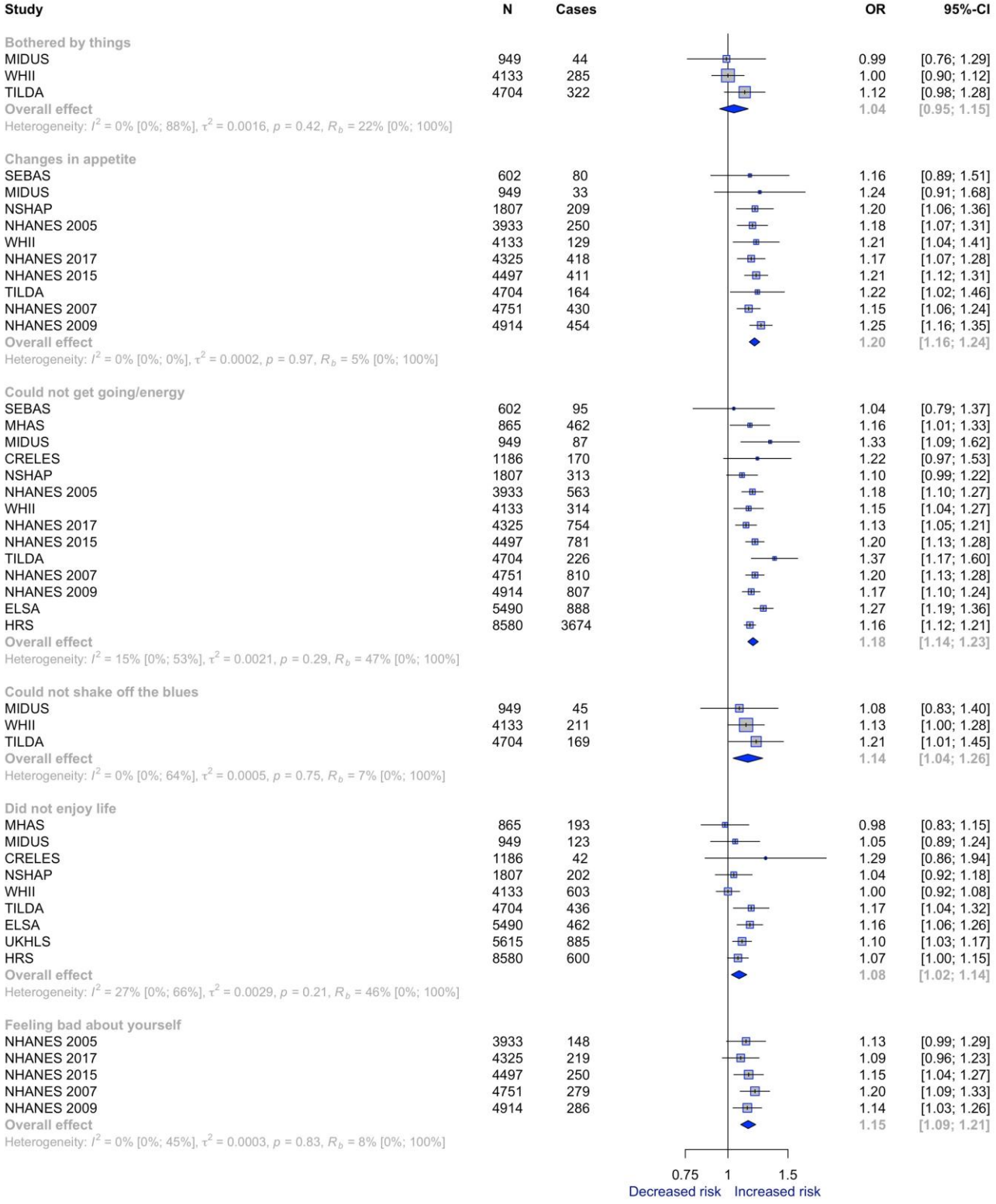


**FIGURE S2b. Random-effects meta-analysis of the cross-sectional association between C-reactive protein and individual depression symptoms (adjusted for age, sex & education)**




*Continues…*

***Figure S2b (continued)***

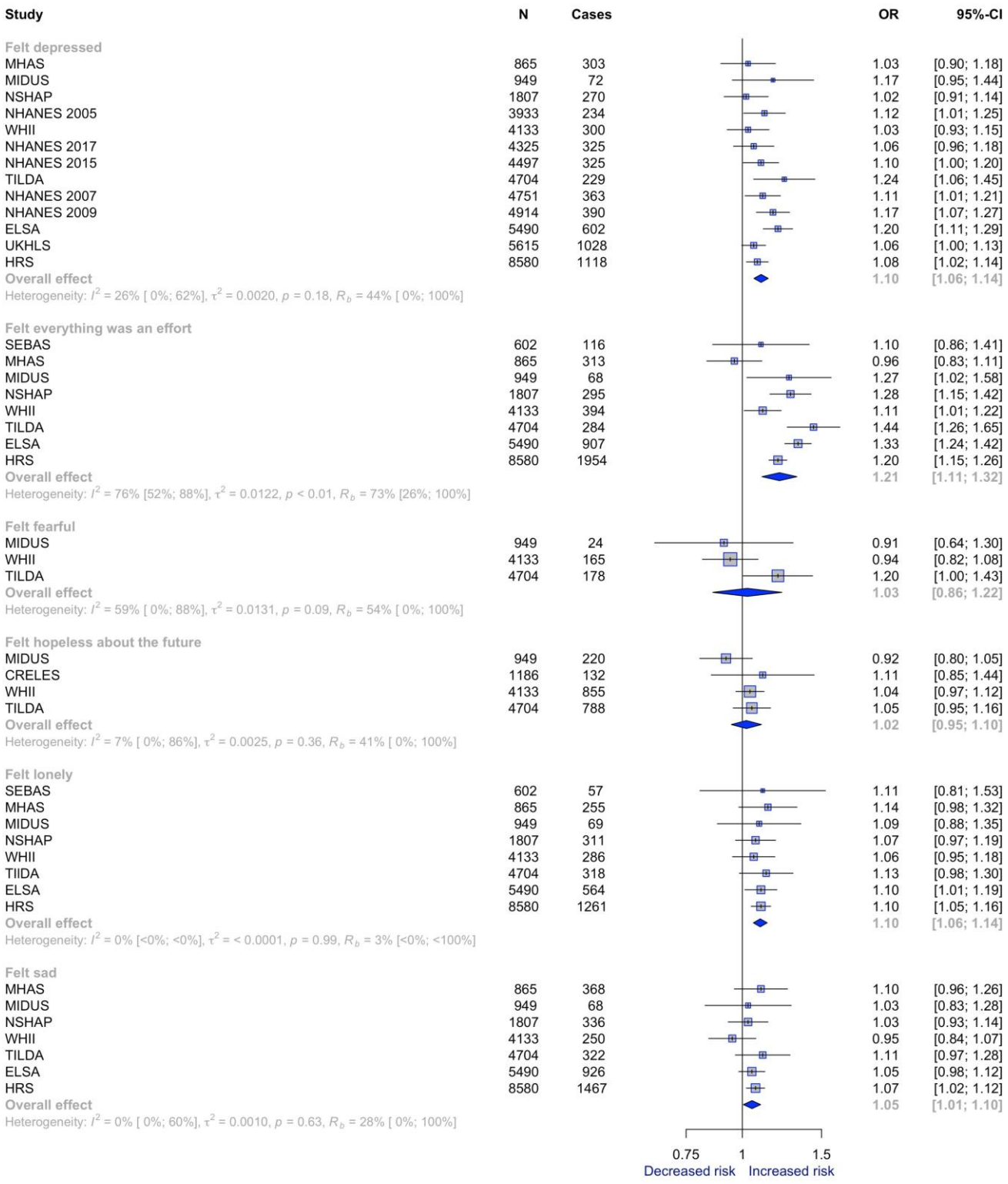



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***Figure S2b (continued)***

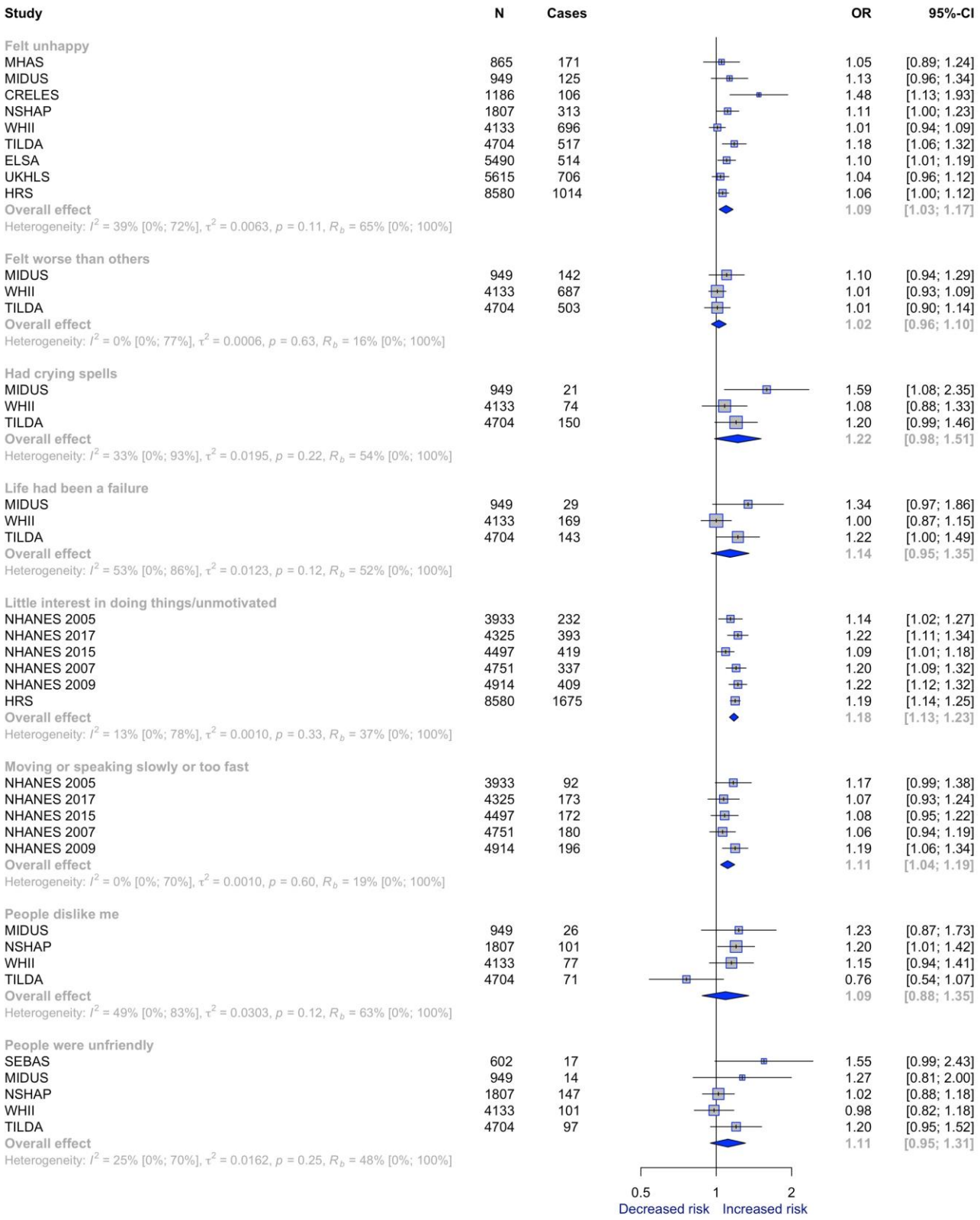


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***Figure S2b (continued)***

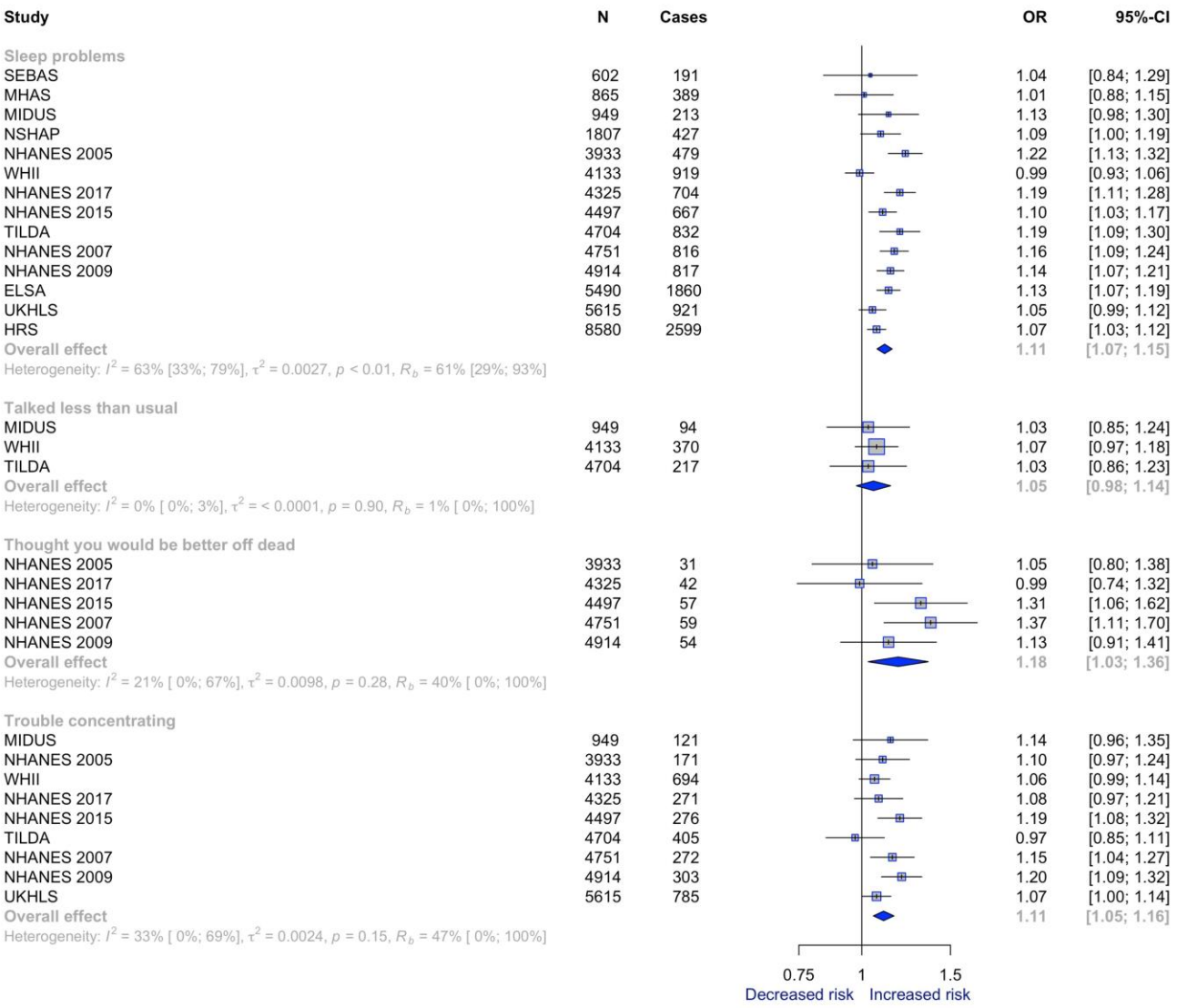

**FIGURE S2c. Random-effects meta-analysis of the cross-sectional association between C-reactive protein and individual depression symptoms (adjusted for age, sex & chronic illness-related factors)**

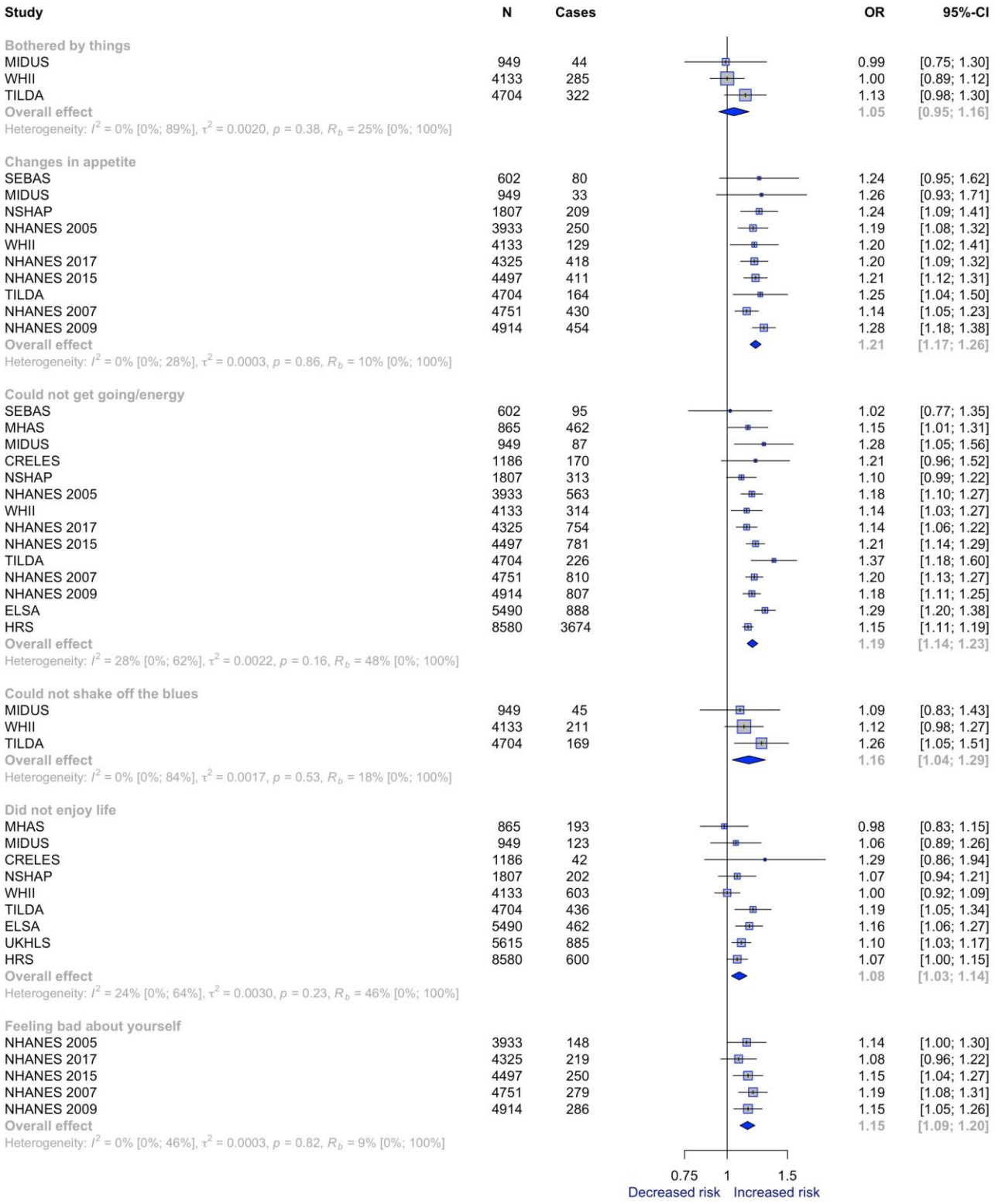


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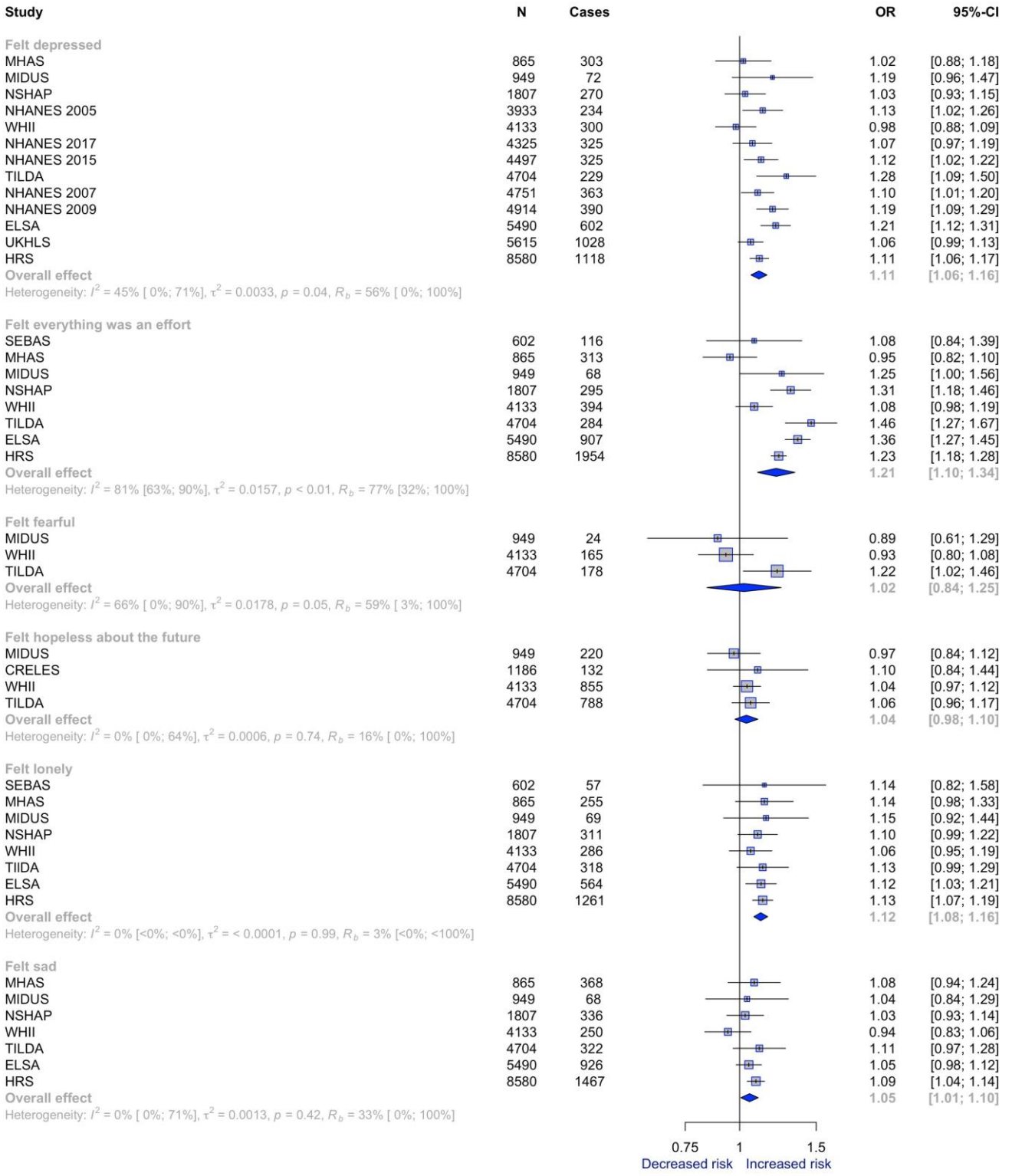
***Figure S2c (continued)***

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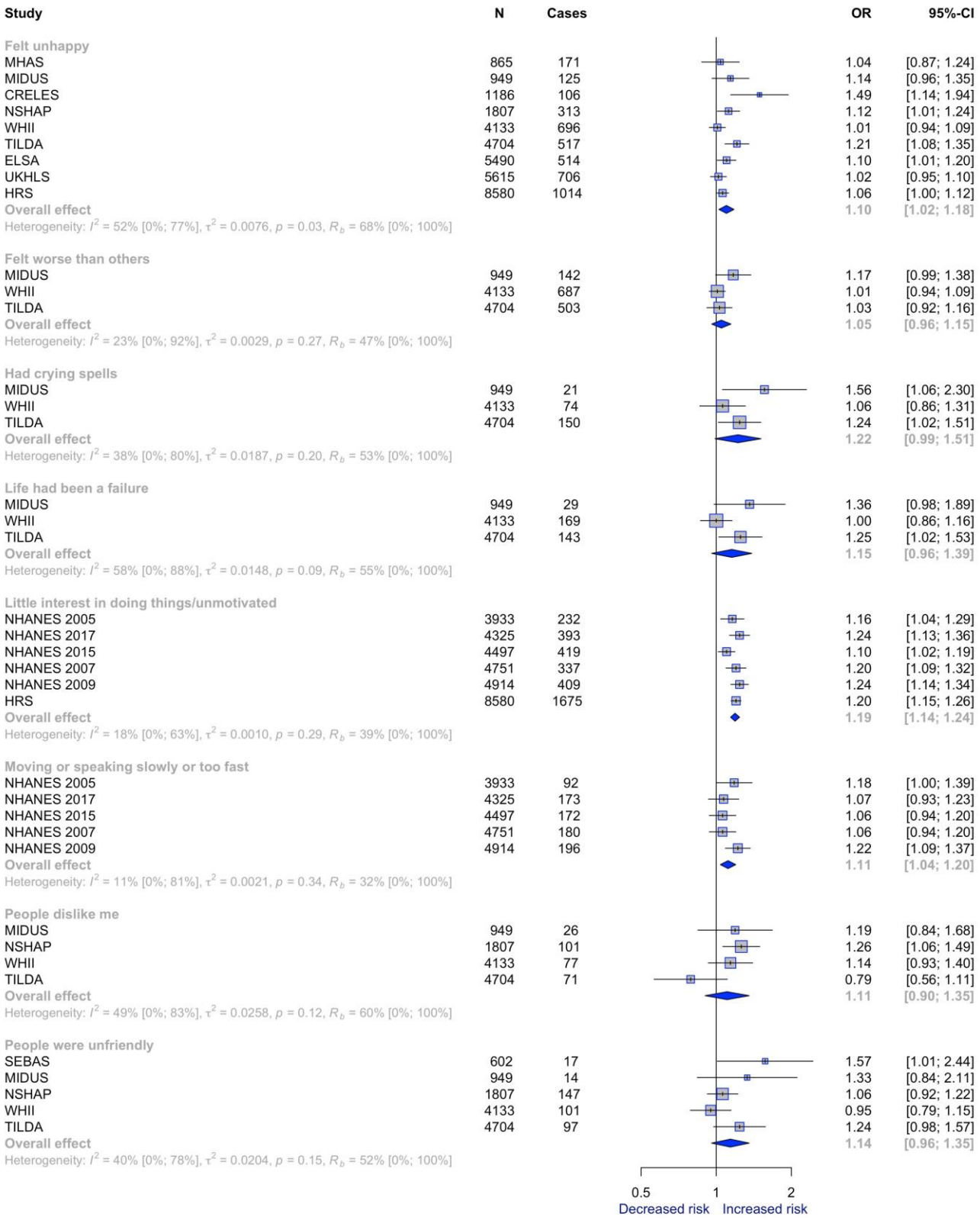


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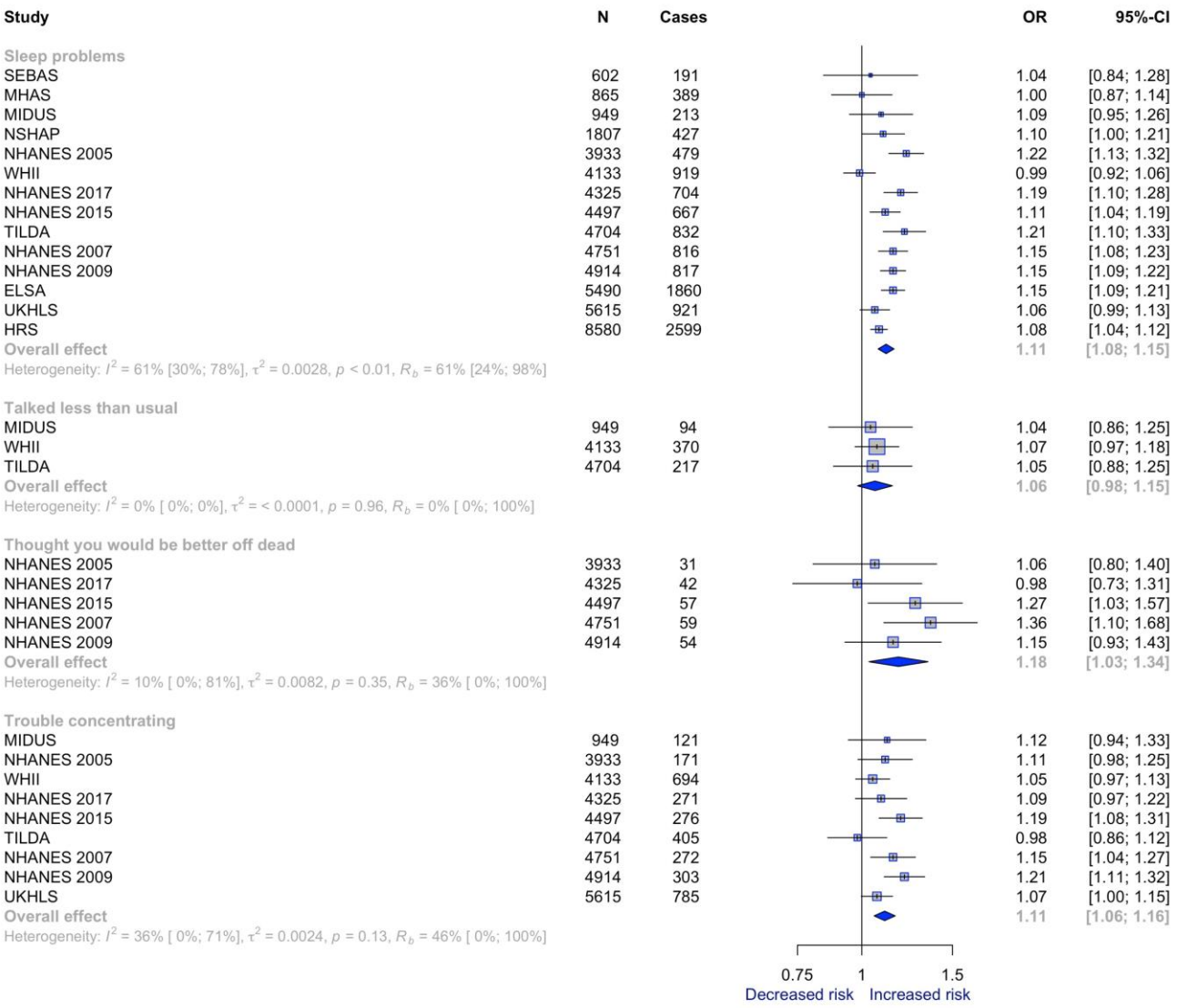
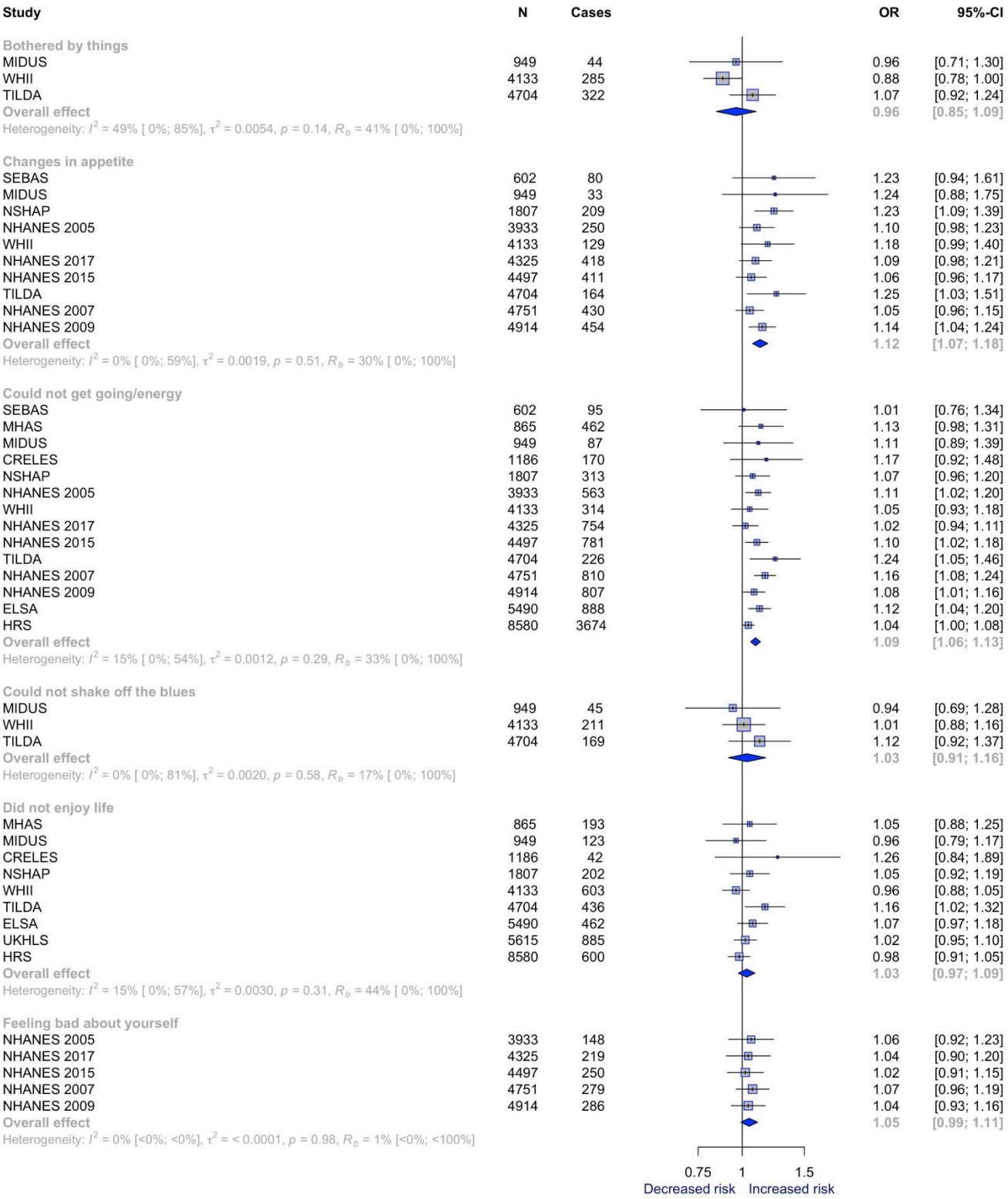


**FIGURE S2d. Random-effects meta-analysis of the cross-sectional association between C-reactive protein and individual depression symptoms (adjusted for age, sex & behavioural factors)**

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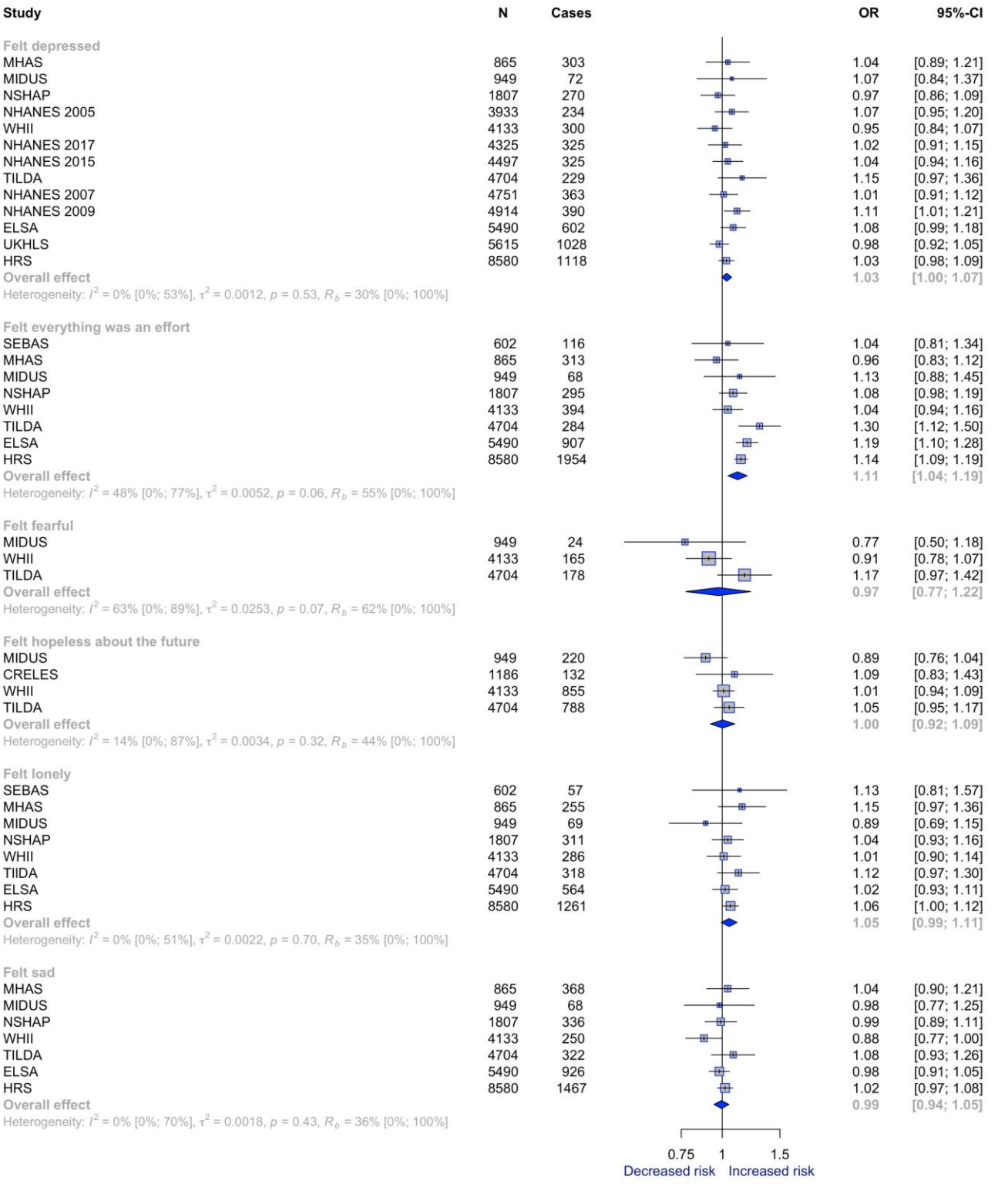


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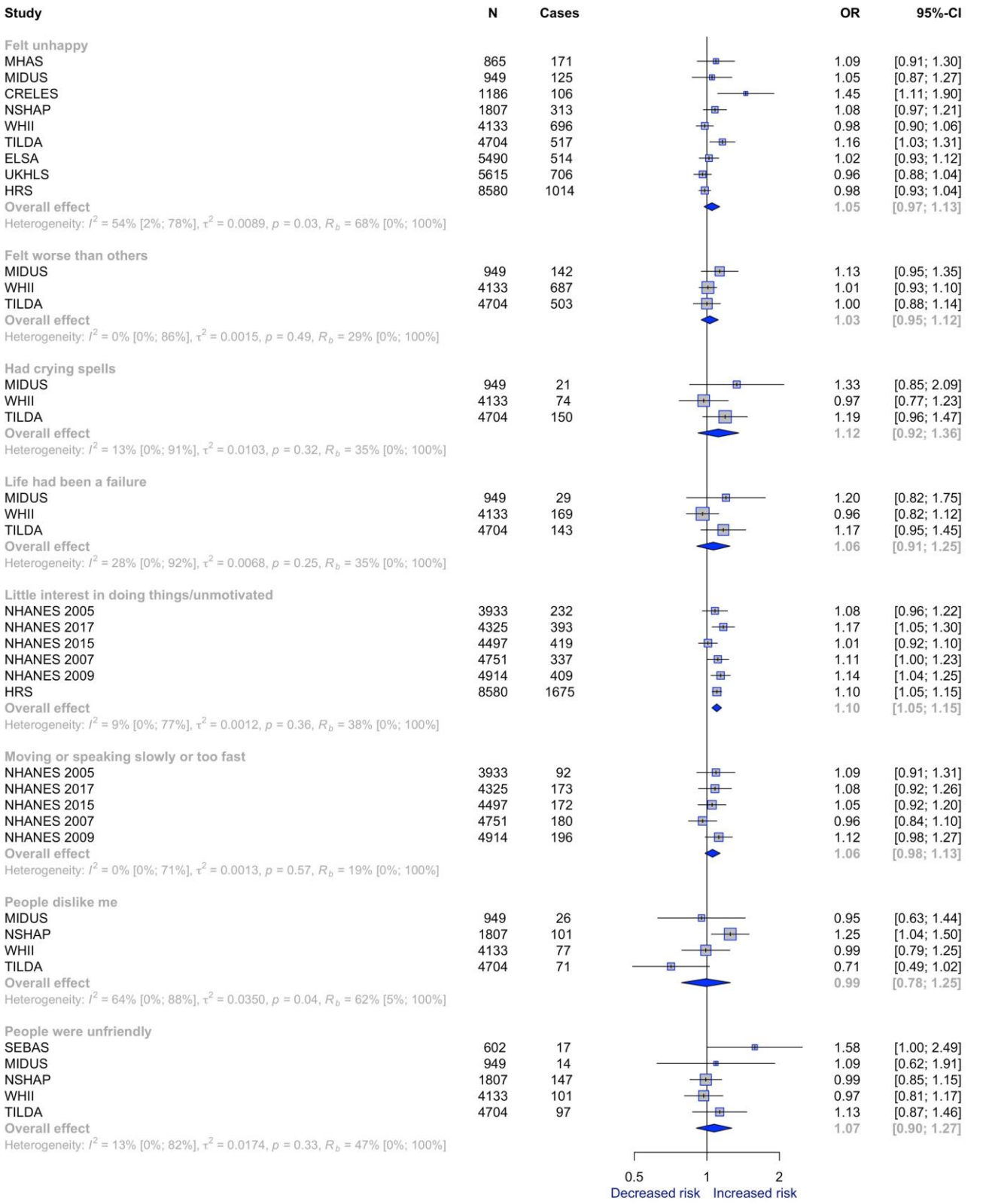
***Figure S2d (continued)***

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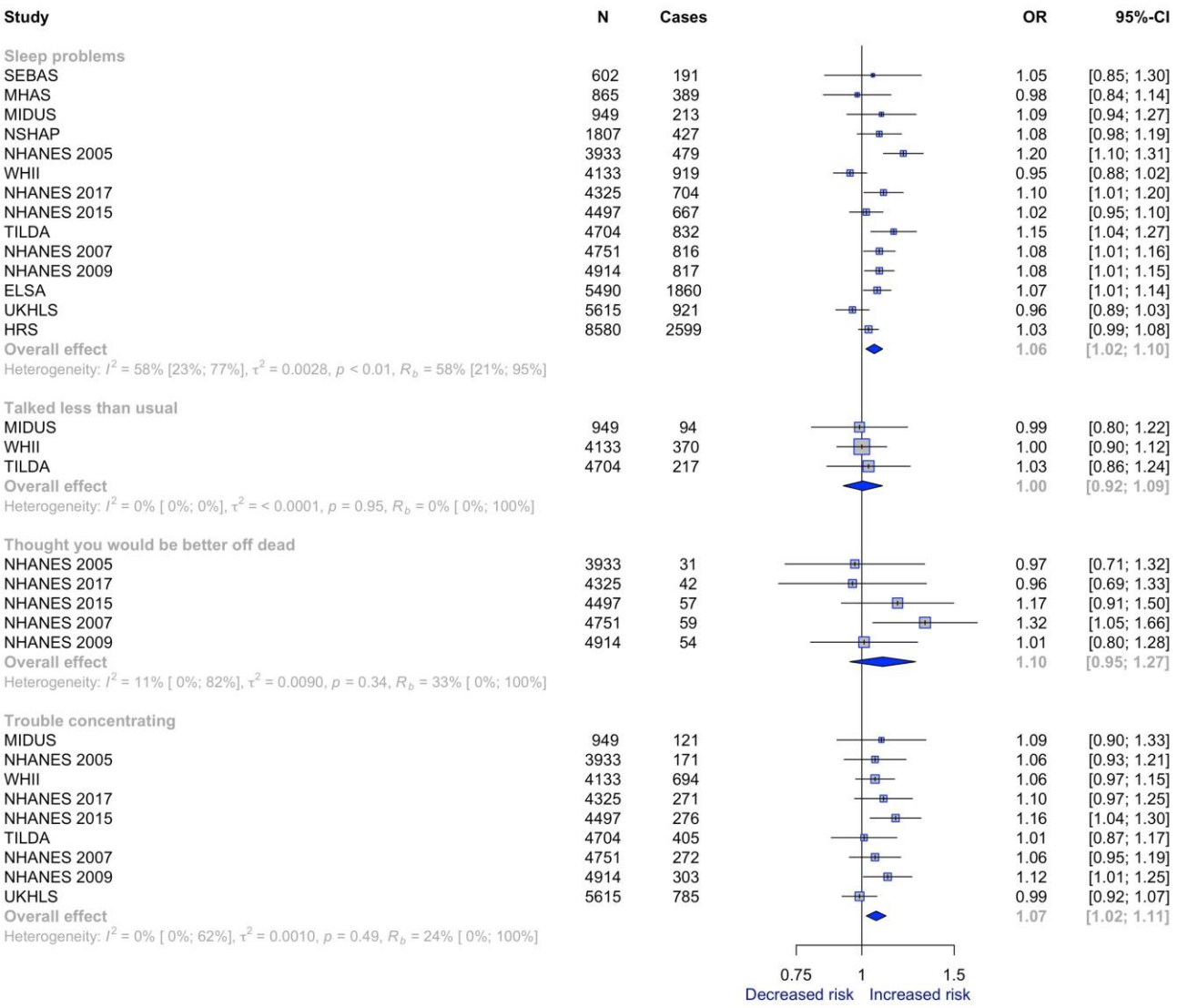

**FIGURE S3a. Random-effects meta-analysis of the longitudinal association between C-reactive protein and individual depression symptoms (adjusted for age, sex & individual baseline symptom)**

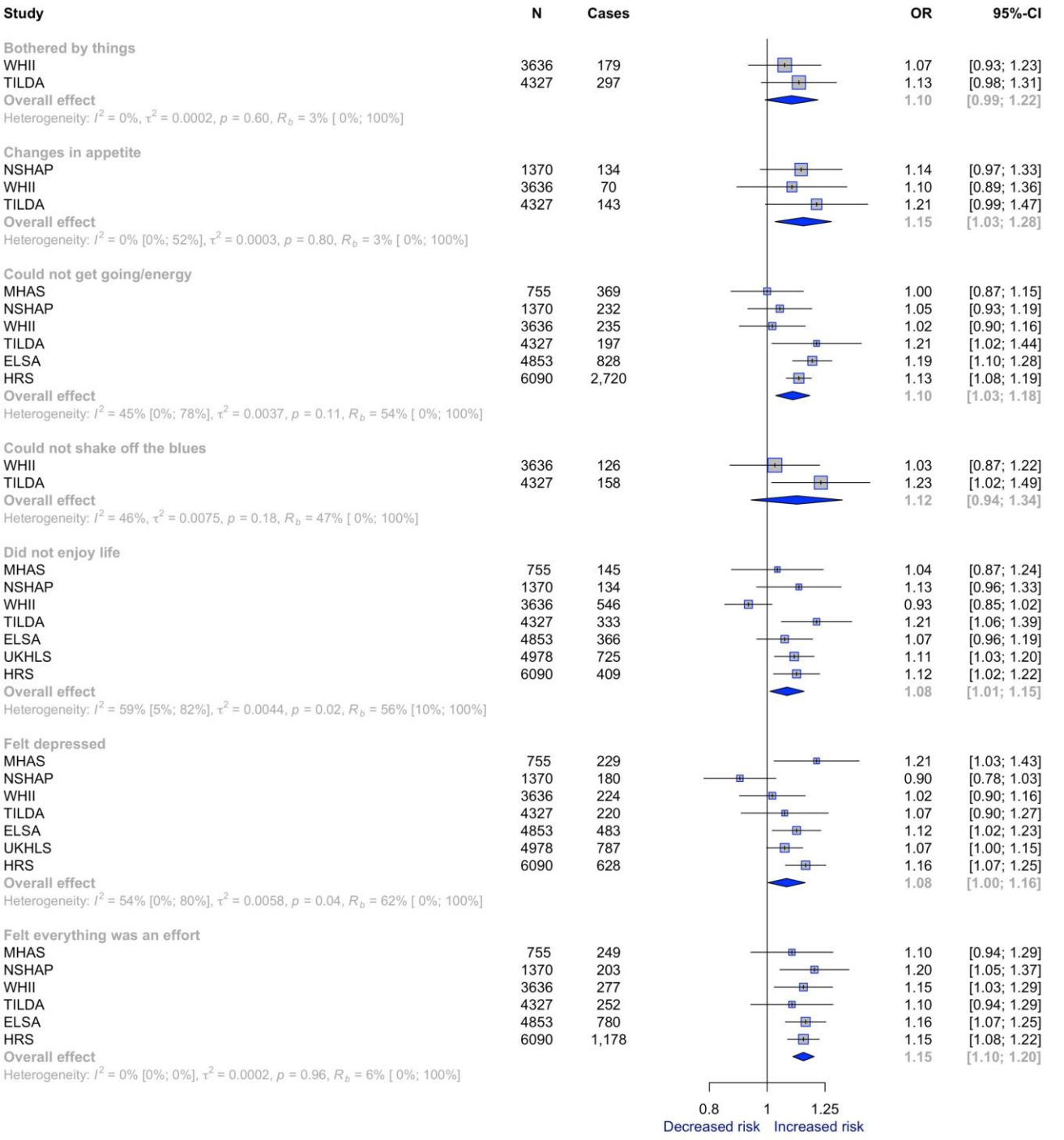


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***Figure S3a (continued)***

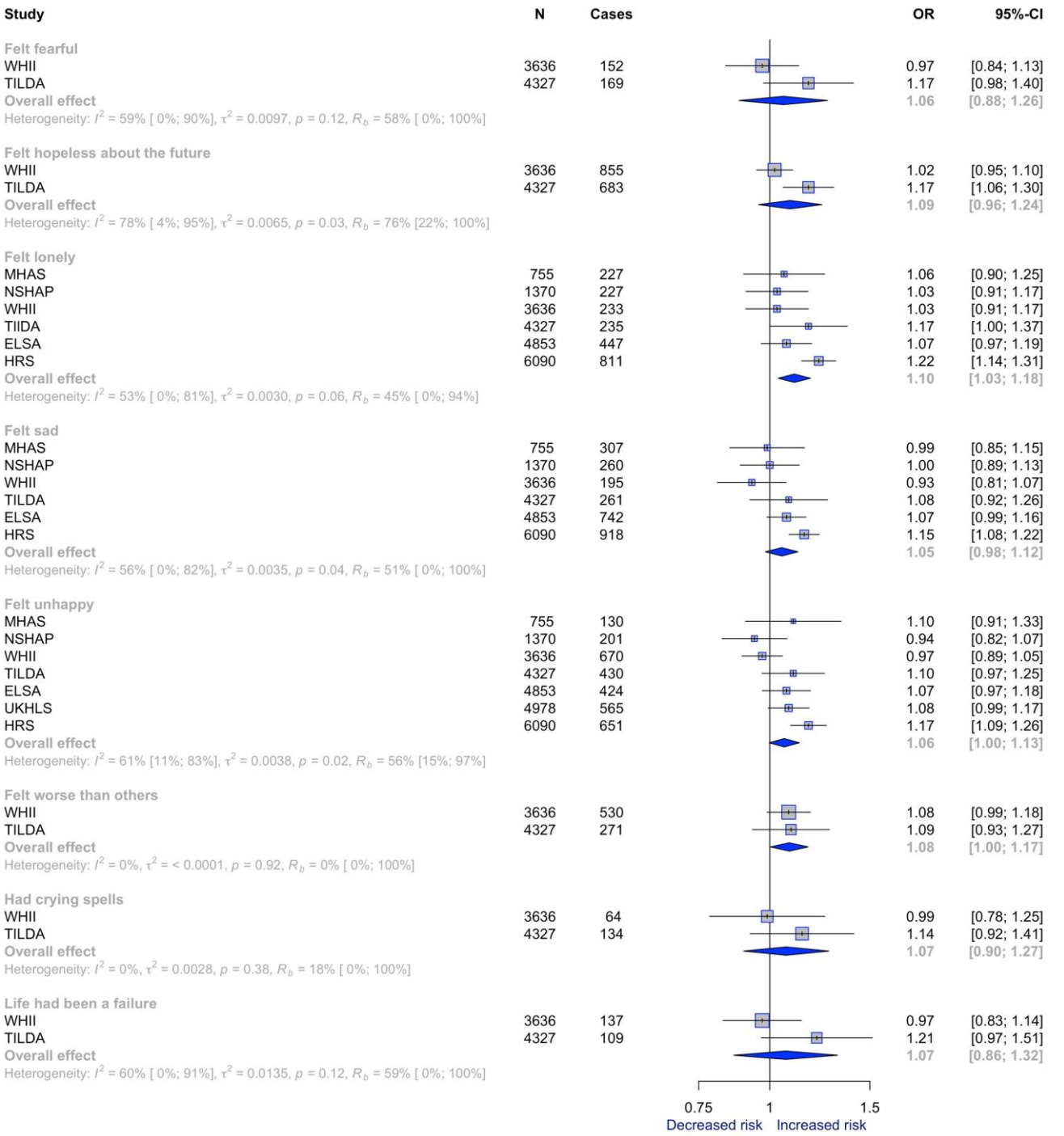


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***Figure S3a (continued)***

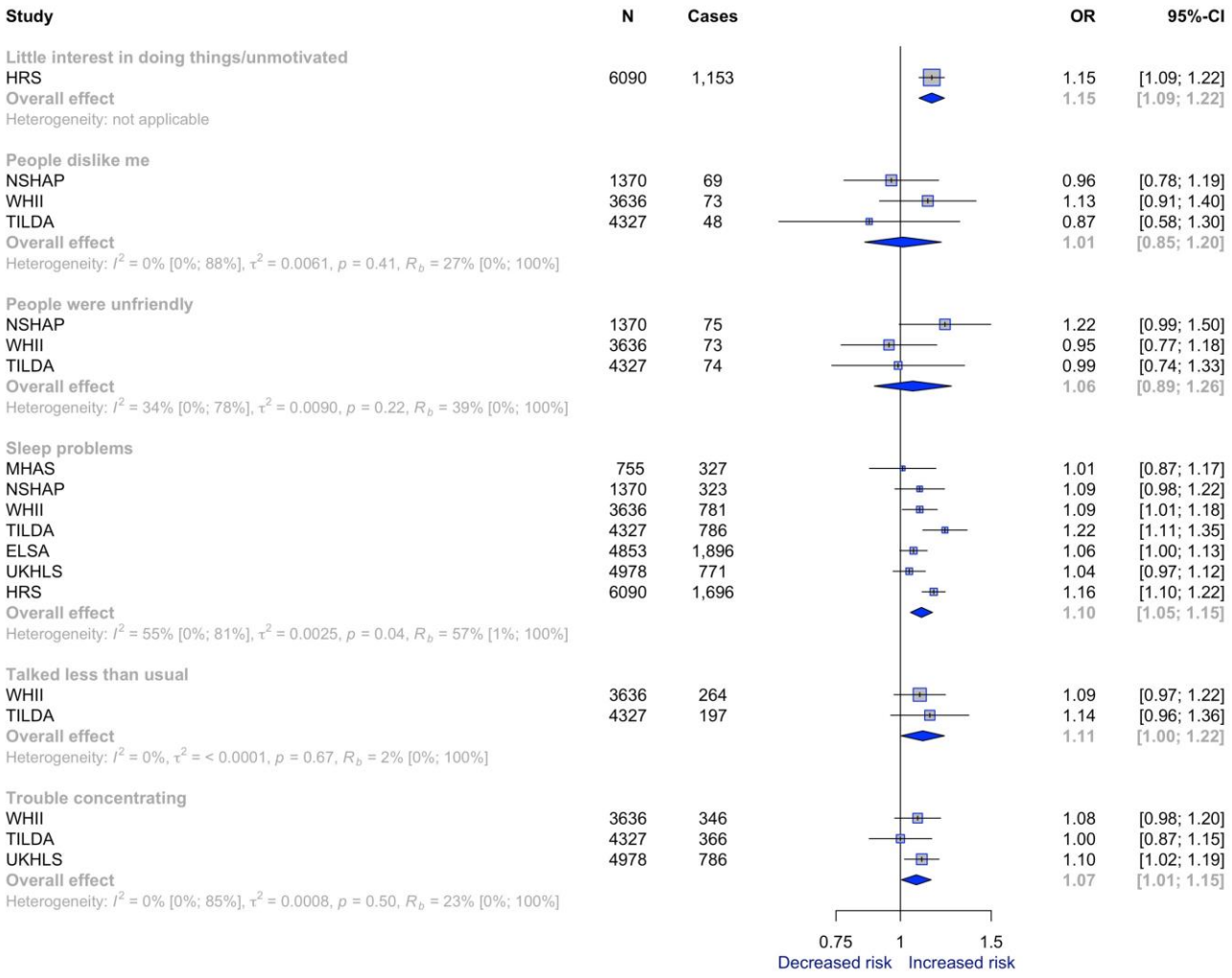

**FIGURE S3b. Random-effects meta-analysis of the longitudinal association between C-reactive protein and individual depression symptoms (adjusted for age, sex, individual baseline symptom & education)**

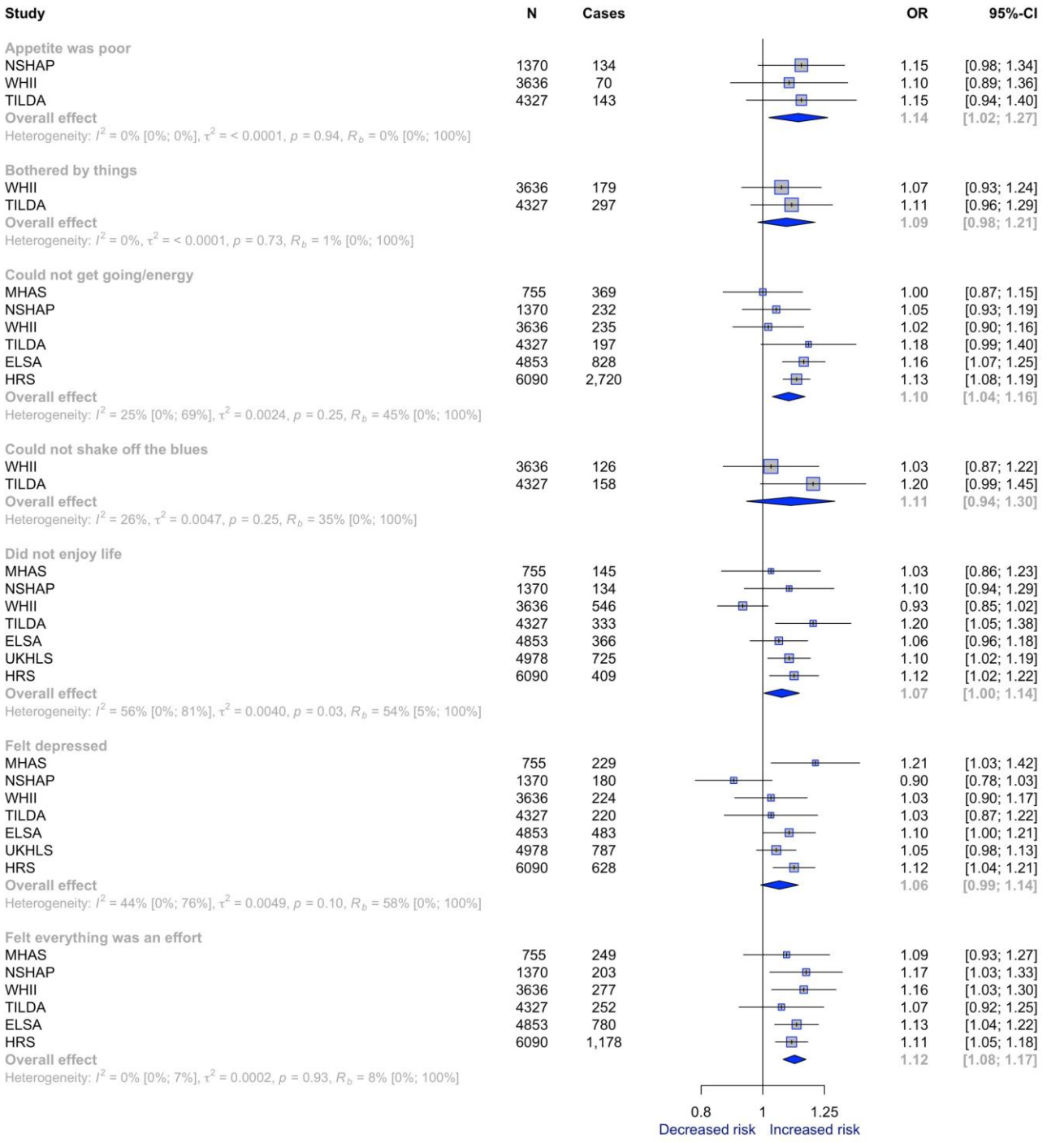


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***Figure S3b (continued)***

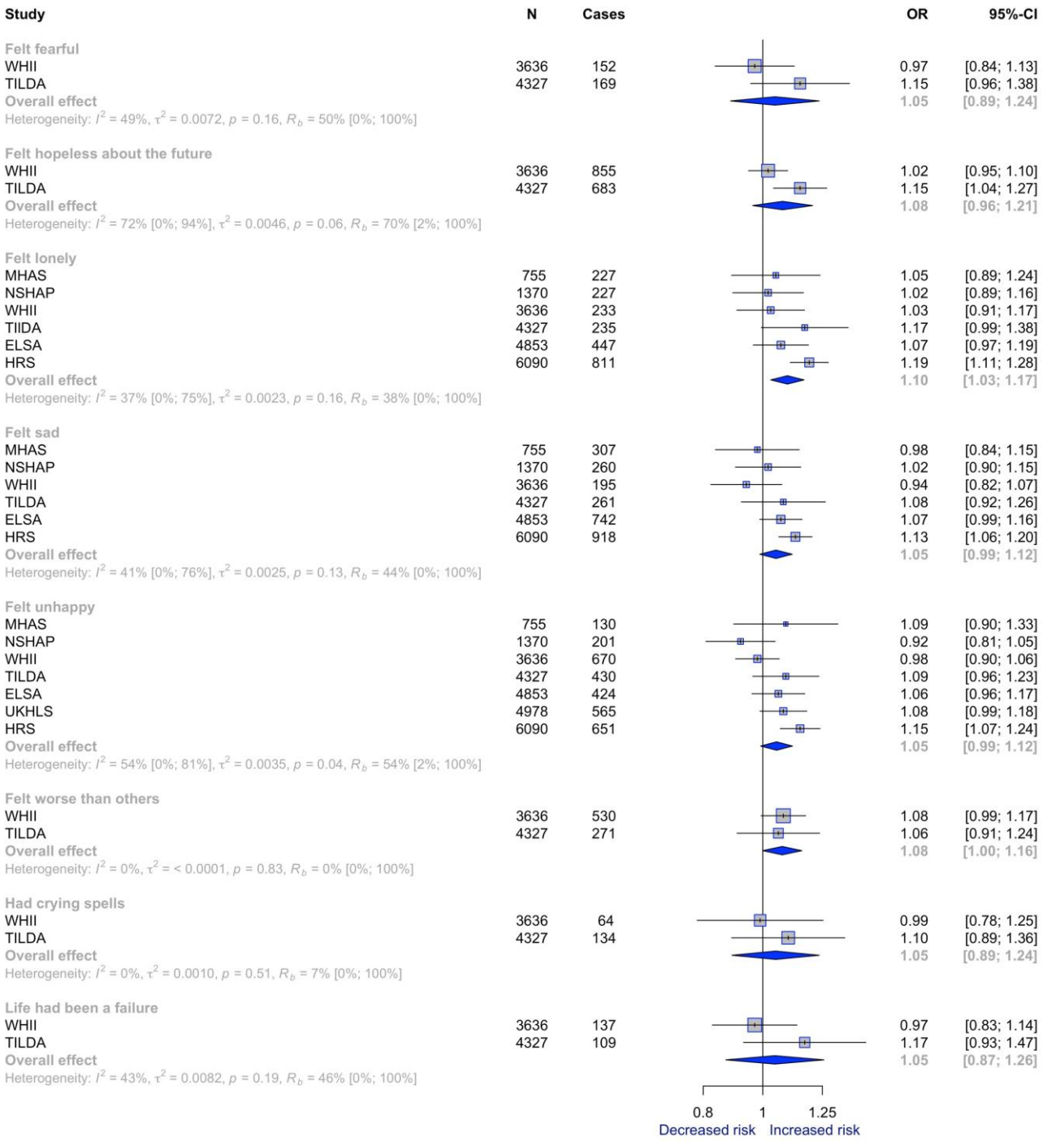


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***Figure S3b (continued)***

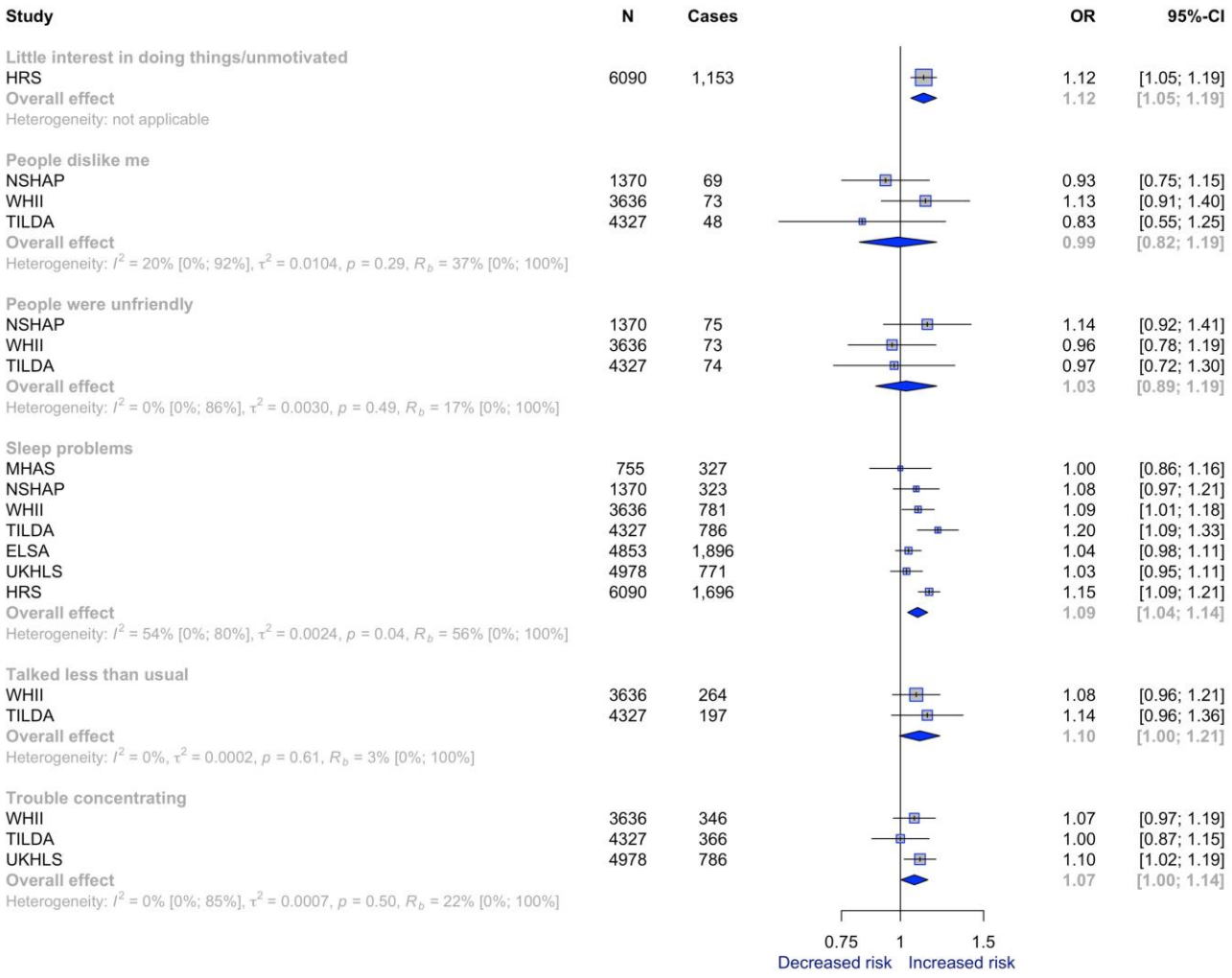

**FIGURE S3c. Random-effects meta-analysis of the longitudinal association between C-reactive protein and individual depression symptoms (adjusted for age, sex, individual baseline symptom & chronic illness-related factors)**

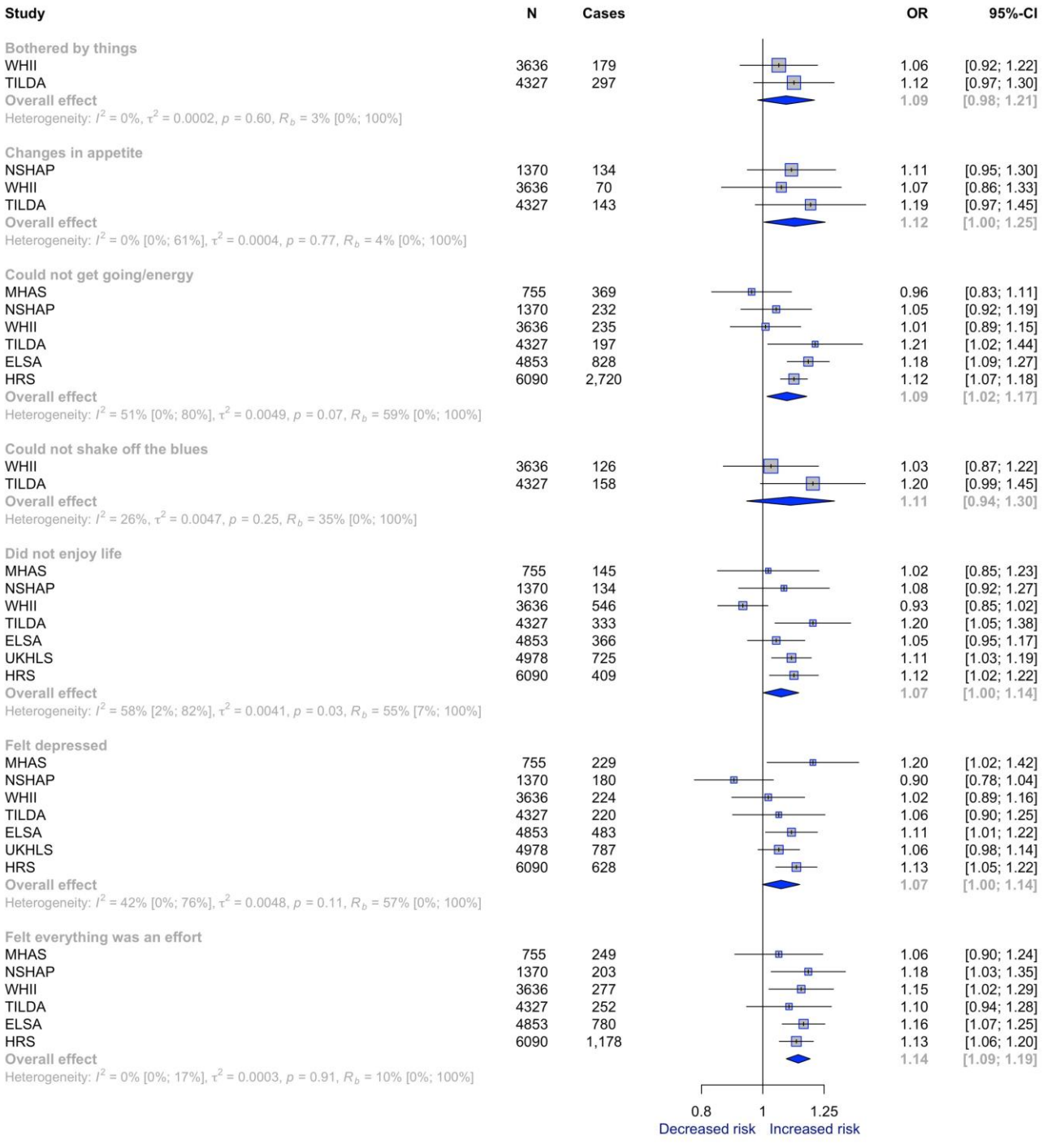


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***Figure S3c (continued)***

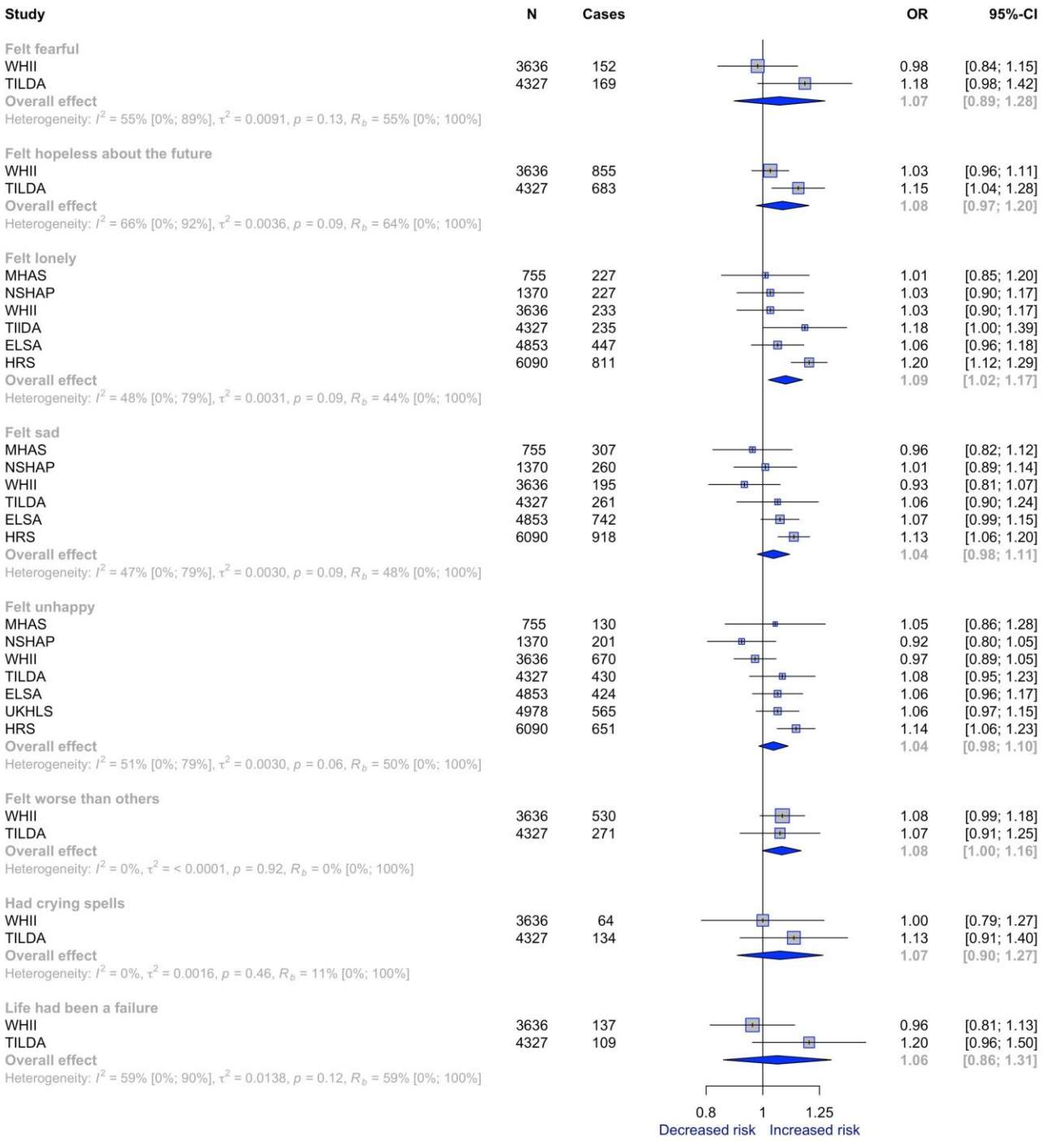


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***Figure S3c (continued)***

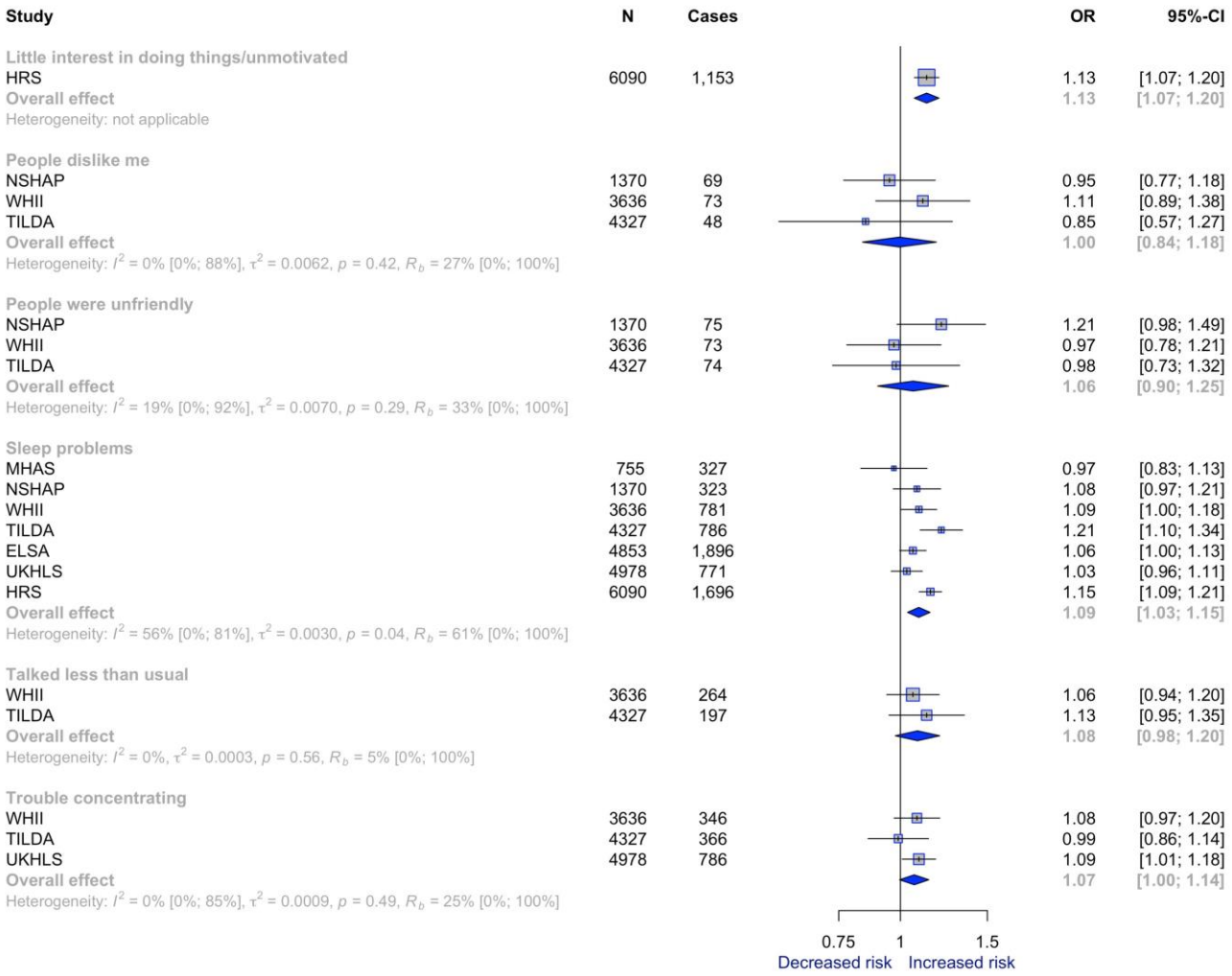

**FIGURE S3d. Random-effects meta-analysis of the longitudinal association between C-reactive protein and individual depression symptoms (adjusted for age, sex, individual baseline symptom & behavioural factors)**

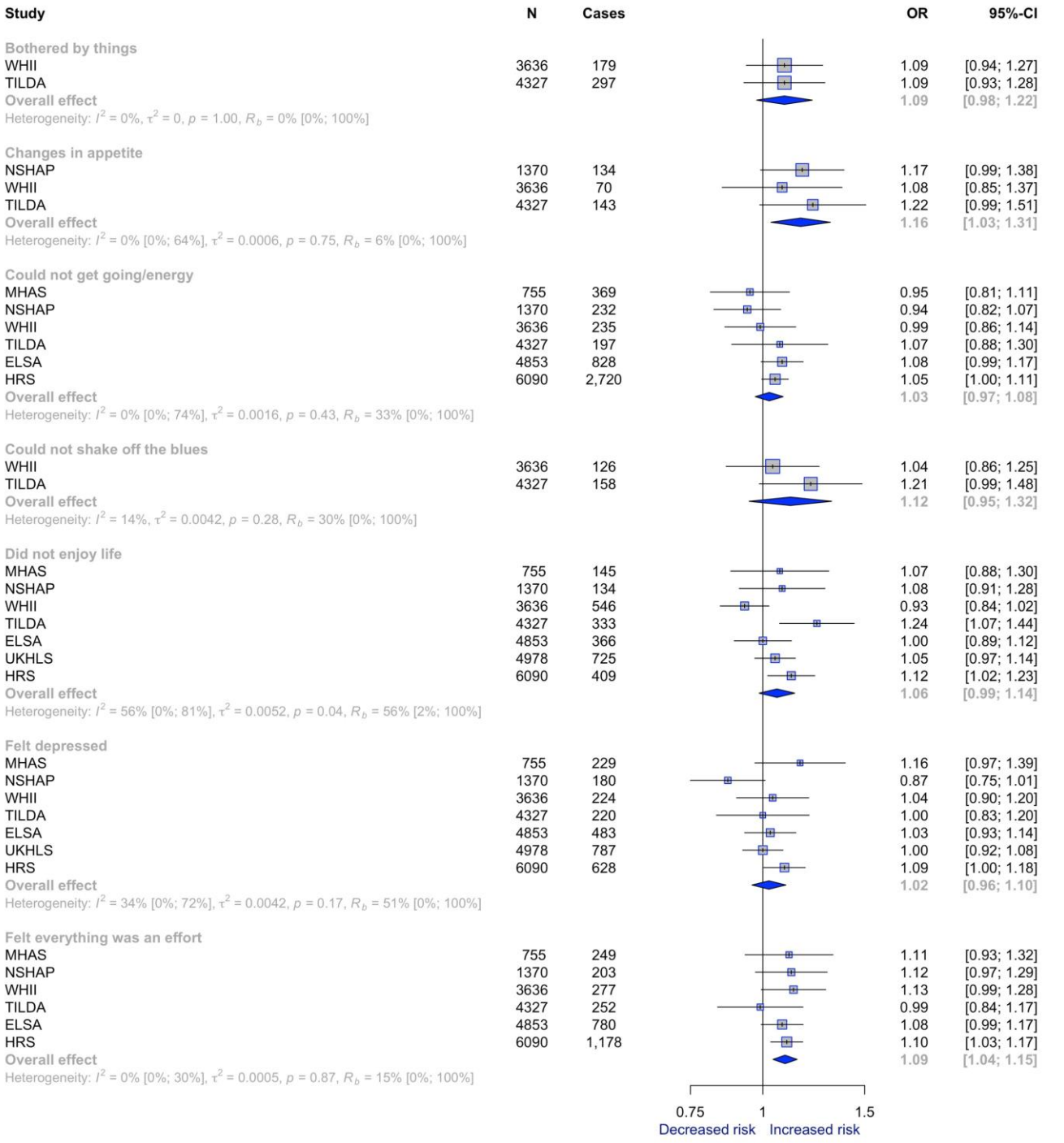


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***Figure S3d (continued)***

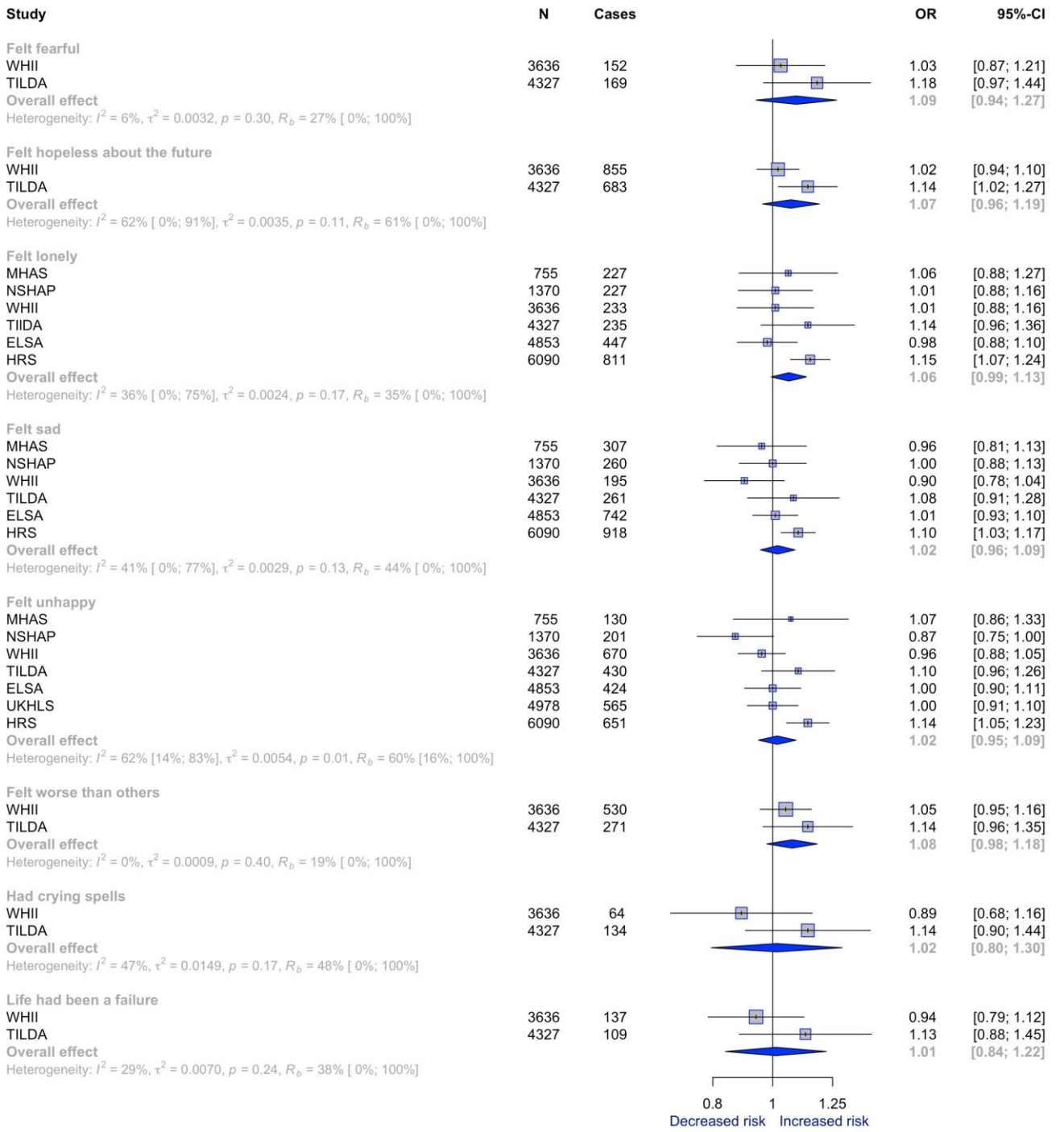


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***Figure S3d (continued)***

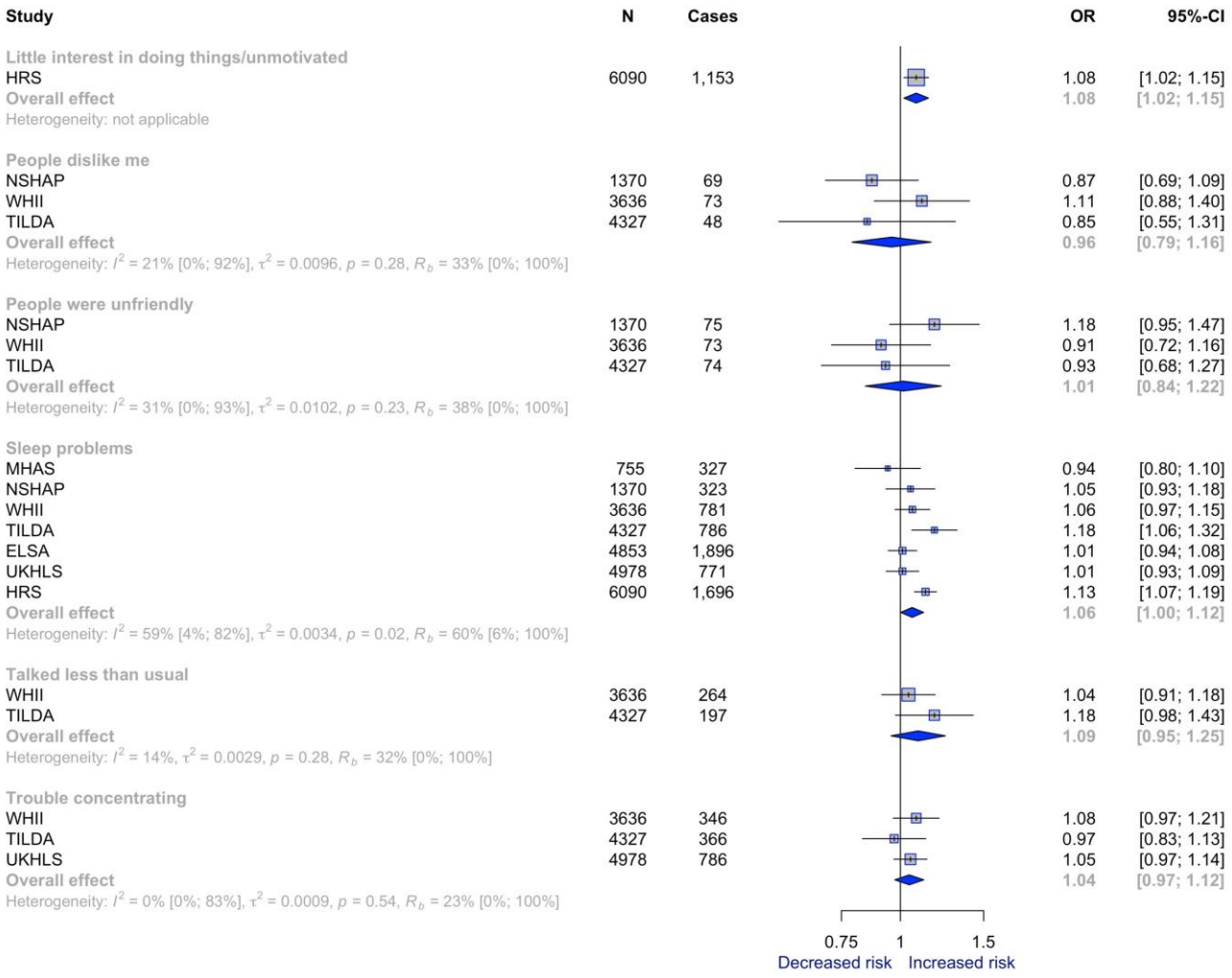

**FIGURE S4a. Random-effects meta-analysis of the cross-sectional association between C-reactive protein (low-grade) and individual depression symptoms (adjusted for age & sex)**

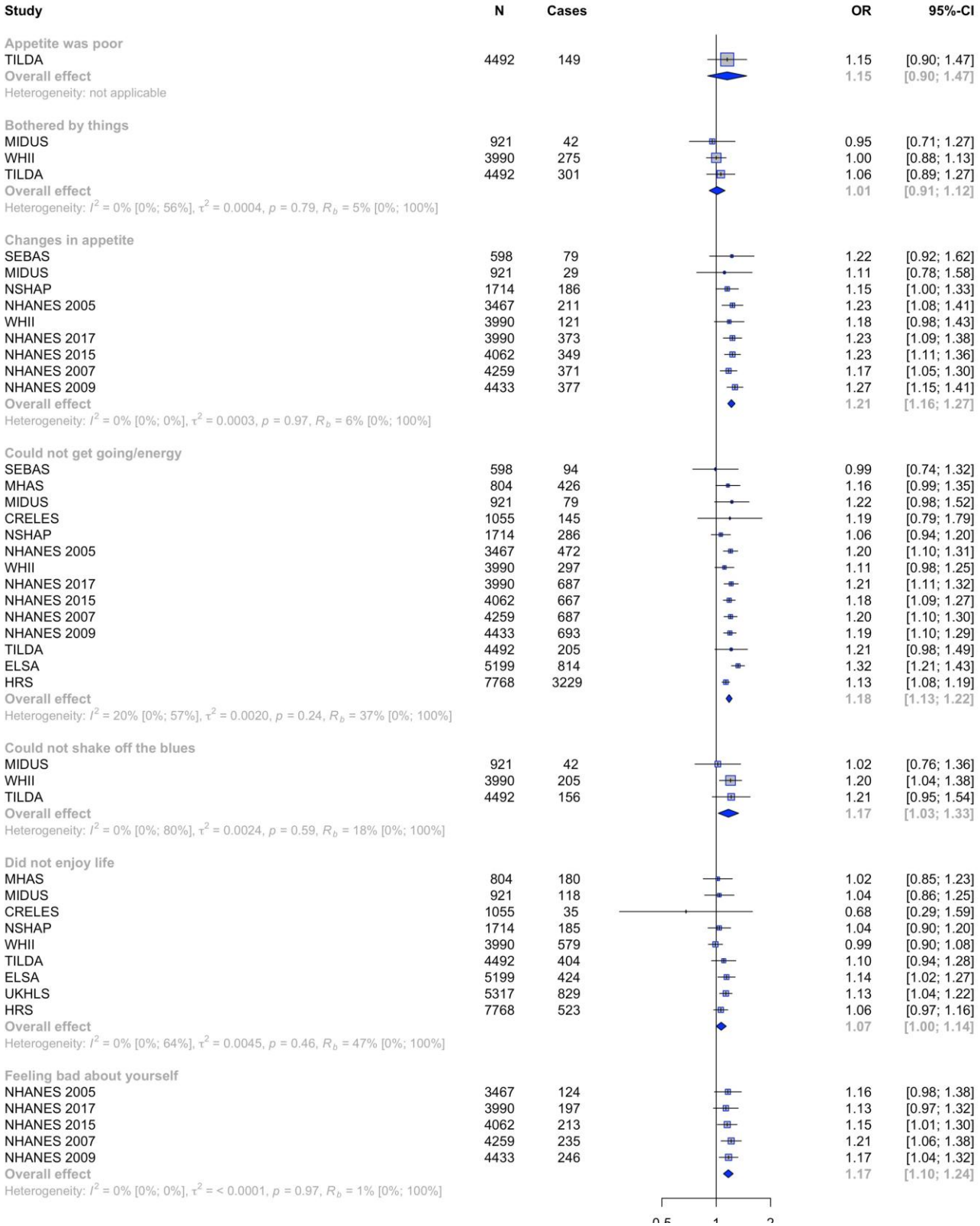


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***Figure S4a (continued)***

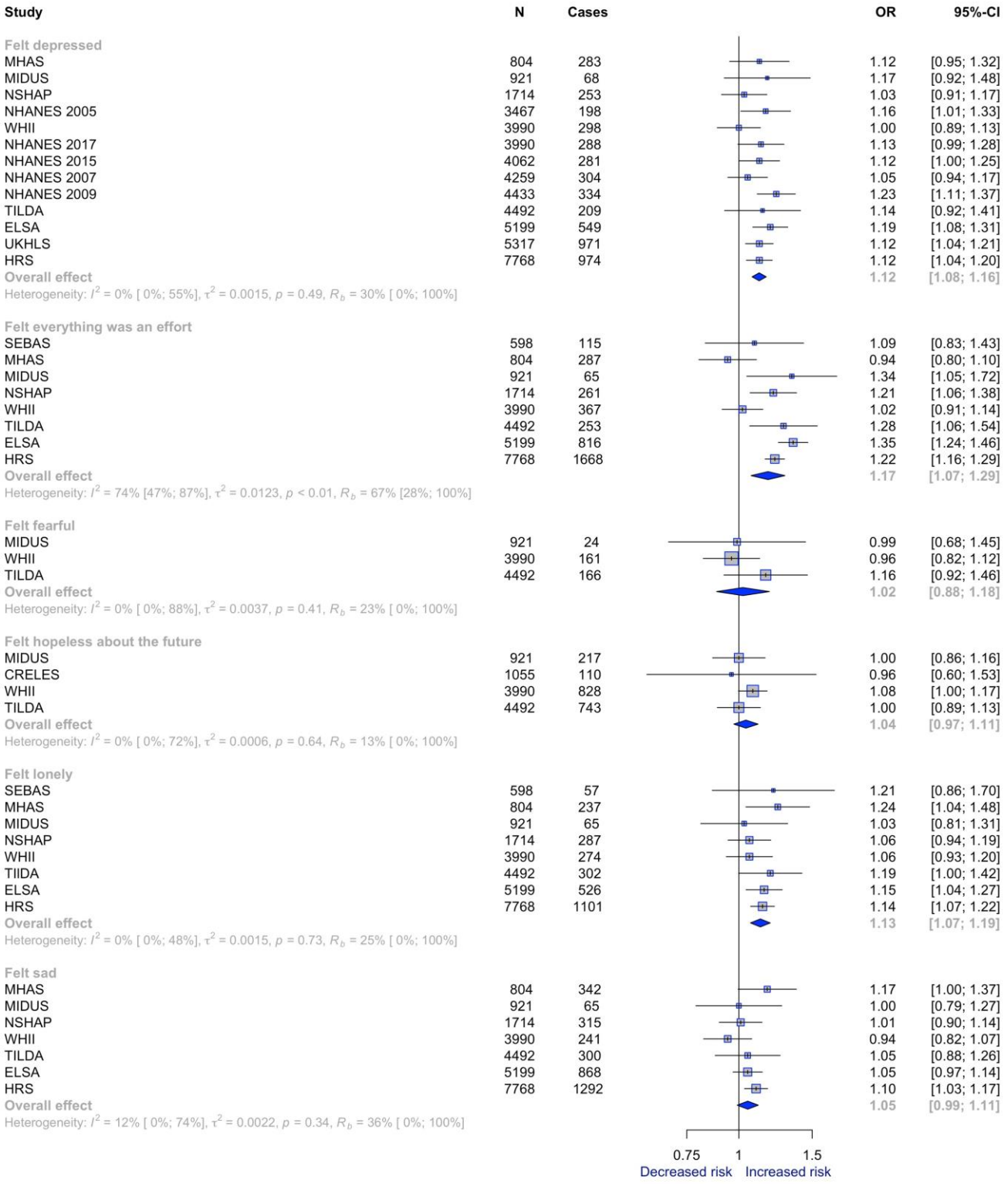


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***Figure S4a (continued)***

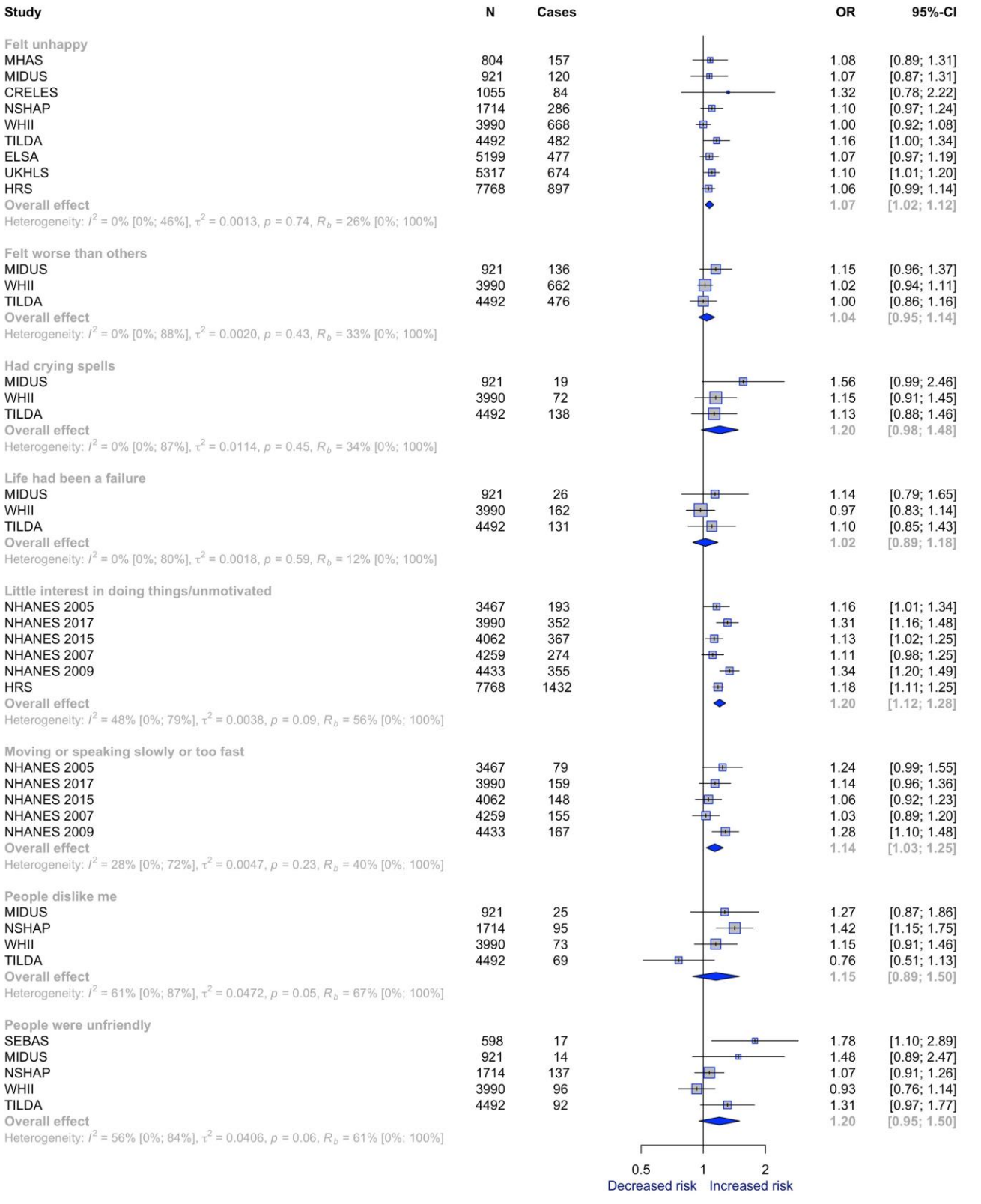


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***Figure S4a (continued)***

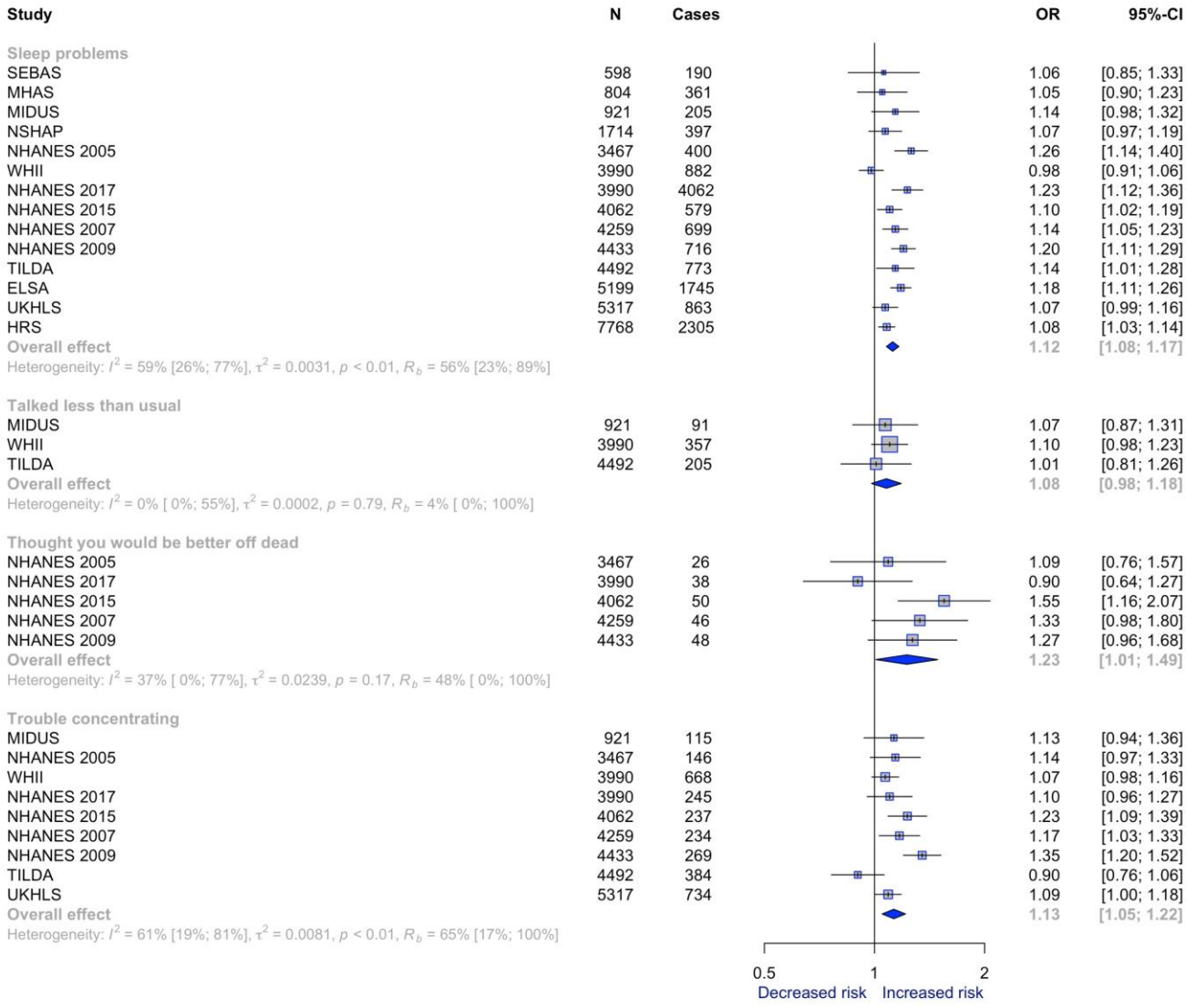
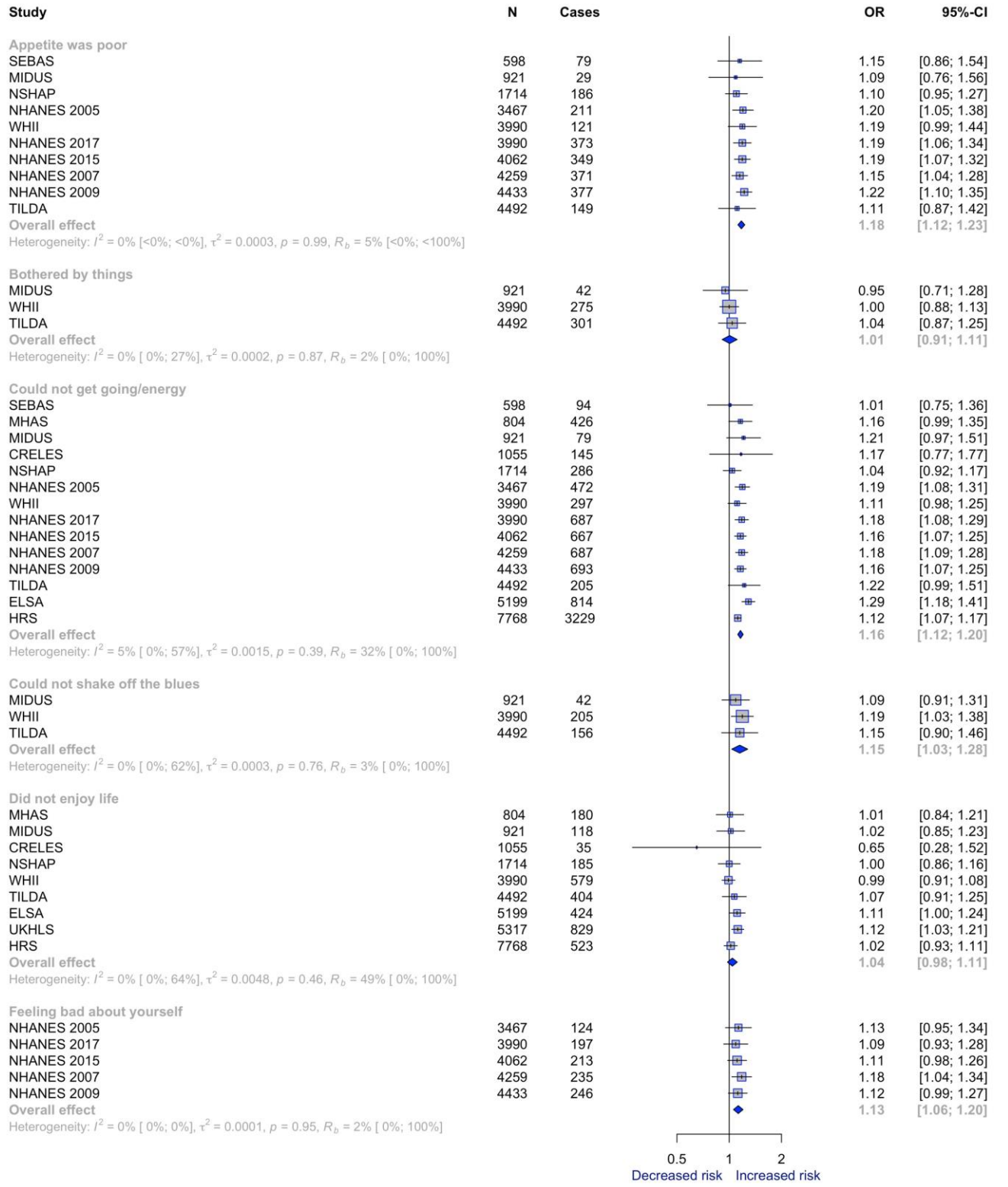


**FIGURE S4b. Random-effects meta-analysis of the cross-sectional association between C-reactive protein (low-grade) and individual depression symptoms (adjusted for age, sex & education)**




*Continues…*

***Figure S4b (continued)***

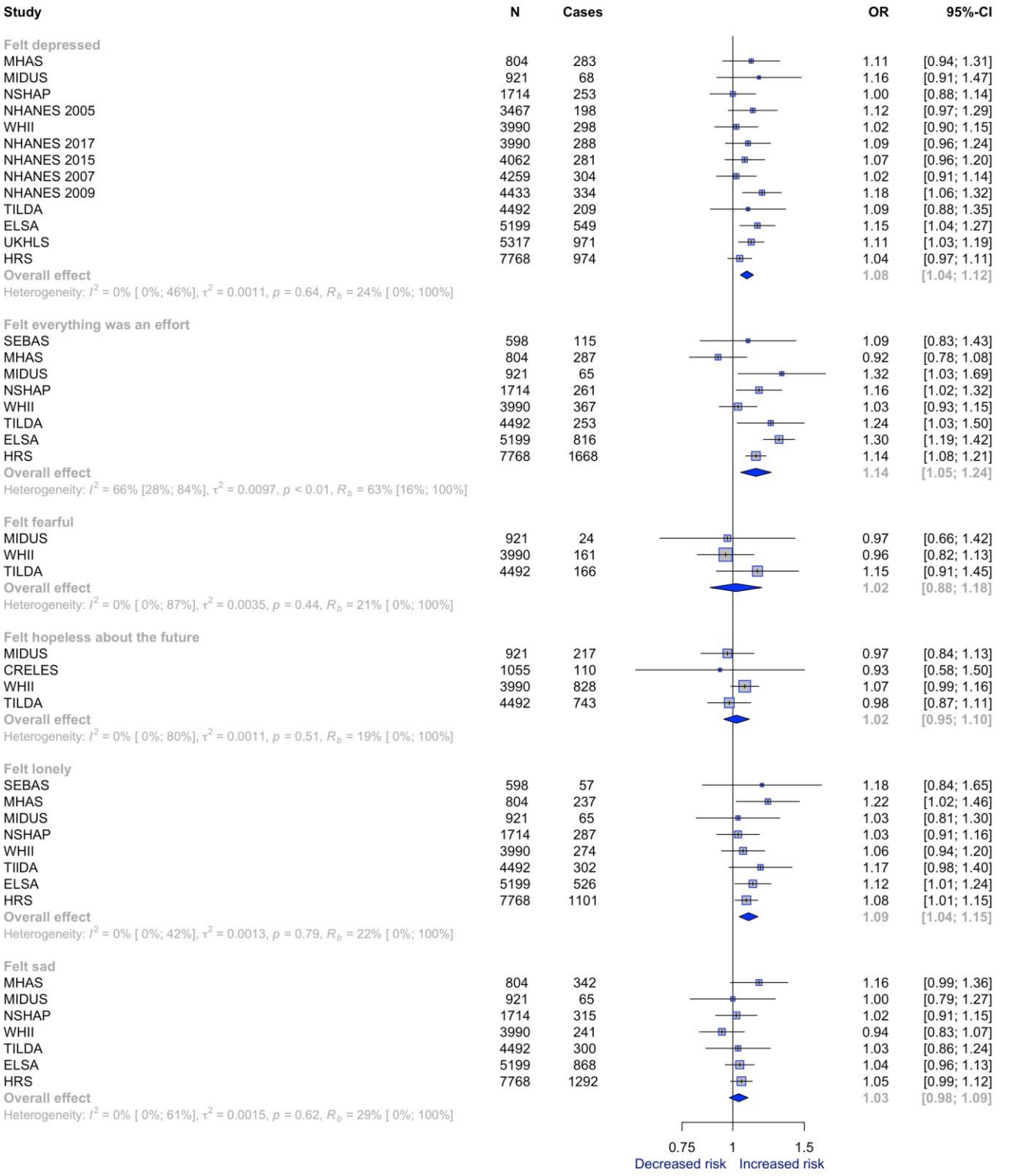



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***Figure S4b (continued)***

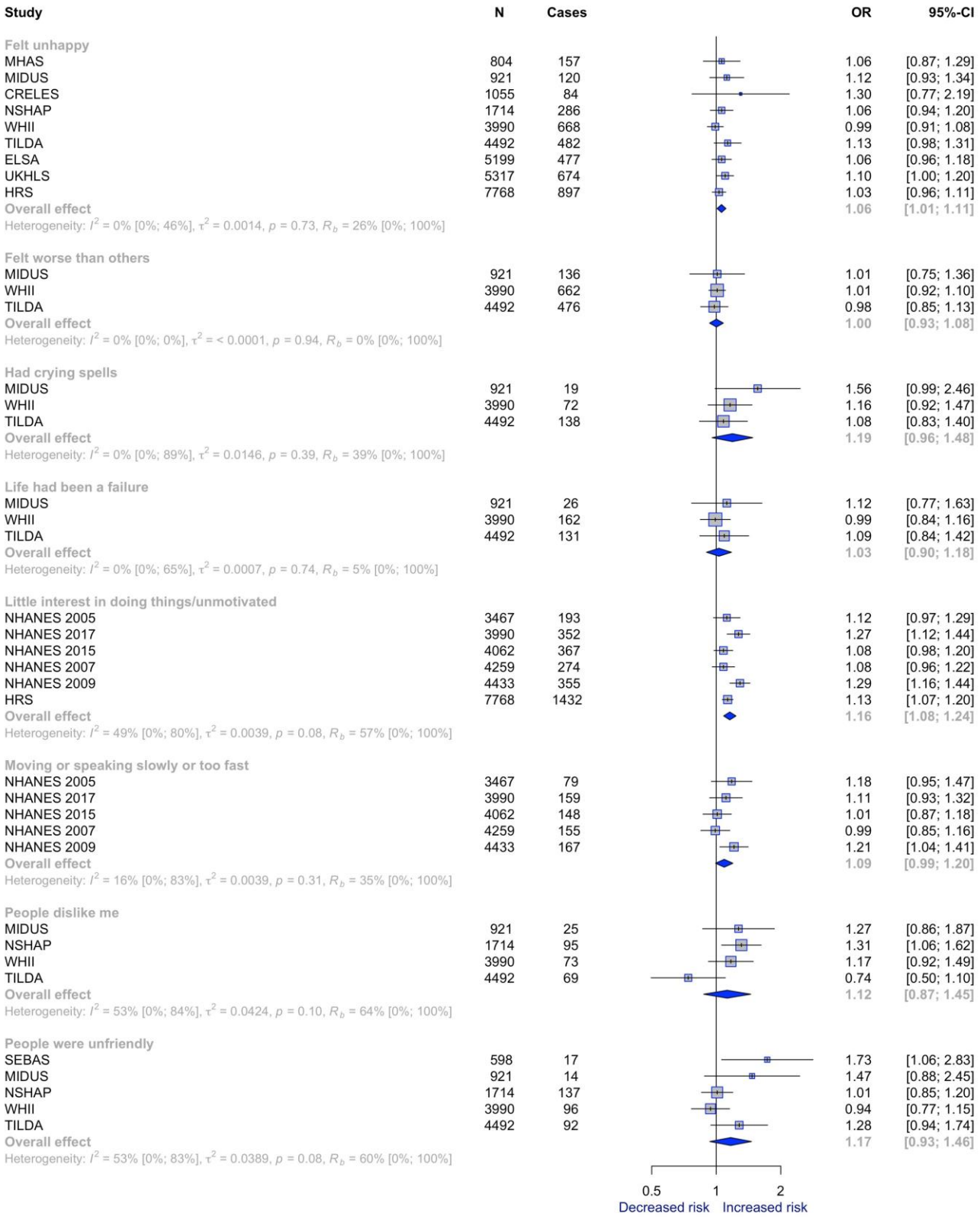


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***Figure S4b (continued)***

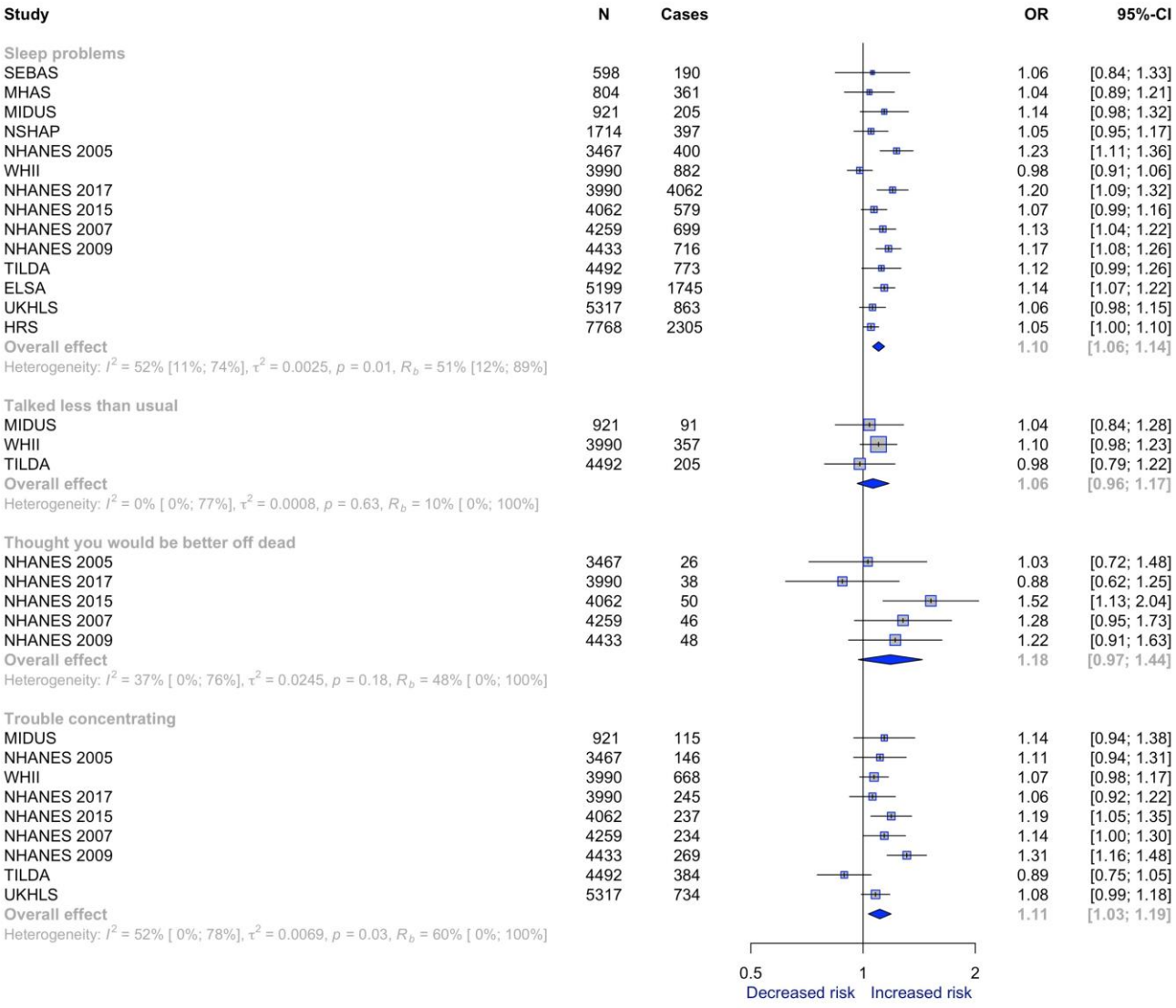

**FIGURE S4c. Random-effects meta-analysis of the cross-sectional association between C-reactive protein (low-grade) and individual depression symptoms (adjusted for age, sex & chronic illness-related factors)**

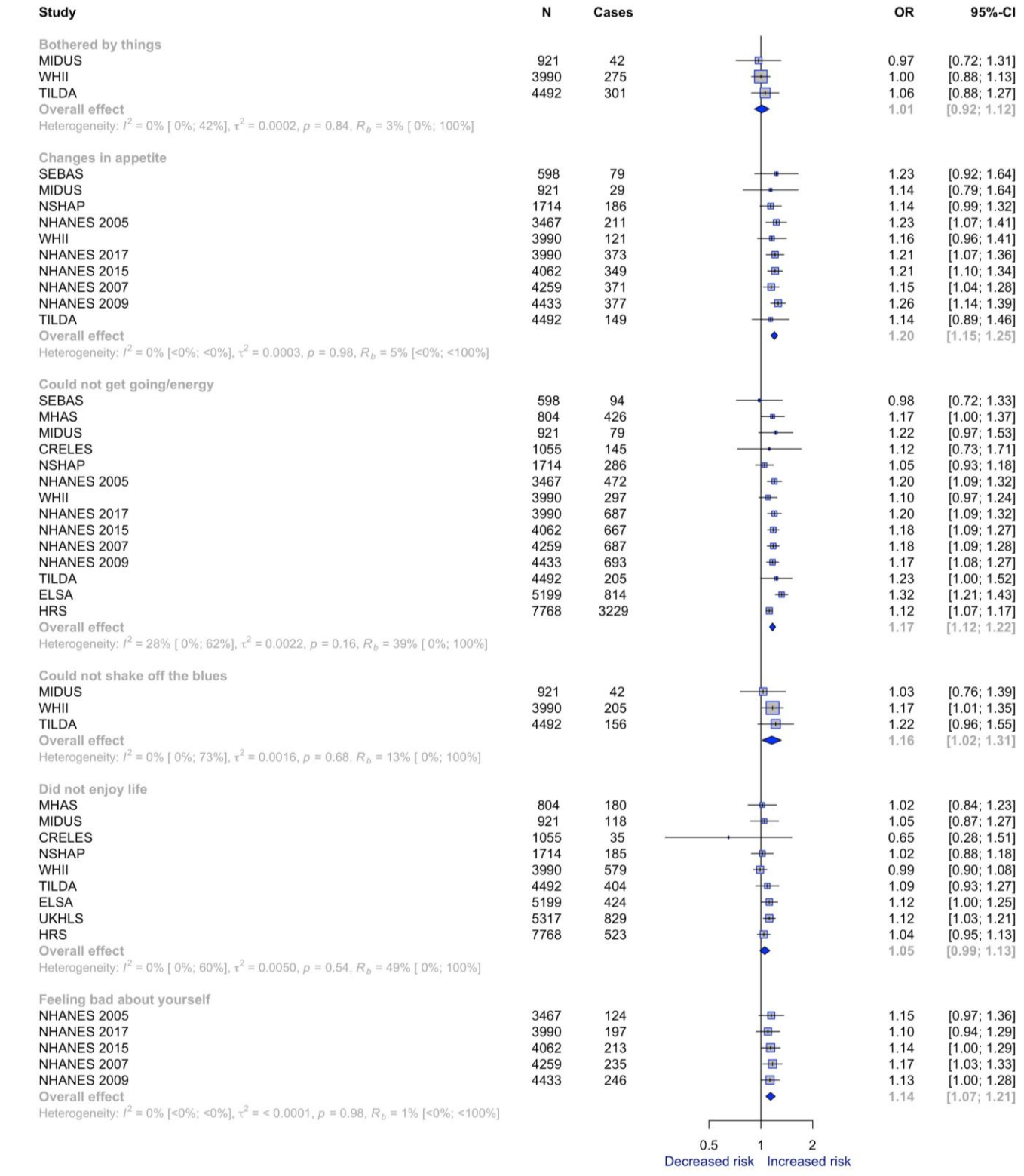


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***Figure S4c (continued)***

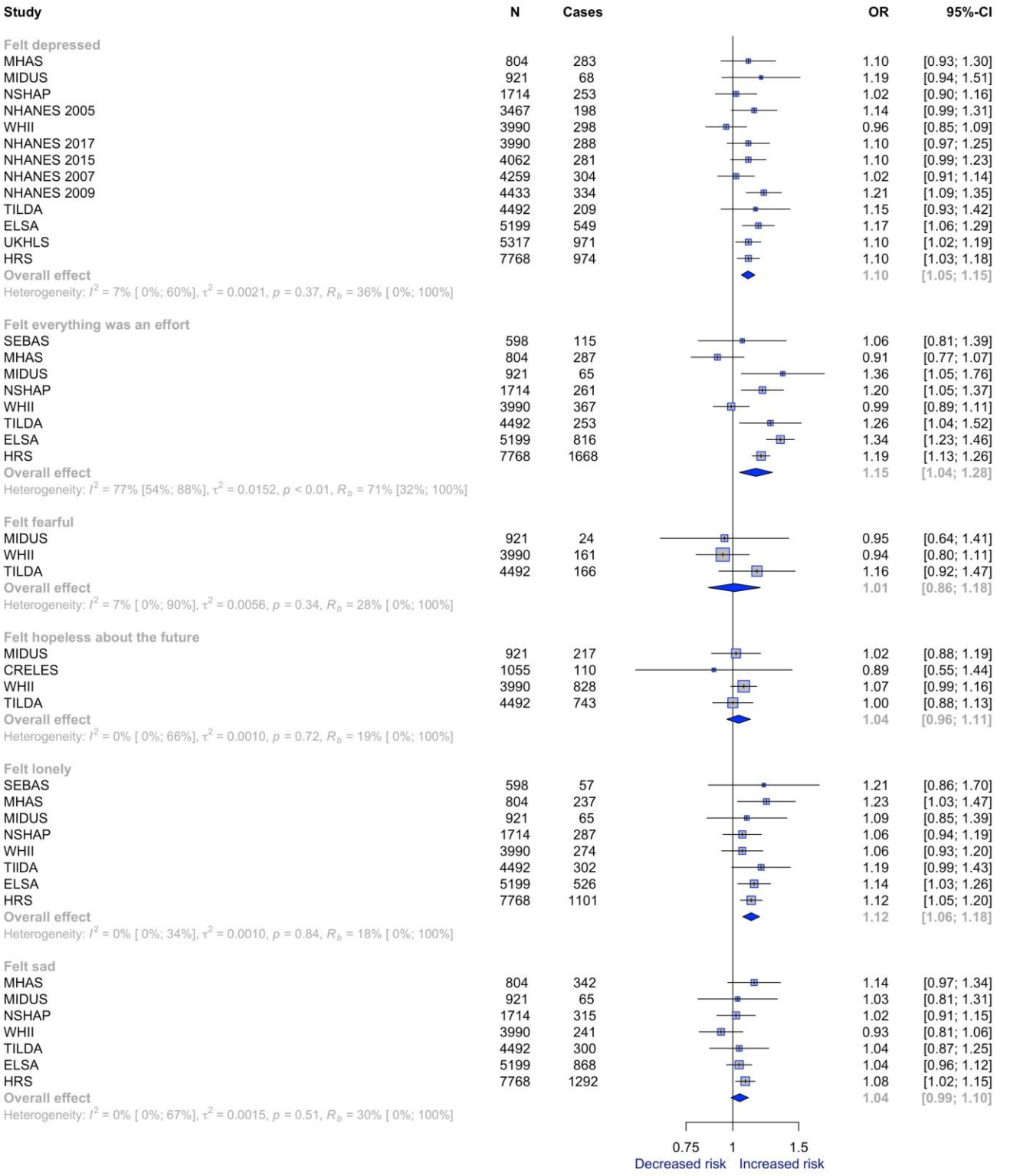


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***Figure S4c (continued)***

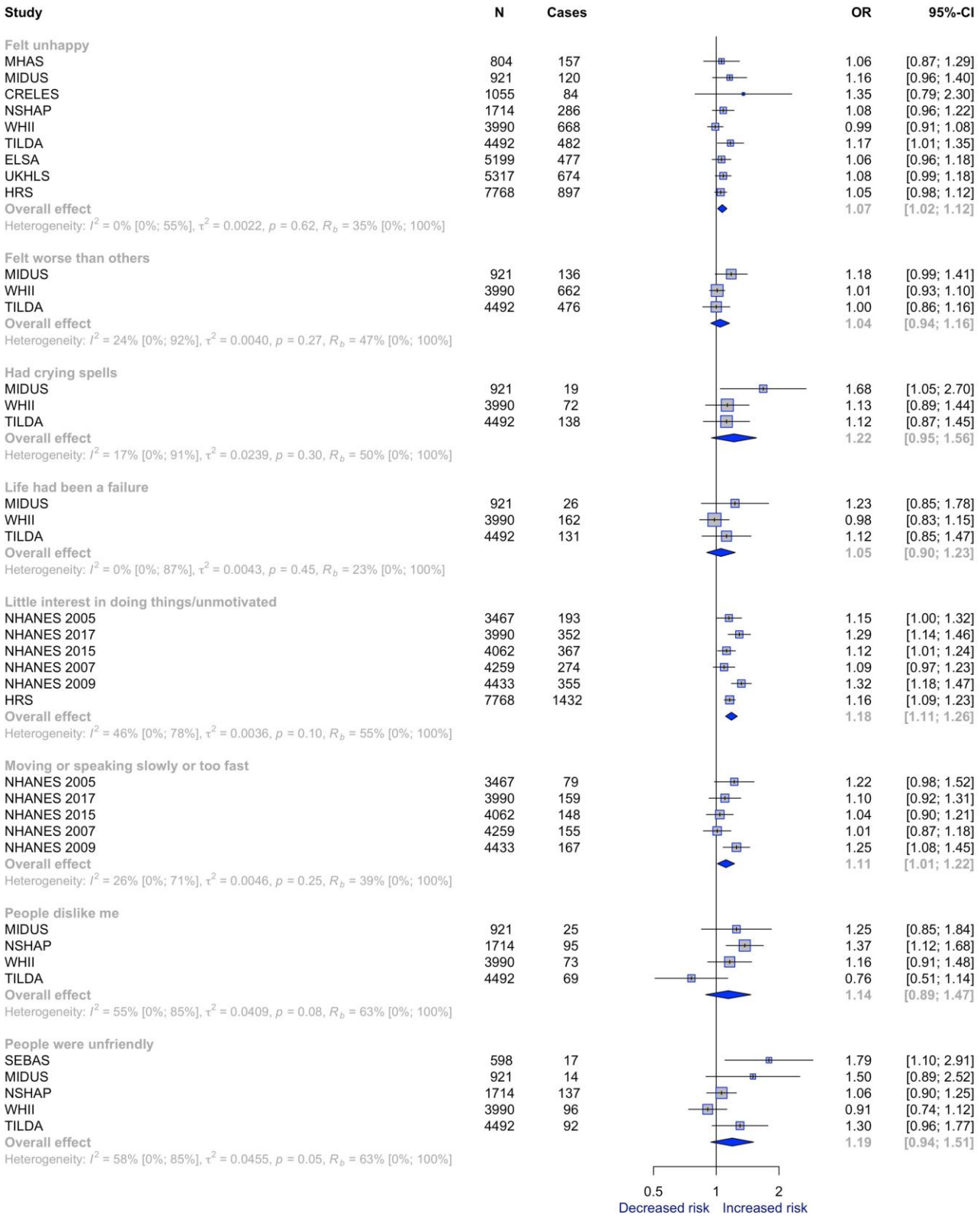


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***Figure S4c (continued)***

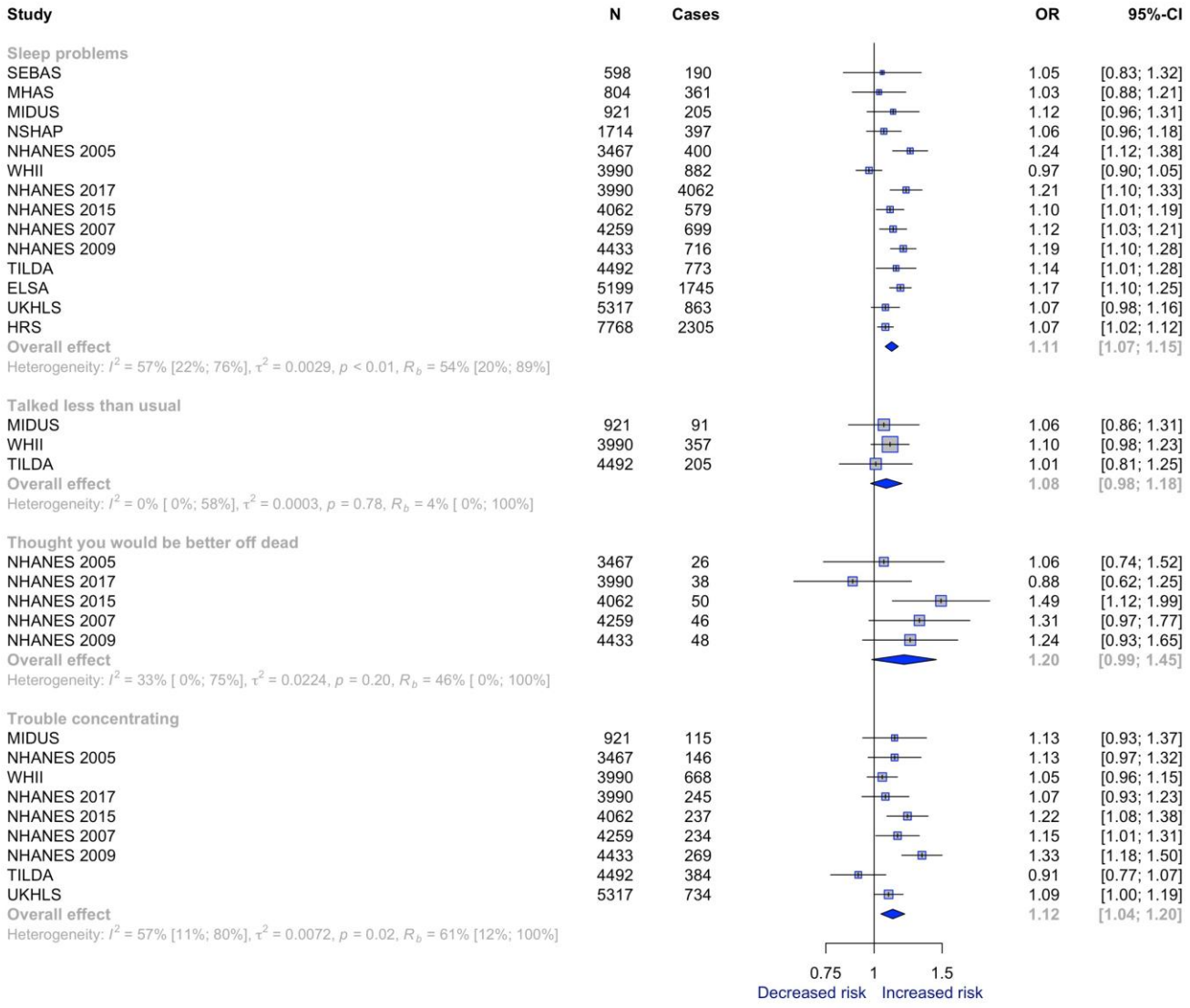

**FIGURE S4d. Random-effects meta-analysis of the cross-sectional association between C-reactive protein (low-grade) and individual depression symptoms (adjusted for age, sex & behavioural factors)**

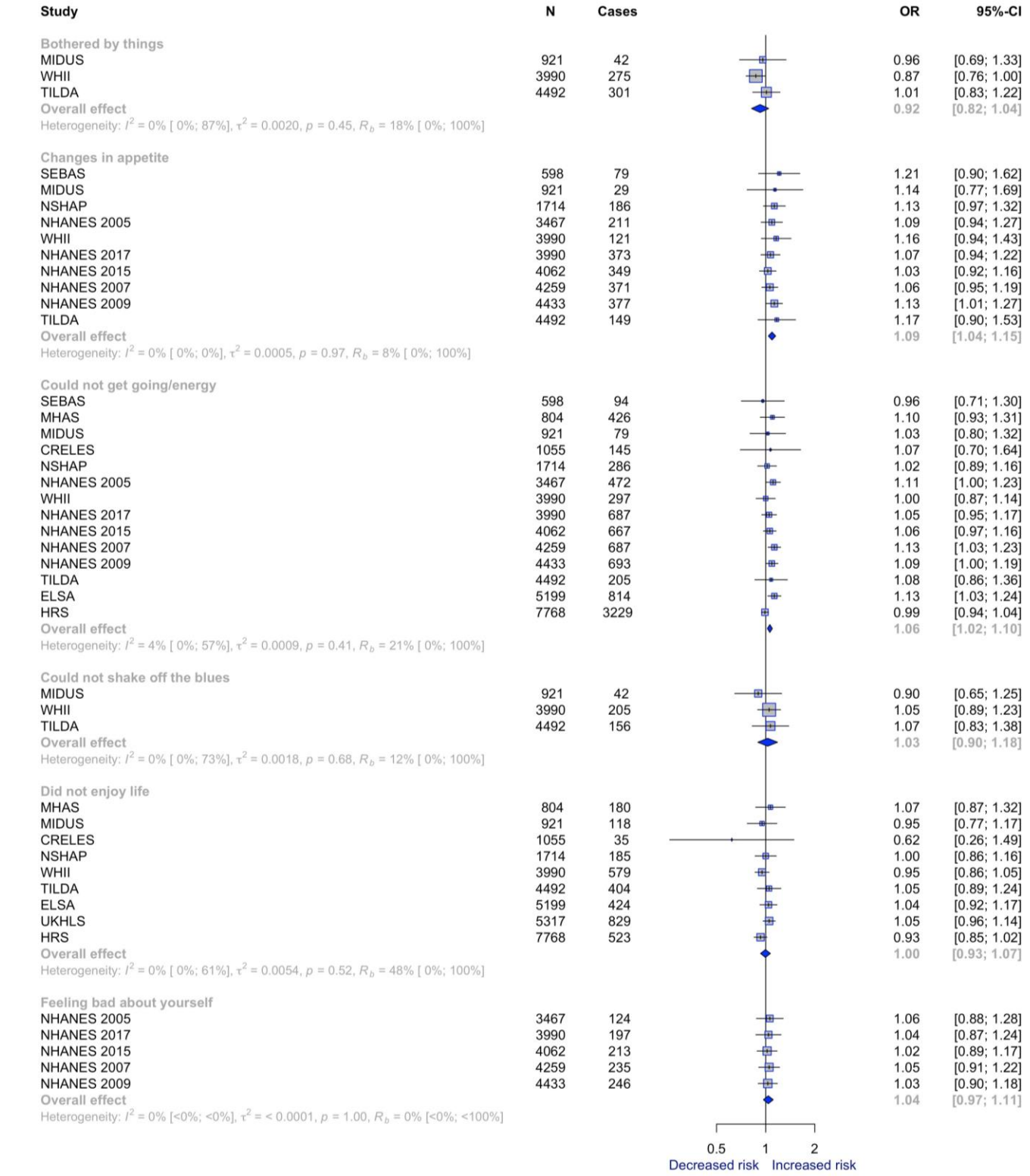


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***Figure S4d (continued)***

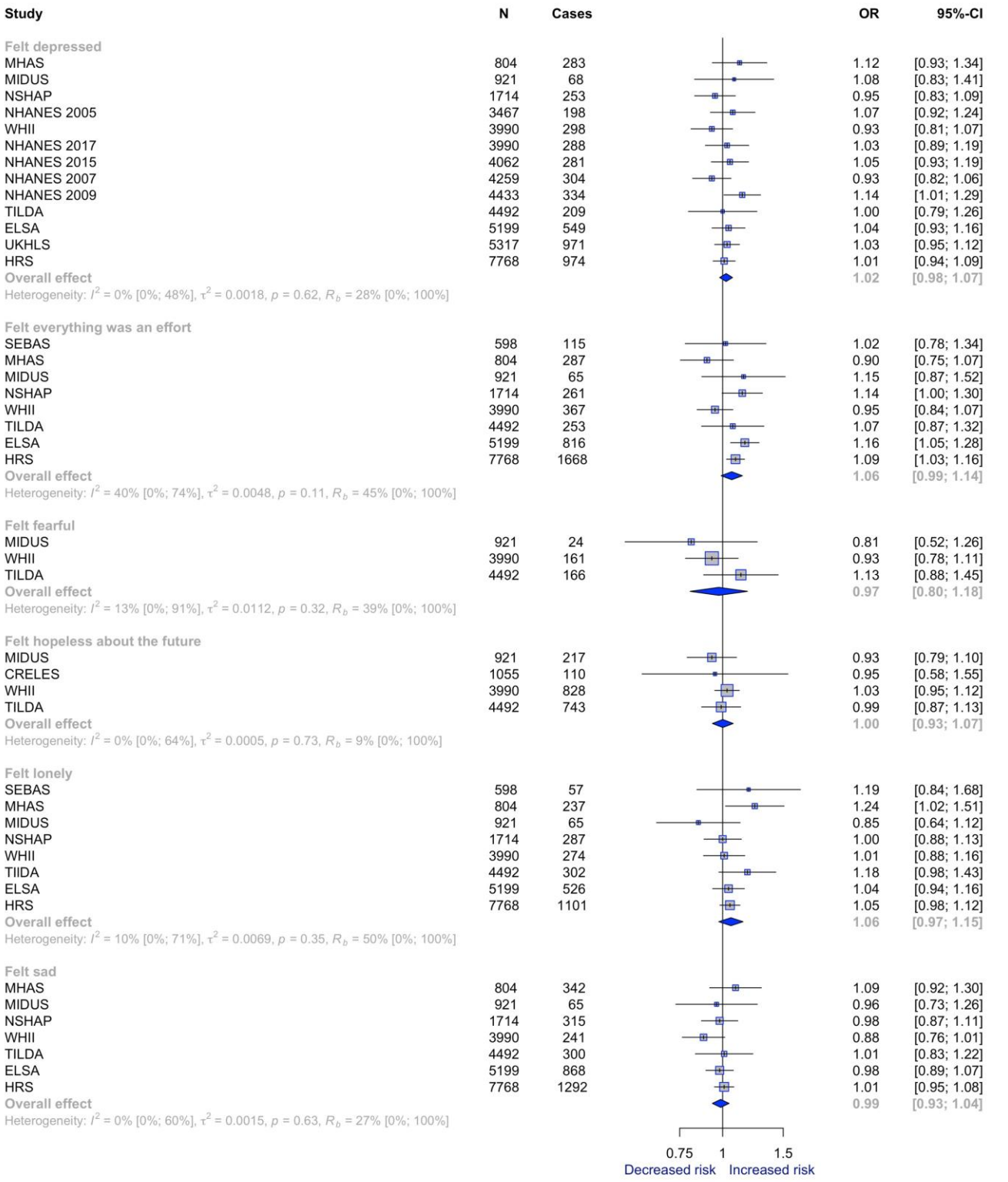


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***Figure S4d (continued)***

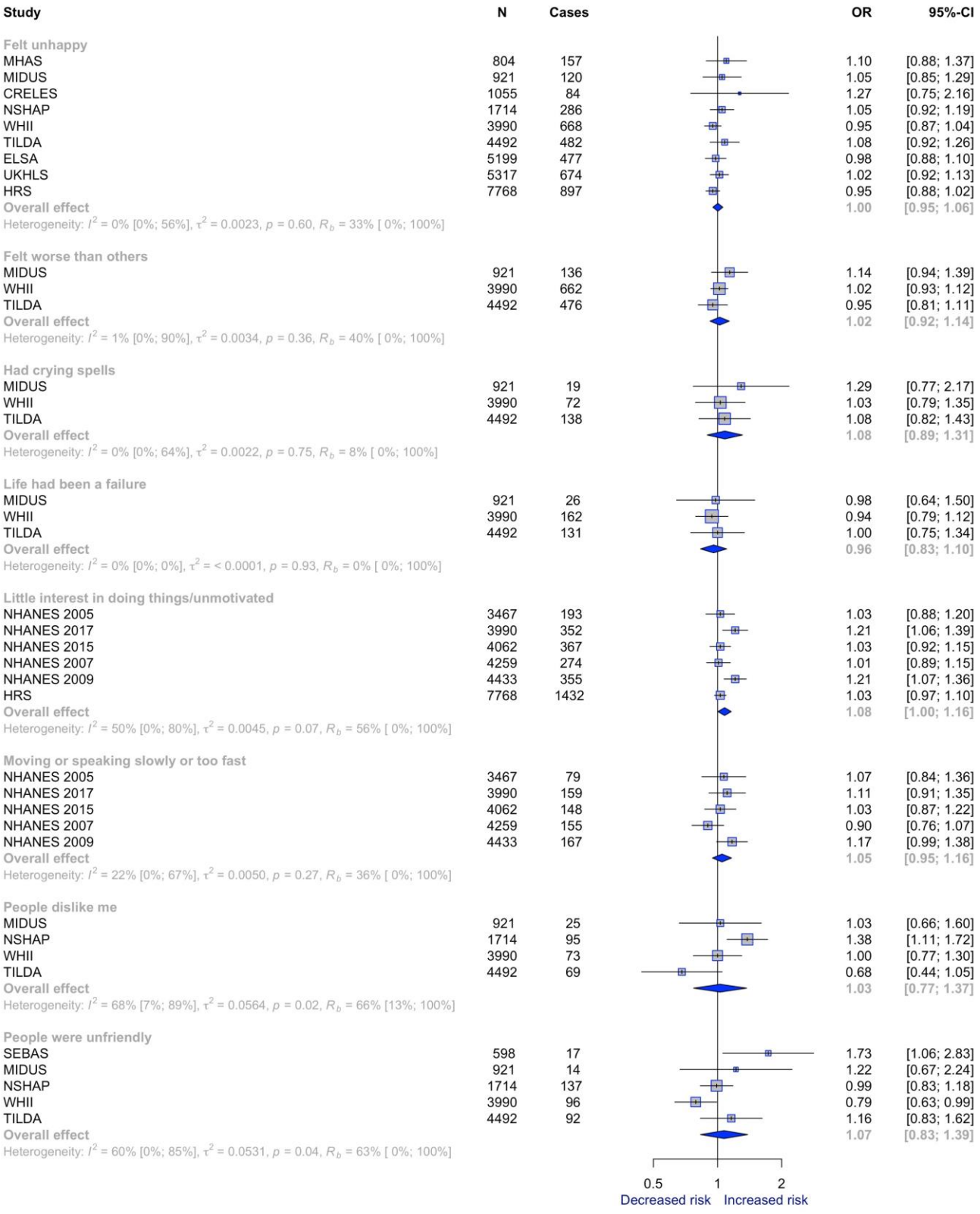


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***Figure S4d (continued)***

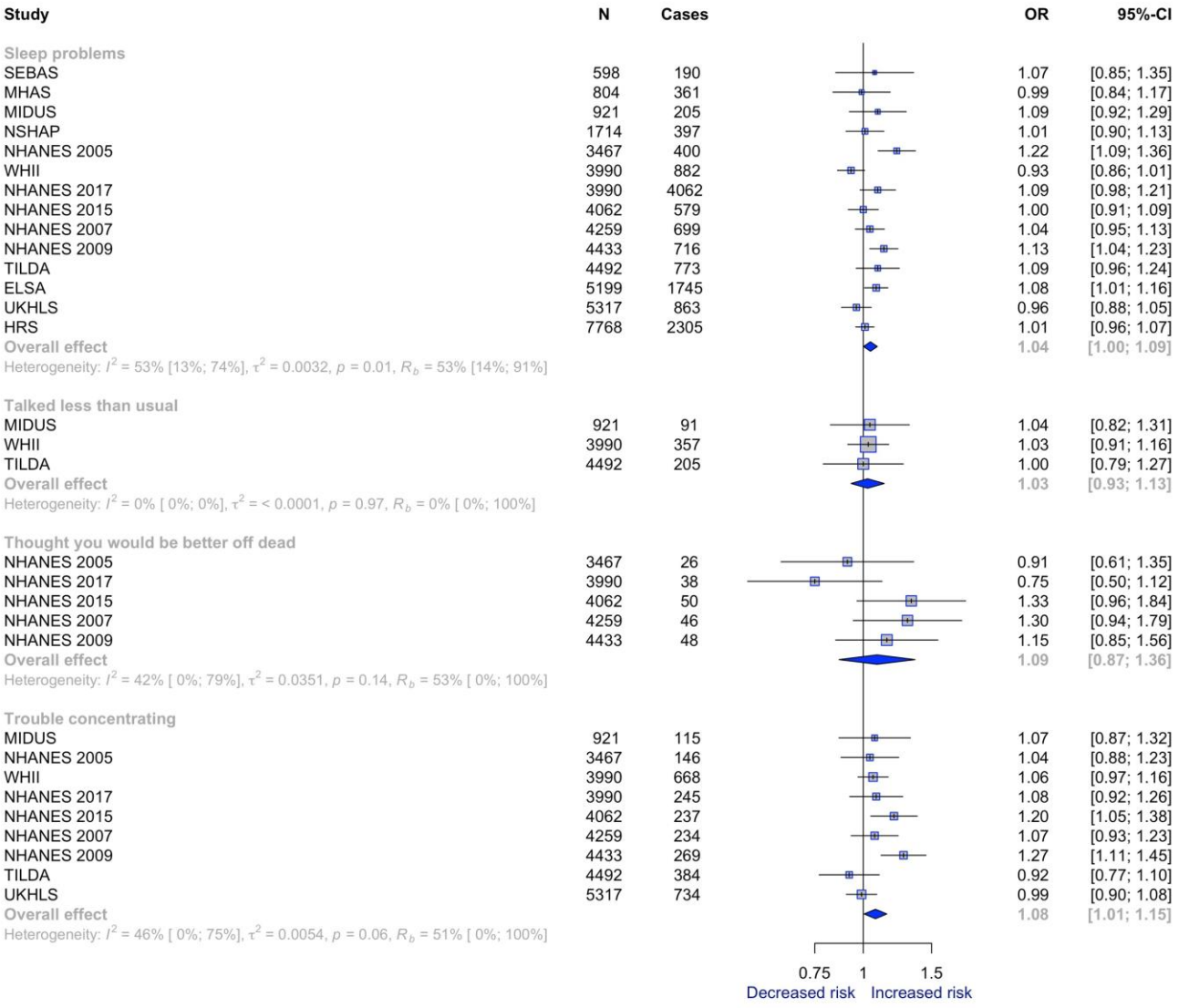

**FIGURE S5a. Random-effects meta-analysis of the cross-sectional association between interleukin-6 and individual depression symptoms (adjusted for age & sex)**

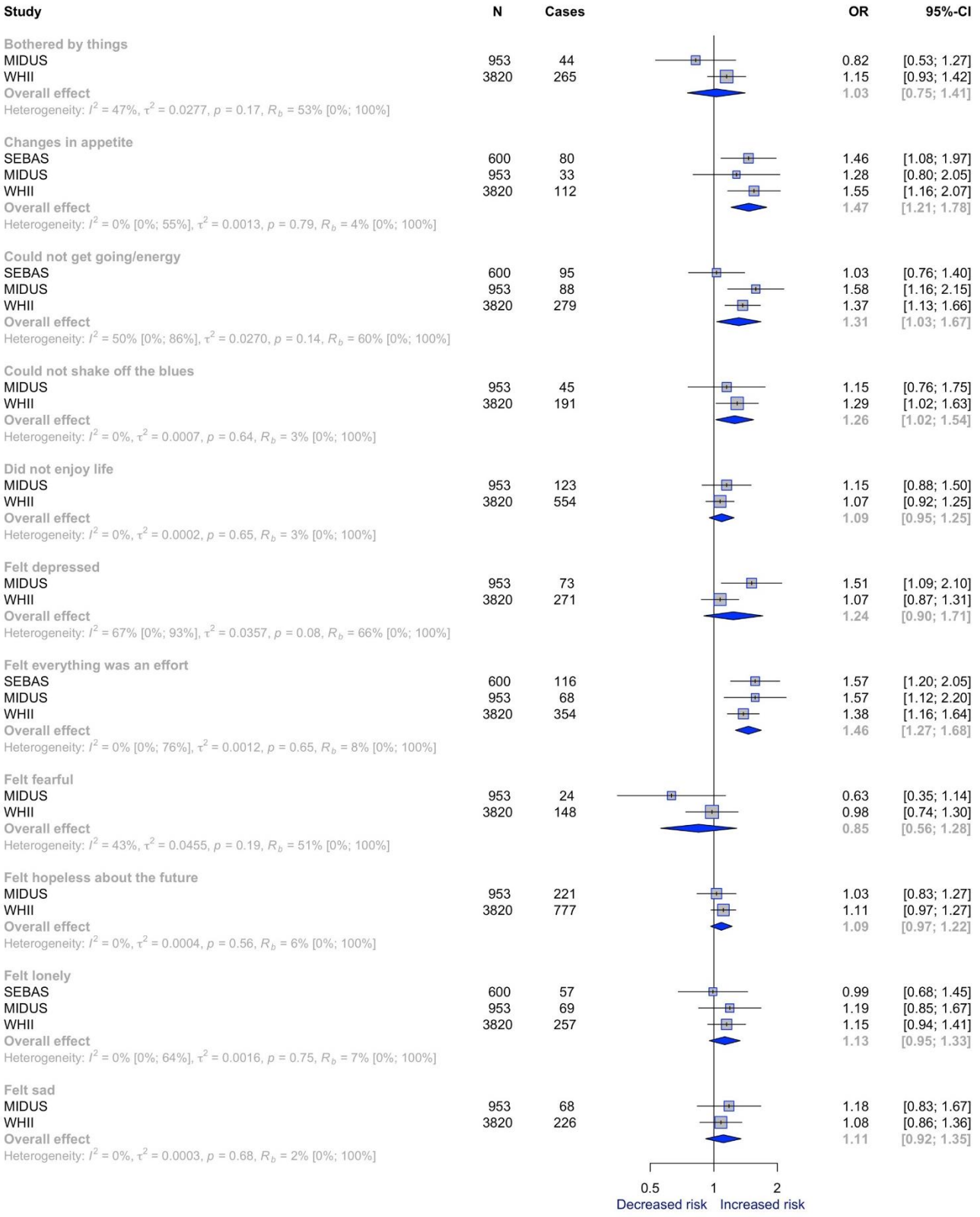


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***Figure S5a (continued)***

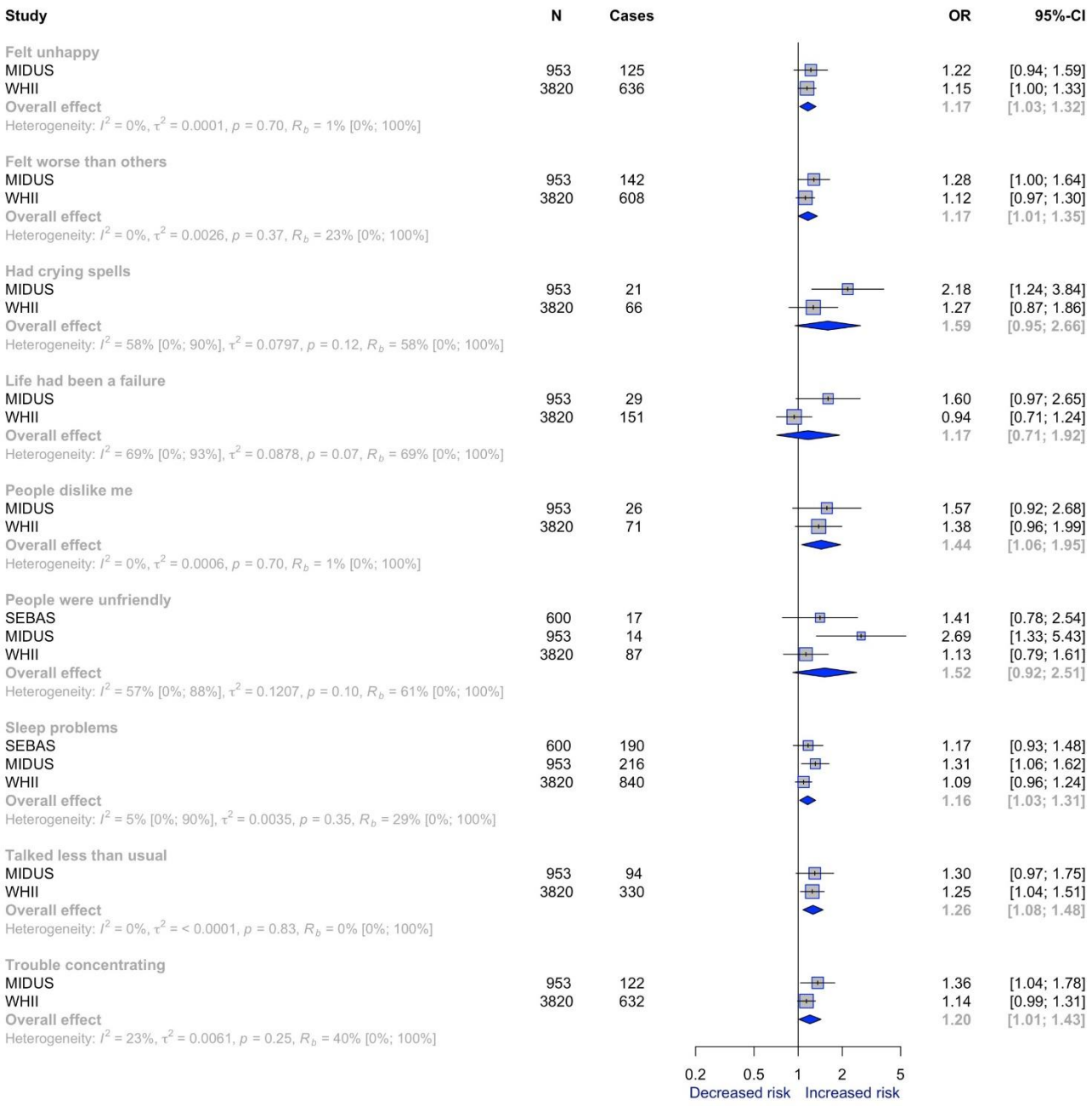

**FIGURE S5b. Random-effects meta-analysis of the cross-sectional association between interleukin-6 and individual depression symptoms (adjusted for age, sex & education)**

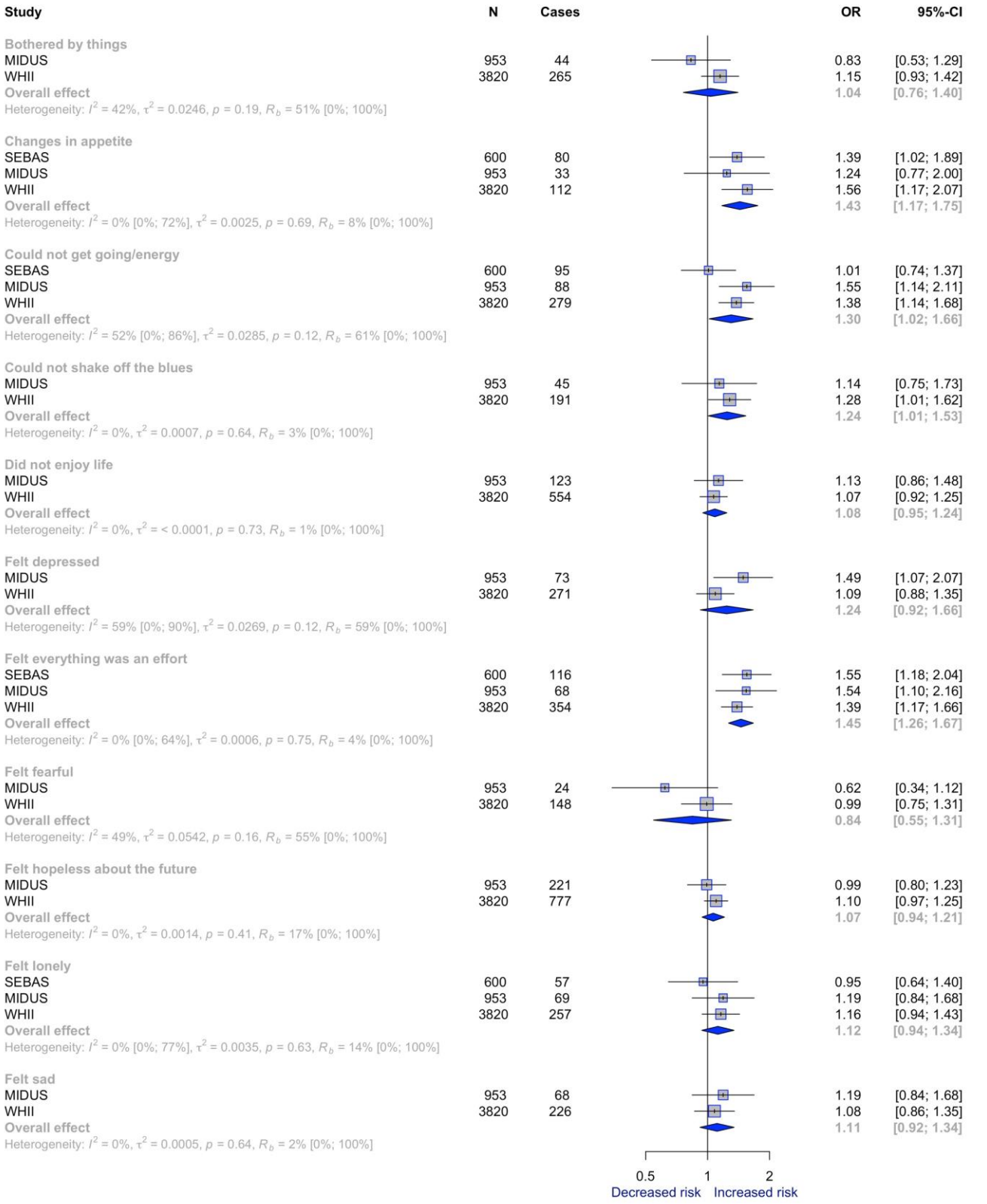


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***Figure S5b (continued)***

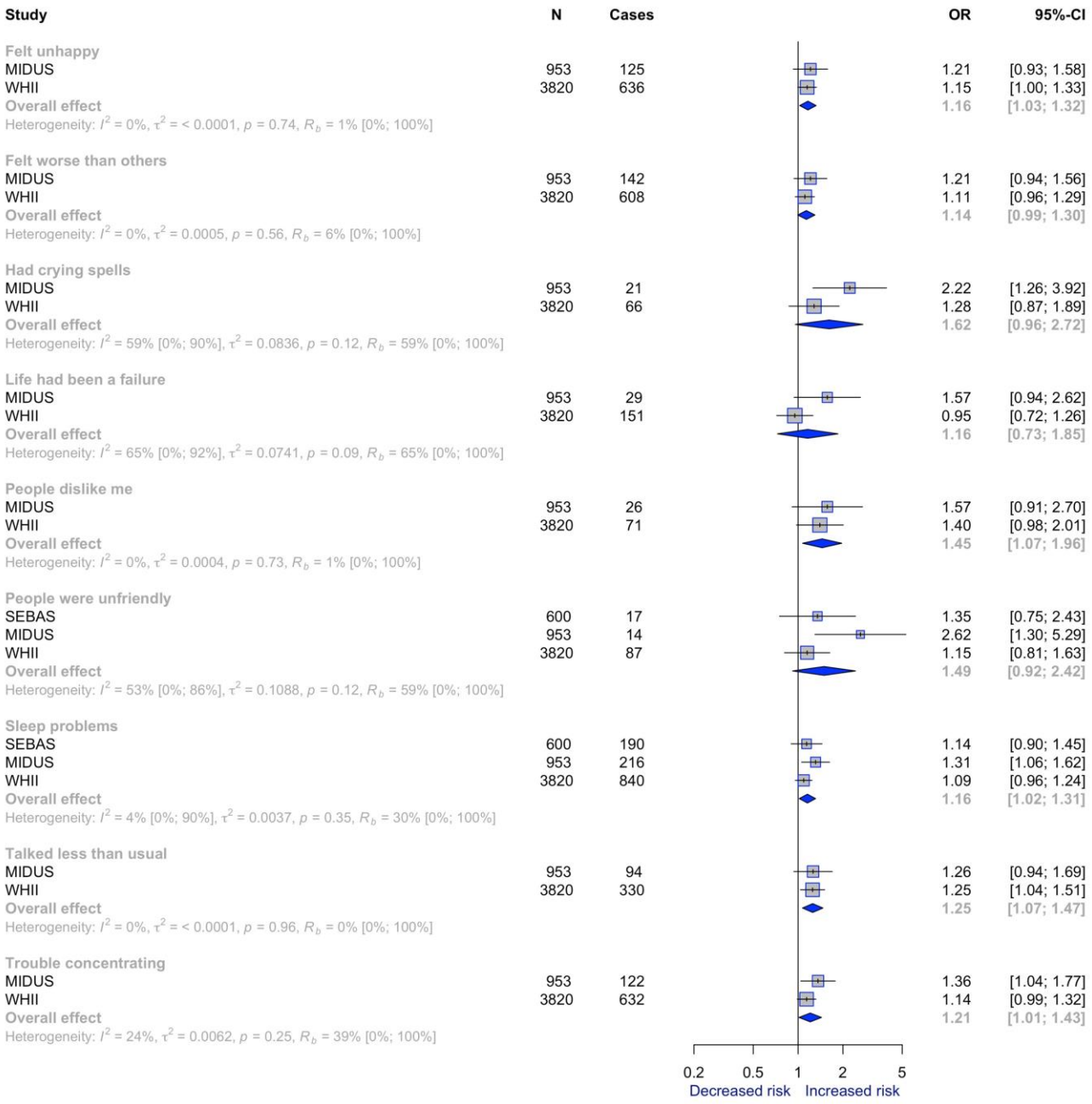

**FIGURE S5c. Random-effects meta-analysis of the cross-sectional association between interleukin-6 and individual depression symptoms (adjusted for age, sex & chronic illness-related factors)**

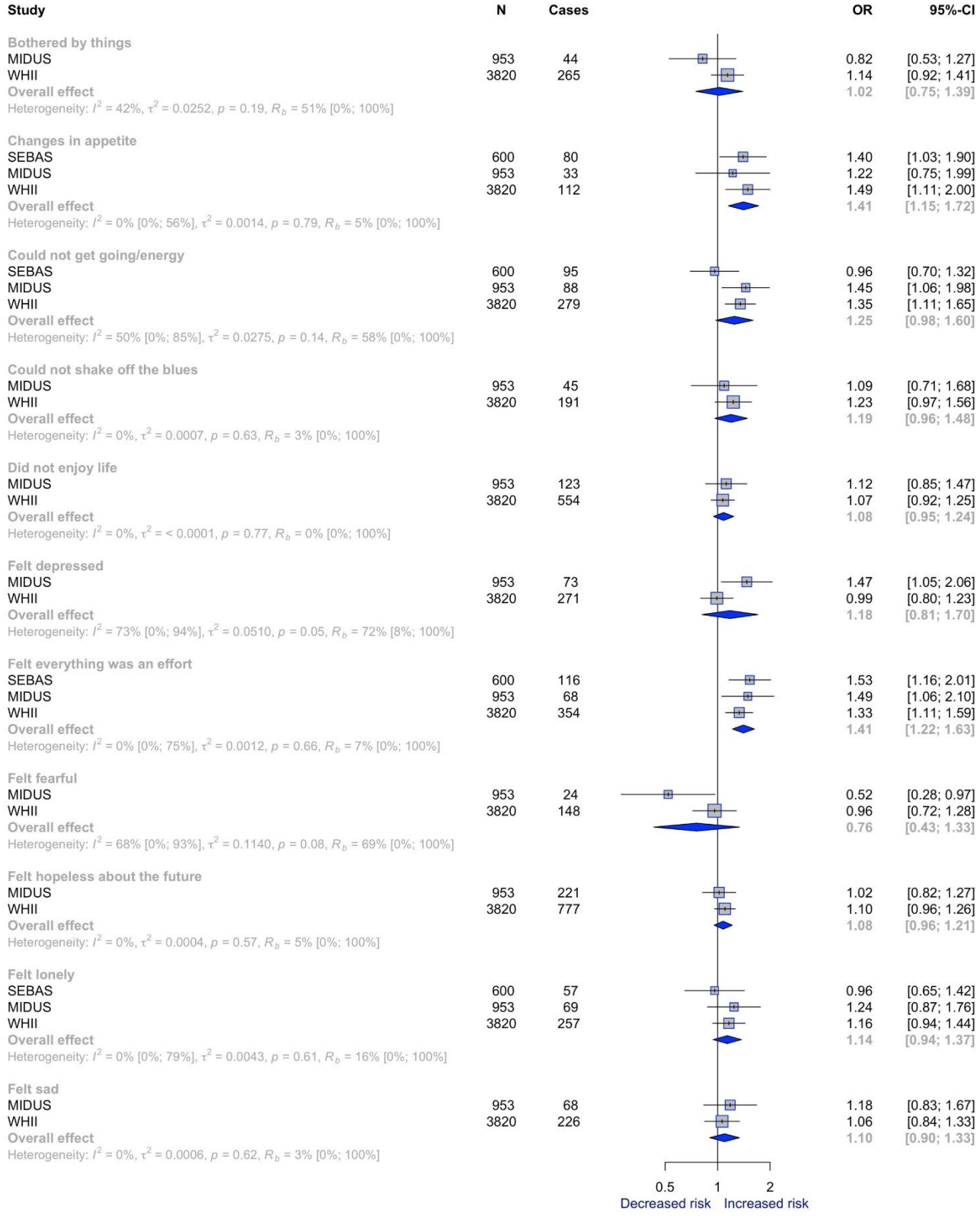


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***Figure S5c* (*continued*)**

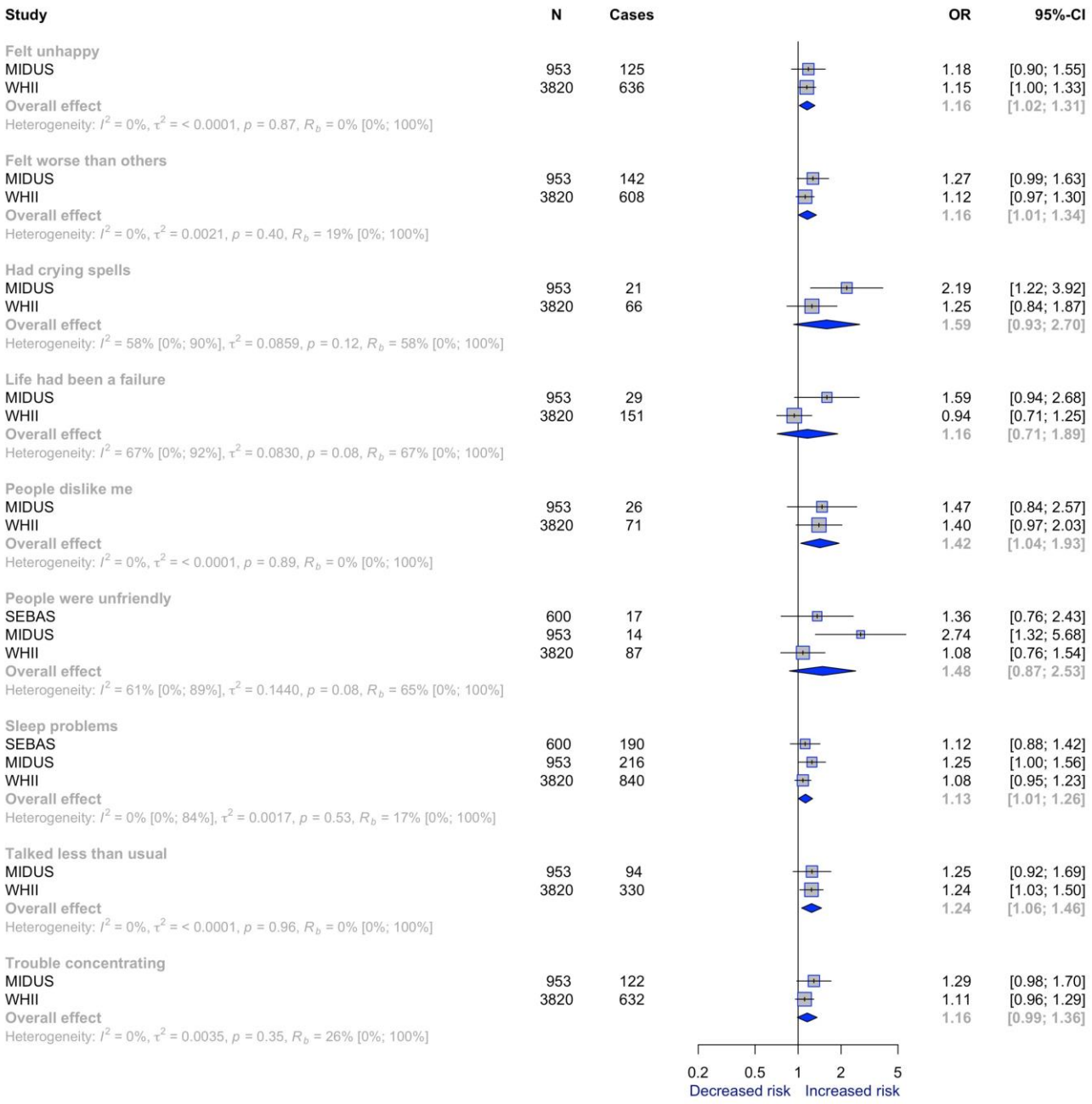

**FIGURE S5d. Random-effects meta-analysis of the cross-sectional association between interleukin-6 and individual depression symptoms (adjusted for age, sex & behavioural factors)**

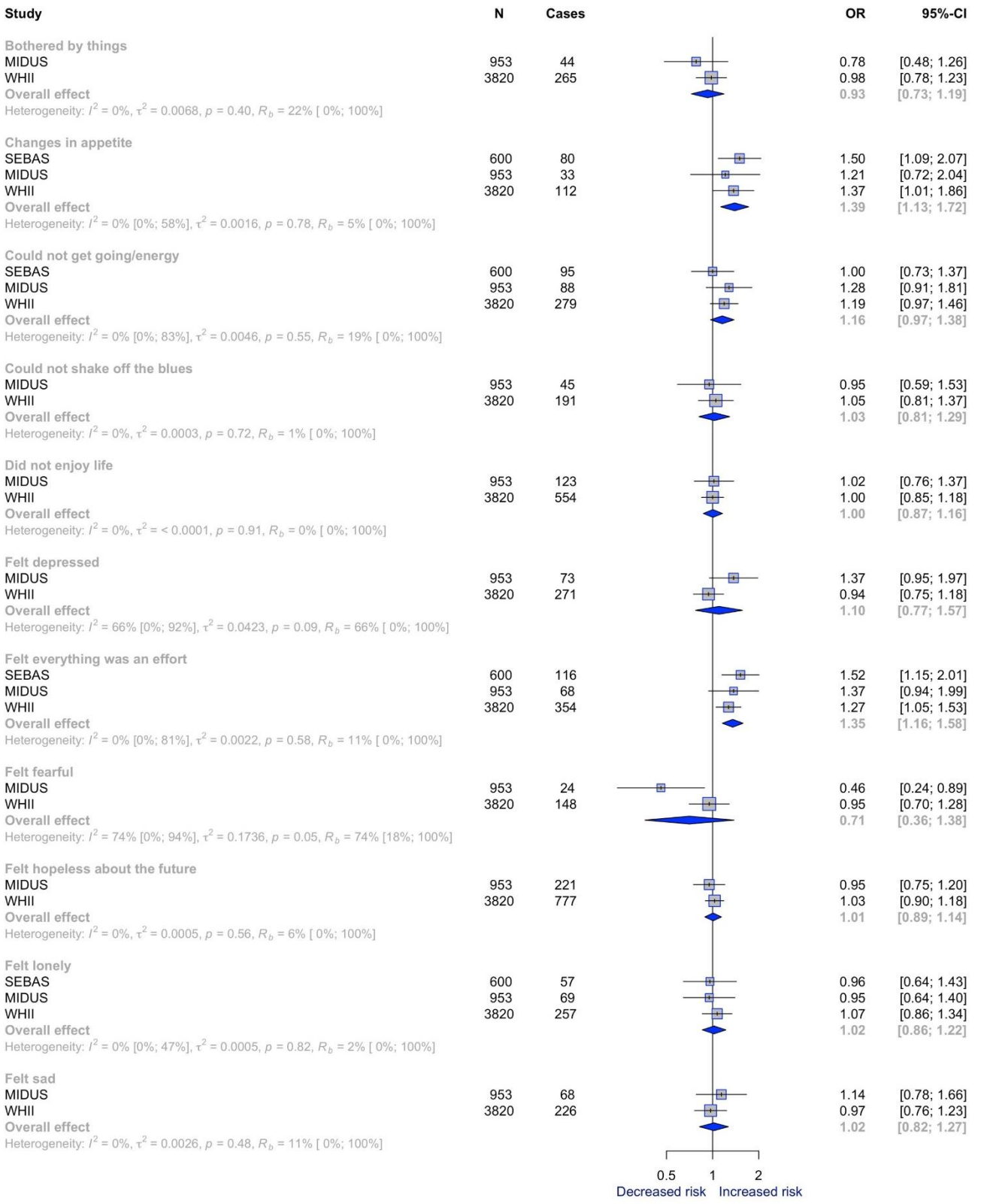


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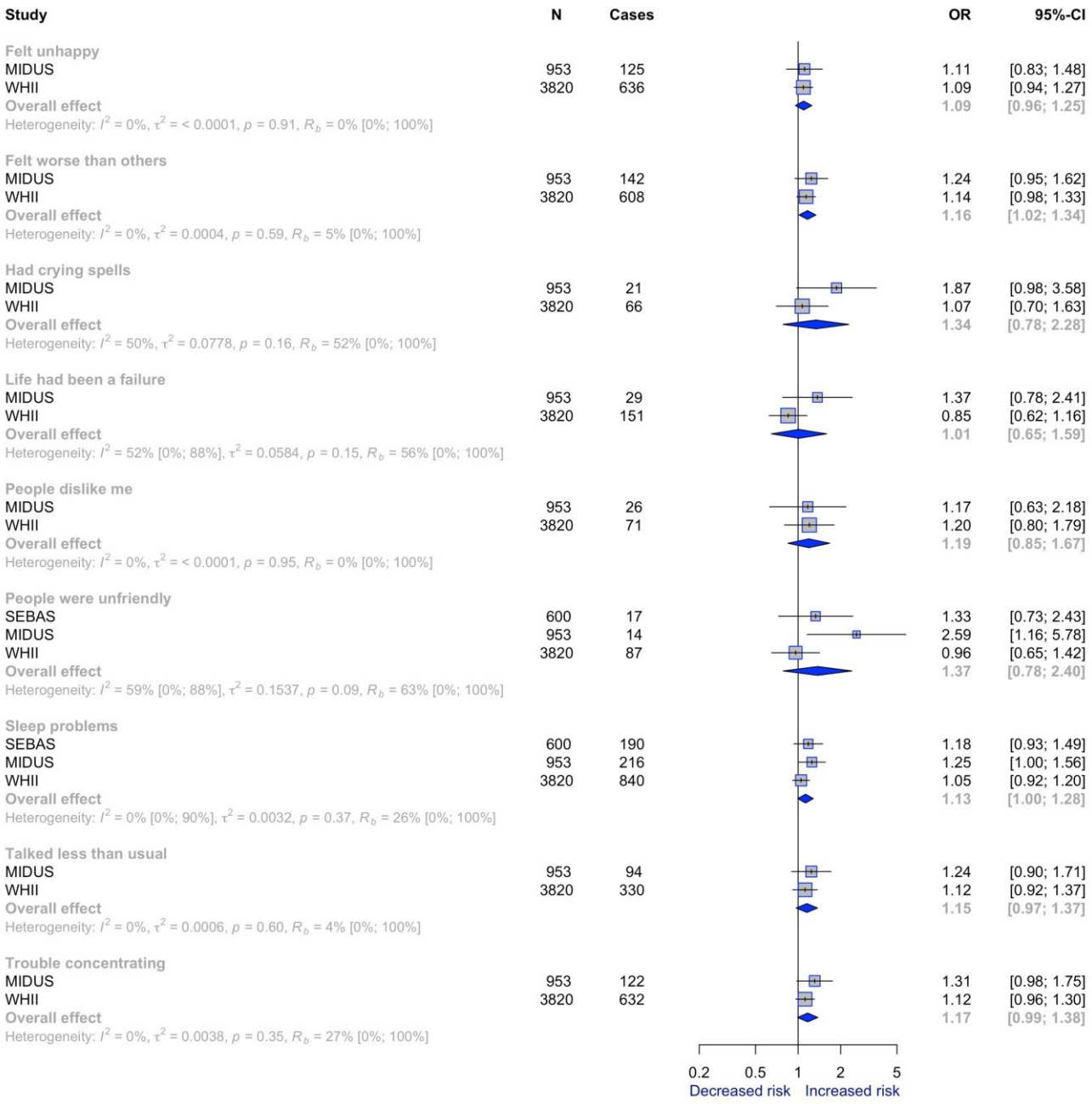
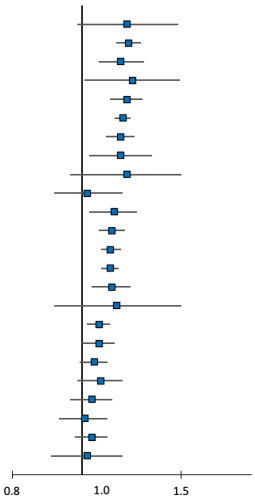
***Figure S5d (continued)***



## Appendix 4. Supplementary Analyses

## FIGURE S6. Serially adjusted cross-sectional associations between CRP (low-grade) and 24 individual symptoms of depression (random-effects meta-analysis)

| Depressive symptom (outcome) | N (participants)/ N (studies) | Odds ratio (95% CI) per 1SD higher CRP* | | | | |
|---|---|---|---|---|---|---|
| | | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 |
| *Had crying spells* | 9403 / 3 | 1.20 (0.98 - 1.48) | 1.19 (0.96 - 1.48) | 1.22 (0.95 - 1.56) | 1.08 (0.89 - 1.31) | 1.09 (0.89 - 1.32) |
| *Changes in appetite* | 31926 / 10 | 1.21 (1.16 - 1.27) | 1.18 (1.12 - 1.23) | 1.20 (1.15 - 1.25) | 1.09 (1.04 - 1.15) | 1.08 (1.02 - 1.13) |
| *Felt everything was an effort* | 25486 / 8 | 1.17 (1.07 - 1.29) | 1.14 (1.05 - 1.24) | 1.15 (1.04 - 1.28) | 1.06 (0.99 - 1.14) | 1.05 (0.97 - 1.13) |
| *Thought you would be better off dead* | 20211 / 5 | 1.23 (1.01 - 1.49) | 1.18 (0.97 - 1.44) | 1.20 (0.99 - 1.45) | 1.09 (0.87 - 1.36) | 1.07 (0.85 - 1.34) |
| *Little insterest in doing things* | 27979 / 6 | 1.20 (1.12 - 1.28) | 1.16 (1.08 - 1.24) | 1.18 (1.11 - 1.26) | 1.08 (1.00 - 1.16) | 1.07 (1.00 - 1.15) |
| *Could not get going* | 46752 / 14 | 1.18 (1.13 - 1.22) | 1.16 (1.12 - 1.20) | 1.17 (1.12 - 1.22) | 1.06 (1.02 - 1.10) | 1.06 (1.02 - 1.09) |
| *Feeling bad about yourself* | 20211 / 5 | 1.17 (1.10 - 1.24) | 1.13 (1.06 - 1.20) | 1.14 (1.07 - 1.21) | 1.04 (0.97 - 1.11) | 1.02 (0.96 - 1.10) |
| *Could not shake off the blues* | 9403 / 3 | 1.17 (1.03 - 1.33) | 1.15 (1.03 - 1.28) | 1.16 (1.02 - 1.31) | 1.03 (0.90 - 1.18) | 1.03 (0.90 - 1.18) |
| *People were unfriendly* | 11715 / 5 | 1.20 (0.95 - 1.50) | 1.17 (0.93 - 1.46) | 1.19 (0.94 - 1.51) | 1.07 (0.83 - 1.33) | 1.06 (0.82 - 1.36) |
| *Life had been a failure* | 9403 / 3 | 1.02 (0.89 - 1.18) | 1.03 (0.90 - 1.18) | 1.05 (0.90 - 1.23) | 0.96 (0.83 - 1.10) | 0.97 (0.84 - 1.12) |
| *Moving or speaking slowly or too fast* | 20211 / 5 | 1.14 (1.03 - 1.25) | 1.09 (0.99 - 1.20) | 1.11 (1.01 - 1.22) | 1.05 (0.95 - 1.16) | 1.04 (0.94 - 1.15) |
| *Felt lonely* | 25486 / 8 | 1.13 (1.07 - 1.19) | 1.09 (1.04 - 1.15) | 1.12 (1.06 - 1.18) | 1.06 (0.97 - 1.15) | 1.04 (0.97 - 1.12) |
| *Sleep problems* | 51014 / 14 | 1.12 (1.08 - 1.17) | 1.10 (1.06 - 1.14) | 1.11 (1.07 - 1.15) | 1.04 (1.00 - 1.09) | 1.04 (1.00 - 1.08) |
| *Felt depressed* | 50416 / 13 | 1.12 (1.08 - 1.16) | 1.08 (1.04 - 1.12) | 1.10 (1.05 - 1.15) | 1.02 (0.98 - 1.07) | 1.01 (0.97 - 1.05) |
| *Trouble concentrating* | 34931 / 9 | 1.13 (1.05 - 1.22) | 1.11 (1.03 - 1.19) | 1.12 (1.04 - 1.20) | 1.08 (1.01 - 1.15) | 1.07 (1.00 - 1.14) |
| *People dislike me* | 11117 / 4 | 1.15 (0.89 - 1.50) | 1.12 (0.87 - 1.45) | 1.14 (0.89 - 1.47) | 1.03 (0.77 - 1.37) | 1.03 (0.78 - 1.35) |
| *Felt unhappy* | 31260 / 9 | 1.07 (1.02 - 1.12) | 1.06 (1.01 - 1.11) | 1.07 (1.02 - 1.12) | 1.00 (0.95 - 1.06) | 1.00 (0.95 - 1.06) |
| *Did not enjoy life* | 31260 / 9 | 1.07 (1.00 - 1.14) | 1.04 (0.98 - 1.11) | 1.05 (0.99 - 1.13) | 1.00 (0.93 - 1.07) | 0.99 (0.92 - 1.07) |
| *Felt sad* | 24888 / 7 | 1.05 (0.99 - 1.11) | 1.03 (0.98 - 1.09) | 1.04 (0.99 - 1.10) | 0.99 (0.93 - 1.04) | 0.98 (0.93 - 1.03) |
| *Talked less than usual* | 9403 / 3 | 1.08 (0.98 - 1.18) | 1.06 (0.96 - 1.17) | 1.08 (0.98 - 1.18) | 1.03 (0.93 - 1.13) | 1.03 (0.93 - 1.13) |
| *Felt worse than others* | 9403 / 3 | 1.04 (0.95 - 1.14) | 1.00 (0.93 - 1.08) | 1.04 (0.94 - 1.16) | 1.02 (0.92 - 1.14) | 1.02 (0.92 - 1.12) |
| *Bothered by things* | 9403 / 3 | 1.01 (0.91 - 1.12) | 1.01 (0.91 - 1.11) | 1.01 (0.92 - 1.12) | 0.92 (0.82 - 1.04) | 0.93 (0.82 - 1.04) |
| *Felt hopeless about the future* | 10458 / 4 | 1.04 (0.97 - 1.11) | 1.02 (0.95 - 1.10) | 1.04 (0.96 - 1.11) | 1.00 (0.93 - 1.07) | 1.00 (0.92 - 1.08) |
| *Felt fearful* | 9403 / 3 | 1.02 (0.88 - 1.18) | 1.02 (0.88 - 1.18) | 1.01 (0.86 - 1.18) | 0.97 (0.80 - 1.18) | 0.97 (0.80 - 1.17) |

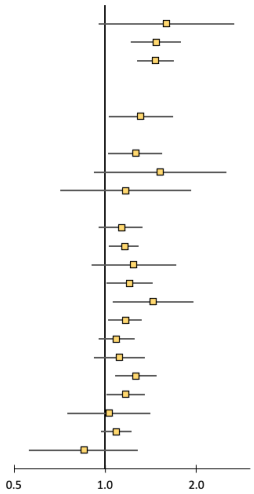



*Model 1: Adjusted for age, sex and baseline depression symptom; Model 2: As Model 1 and additionally adjusted for education; Model 3: As Model 1 and additionally adjusted for chronic illness-related risk factors; Model 4: as Model 1 and additionally adjusted for behavioural risk factors; Model 5: adjusted for all of the above covariates.

Note: These analyses excluded participants with CRP values ≥ 10 mg/L. (i.e., low-grade inflammation)

# FIGURE S7. Serially adjusted cross-sectional associations between interleukin-6 and 21 individual symptoms of depression (random-effects meta-analysis)

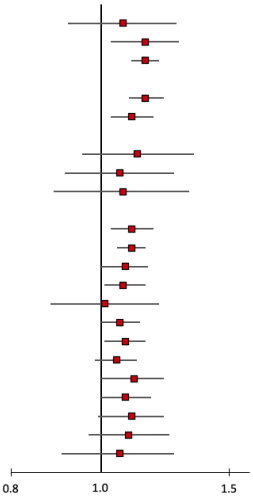
| Depressive symptom (outcome) | N (participants)/ N (studies) | Odds ratio (95% CI) per 1SD higher IL-6* | | | | |
|---|---|---|---|---|---|---|
| | | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 |
| *Had crying spells* | 4773 / 2 | 1.59 (0.95 - 2.66) | 1.62 (0.96 - 2.72) | 1.59 (0.93 - 2.70) | 1.34 (0.78 - 2.28) | 1.34 (0.78 - 2.28) |
| *Changes in appetite* | 5373 / 3 | 1.47 (1.21 - 1.78) | 1.43 (1.17 - 1.75) | 1.41 (1.15 - 1.72) | 1.39 (1.13 - 1.72) | 1.31 (1.06 - 1.63) |
| *Felt everything was an effort* | 5373 / 3 | 1.46 (1.27 - 1.68) | 1.45 (1.26 - 1.67) | 1.41 (1.22 - 1.63) | 1.35 (1.16 - 1.58) | 1.31 (1.12 - 1.53) |
| *Thought you would be better off dead* | No data | | | | | |
| *Little insterest in doing things* | No data | | | | | |
| *Could not get going* | 5373 / 3 | 1.31 (1.03 - 1.67) | 1.30 (1.02 - 1.66) | 1.25 (0.98 - 1.60) | 1.16 (0.97 - 1.38) | 1.12 (0.92 - 1.35) |
| *Feeling bad about yourself* | No data | | | | | |
| *Could not shake off the blues* | 4773 / 2 | 1.26 ( 1.02 - 1.54) | 1.24 (1.01 - 1.53) | 1.19 (0.96 - 1.48) | 1.03 (0.81 - 1.29) | 1.00 (0.78 - 1.26) |
| *People were unfriendly* | 5373 / 3 | 1.52 (0.92 - 2.51) | 1.49 (0.92 - 2.42) | 1.48 (0.87 - 2.53) | 1.37 (0.78 - 2.40) | 1.33 (0.75 - 2.34) |
| *Life had been a failure* | 4773 / 2 | 1.17 (0.71 - 1.92 | 1.16 (0.73 - 1.85) | 1.16 (0.71 - 1.89) | 1.01 (0.65 - 1.59) | 1.00 (0.66 - 1.52) |
| *Moving or speaking slowly or too fast* | No data | | | | | |
| *Felt lonely* | 5373 / 3 | 1.13 (0.95 - 1.33) | 1.12 (0.94 - 1.34) | 1.14 (0.94 - 1.37) | 1.02 (0.86 - 1.22) | 1.02 (0.85 - 1.22) |
| *Sleep problems* | 5373 / 3 | 1.16 (1.03 - 1.31) | 1.16 (1.02 - 1.31) | 1.13 (1.01 - 1.26) | 1.13 (1.00 - 1.28) | 1.09 (0.97 - 1.22) |
| *Felt depressed* | 4773 / 2 | 1.24 (0.90 - 1.71) | 1.24 (0.92 - 1.66) | 1.18 (0.81 - 1.70) | 1.10 (0.77 - 1.57) | 1.05 (0.75 - 1.47) |
| *Trouble concentrating* | 4773 / 2 | 1.20 (1.01 - 1.43) | 1.21 (1.01 - 1.43) | 1.16 (0.99 - 1.36) | 1.17 (0.99 - 1.38) | 1.13 (0.98 - 1.30) |
| *People dislike me* | 4773 / 2 | 1.44 (1.06 - 1.95) | 1.45 (1.07 - 1.96) | 1.42 (1.04 - 1.93) | 1.19 (0.85 - 1.67) | 1.19 (0.85 - 1.68) |
| *Felt unhappy* | 4773 / 2 | 1.17 (1.03 - 1.32) | 1.16 (1.03 - 1.32) | 1.16 (1.02 - 1.31) | 1.09 (0.96 - 1.25) | 1.08 (0.95 - 1.24) |
| *Did not enjoy life* | 4773 / 2 | 1.09 (0.95 - 1.25) | 1.08 (0.95 - 1.24) | 1.08 (0.95 - 1.24) | 1.00 (0.87 - 1.16) | 1.00 (0.87 - 1.15) |
| *Felt sad* | 4773 / 2 | 1.11 (0.92 - 1.35) | 1.11 (0.92 - 1.34) | 1.10 (0.90 - 1.33) | 1.02 (0.82 - 1.27) | 1.00 (0.81 - 1.26) |
| *Talked less than usual* | 4773 / 2 | 1.26 (1.08 - 1.48) | 1.25 (1.07 - 1.47) | 1.24 (1.06 - 1.46) | 1.15 (0.97 - 1.37) | 1.13 (0.96 - 1.34) |
| *Felt worse than others* | 4773 / 2 | 1.17 (1.01 - 1.35) | 1.14 (0.99 - 1.30) | 1.16 (1.01 - 1.34) | 1.16 (1.02 - 1.34) | 1.14 (1.00 - 1.31) |
| *Bothered by things* | 4773 / 2 | 1.03 (0.75 - 1.41) | 1.04 (0.76 - 1.40) | 1.02 (0.75 - 1.39) | 0.93 (0.73 - 1.19) | 0.93 (0.71 - 1.21) |
| *Felt hopeless about the future* | 4773 / 2 | 1.09 (0.97 - 1.22) | 1.07 (0.94 - 1.21) | 1.08 (0.96 - 1.21) | 1.01 (0.89 - 1.14) | 0.99 (0.86 - 1.14) |
| *Felt fearful* | 4773 / 2 | 0.85 (0.56 - 1.28) | 0.84 (0.55 - 1.31) | 0.76 (0.43 - 1.33) | 0.71 (0.36 - 1.38) | 0.62 (0.86 - 1.14) |




*Model 1: Adjusted for age, sex and baseline depression symptom; Model 2: As Model 1 and additionally adjusted for education; Model 3: As Model 1 and additionally adjusted for chronic illness-related risk factors; Model 4: as Model 1 and additionally adjusted for behavioural risk factors; Model 5: adjusted for all of the above covariates.

## FIGURE S8. Serially adjusted longitudinal associations between CRP and 21 individual symptoms of depression (random-effects meta-analysis)

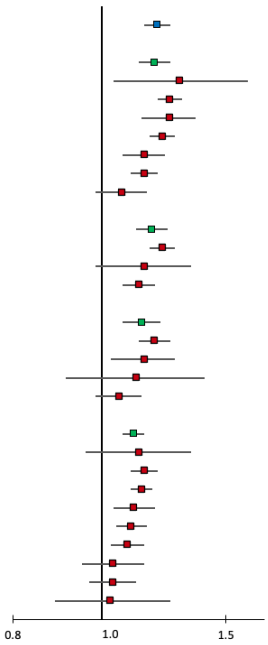
| Depressive symptom (outcome) | N (participants)/ N (studies) | Odds ratio (95% CI) per 1SD higher CRP* | | | | | |
|---|---|---|---|---|---|---|---|
| | | Model 1 | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 |
| *Had crying spells* | 7963 / 2 | | 1.07 (0.90 - 1.27) | 1.05 (0.89 - 1.24) | 1.07 (0.90 - 1.27) | 1.02 (0.80 - 1.30) | 1.02 (0.81 - 1.29) |
| *Changes in appetite* | 9333 / 3 | | 1.15 (1.03 - 1.28) | 1.14 (1.02 - 1.27) | 1.12 (1.00 - 1.25) | 1.16 (1.03 - 1.31) | 1.15 (1.02 - 1.31) |
| *Felt everything was an effort* | 21031 / 6 | | 1.15 (1.10 - 1.20) | 1.12 (1.08 - 1.17) | 1.14 (1.09 - 1.19) | 1.09 (1.04 - 1.15) | 1.09 (1.04 - 1.14) |
| *Thought you would be better off dead* | No data | | | | | | |
| *Little insterest in doing things* | 6090 / 1 | | 1.15 (1.09 - 1.22) | 1.12 (1.05 - 1.19) | 1.13 (1.07 - 1.20) | 1.08 (1.02 - 1.15) | 1.08 (1.01 - 1.15) |
| *Could not get going* | 21031 / 6 | | 1.10 (1.03 - 1.18) | 1.10 (1.04 - 1.16) | 1.09 (1.02 - 1.17) | 1.03 (0.97 - 1.08) | 1.02 (0.96 - 1.09) |
| *Feeling bad about yourself* | No data | | | | | | |
| *Could not shake off the blues* | 7963 / 2 | | 1.12 (0.94 - 1.34) | 1.11 (0.94 - 1.30) | 1.11 (0.94 - 1.30) | 1.12 (0.95 - 1.32) | 1.12 (0.95 - 1.32) |
| *People were unfriendly* | 9333 / 3 | | 1.06 (0.89 - 1.26) | 1.03 (0.89 - 1.19) | 1.06 (0.90 - 1.25) | 1.01 (0.84 - 1.22) | 1.02 (0.85 - 1.22) |
| *Life had been a failure* | 7963 / 2 | | 1.07 (0.86 - 1.32) | 1.05 (0.87 - 1.26) | 1.06 (0.86 - 1.31) | 1.01 (0.84 - 1.22) | 1.01 (0.84 - 1.22) |
| *Moving or speaking slowly or too fast* | No data | | | | | | |
| *Felt lonely* | 21031 / 6 | | 1.10 (1.03 - 1.18) | 1.10 (1.03 - 1.17) | 1.09 (1.02 - 1.17) | 1.06 (0.99 - 1.13) | 1.06 (0.99 - 1.13) |
| *Sleep problems* | 26009 / 7 | | 1.10 (1.05 - 1.15) | 1.09 (1.04 - 1.14) | 1.09 (1.03 - 1.15) | 1.06 (1.00 - 1.12) | 1.05 (0.99 - 1.12) |
| *Felt depressed* | 26009 / 7 | | 1.08 (1.00 - 1.16) | 1.06 (0.99 - 1.14) | 1.07 (1.00 - 1.14) | 1.02 (0.96 - 1.10) | 1.02 (0.96 - 1.09) |
| *Trouble concentrating* | 12941 / 3 | | 1.07 (1.01 - 1.15) | 1.07 (1.00 - 1.14) | 1.07 (1.00 - 1.14) | 1.04 (0.97 - 1.12) | 1.04 (0.97 - 1.12) |
| *People dislike me* | 9333 / 3 | | 1.01 (0.85 - 1.20) | 0.99 (0.82 - 1.22) | 1.00 (0.84 - 1.18) | 0.96 (0.79 - 1.16) | 0.96 (0.79 - 1.15) |
| *Felt unhappy* | 26009 / 7 | | 1.06 (1.00 - 1.13) | 1.05 (0.99 - 1.12) | 1.04 (0.98 - 1.10) | 1.02 (0.95 - 1.09) | 1.01 (0.95 - 1.08) |
| *Did not enjoy life* | 26009 / 7 | | 1.08 (1.01 - 1.15) | 1.07 (1.00 - 1.14) | 1.07 (1.00 - 1.14) | 1.06 (0.99 - 1.14) | 1.05 (0.98 - 1.13) |
| *Felt sad* | 21031 / 6 | | 1.05 (0.98 - 1.12) | 1.05 (0.99 - 1.12) | 1.04 (0.98 - 1.11) | 1.02 (0.96 - 1.09) | 1.02 (0.95 - 1.08) |
| *Talked less than usual* | 7963 / 2 | | 1.11 (1.00 - 1.22) | 1.10 (1.00 - 1.21) | 1.08 (0.98 - 1.20) | 1.09 (0.95 - 1.25) | 1.08 (0.93 - 1.25) |
| *Felt worse than others* | 7963 / 2 | | 1.08 (1.00 - 1.17) | 1.08 (1.00 - 1.16) | 1.08 (1.00 - 1.16) | 1.08 (0.98 - 1.18) | 1.07 (0.98 - 1.17) |
| *Bothered by things* | 7963 / 2 | | 1.10 (0.99 - 1.22) | 1.09 (0.98 - 1.21) | 1.09 (0.98 - 1.21) | 1.09 (0.98 - 1.22) | 1.09 (0.97 - 1.21) |
| *Felt hopeless about the future* | 7963 / 2 | | 1.09 (0.96 - 1.24) | 1.08 (0.96 - 1.21) | 1.08 (0.97 - 1.20) | 1.07 (0.96 - 1.19) | 1.07 (0.96 - 1.18) |
| *Felt fearful* | 7963 / 2 | | 1.06 (0.88 - 1.26) | 1.05 (0.89 - 1.24) | 1.07 (0.89 - 1.28) | 1.09 (0.94 - 1.27) | 1.09 (0.94 - 1.27) |




*Model 1: Adjusted for age, sex and baseline depression symptom; Model 2: As Model 1 and additionally adjusted for education; Model 3: As Model 1 and additionally adjusted for chronic illness-related risk factors; Model 4: as Model 1 and additionally adjusted for behavioural risk factors; Model 5: adjusted for all of the above covariates.

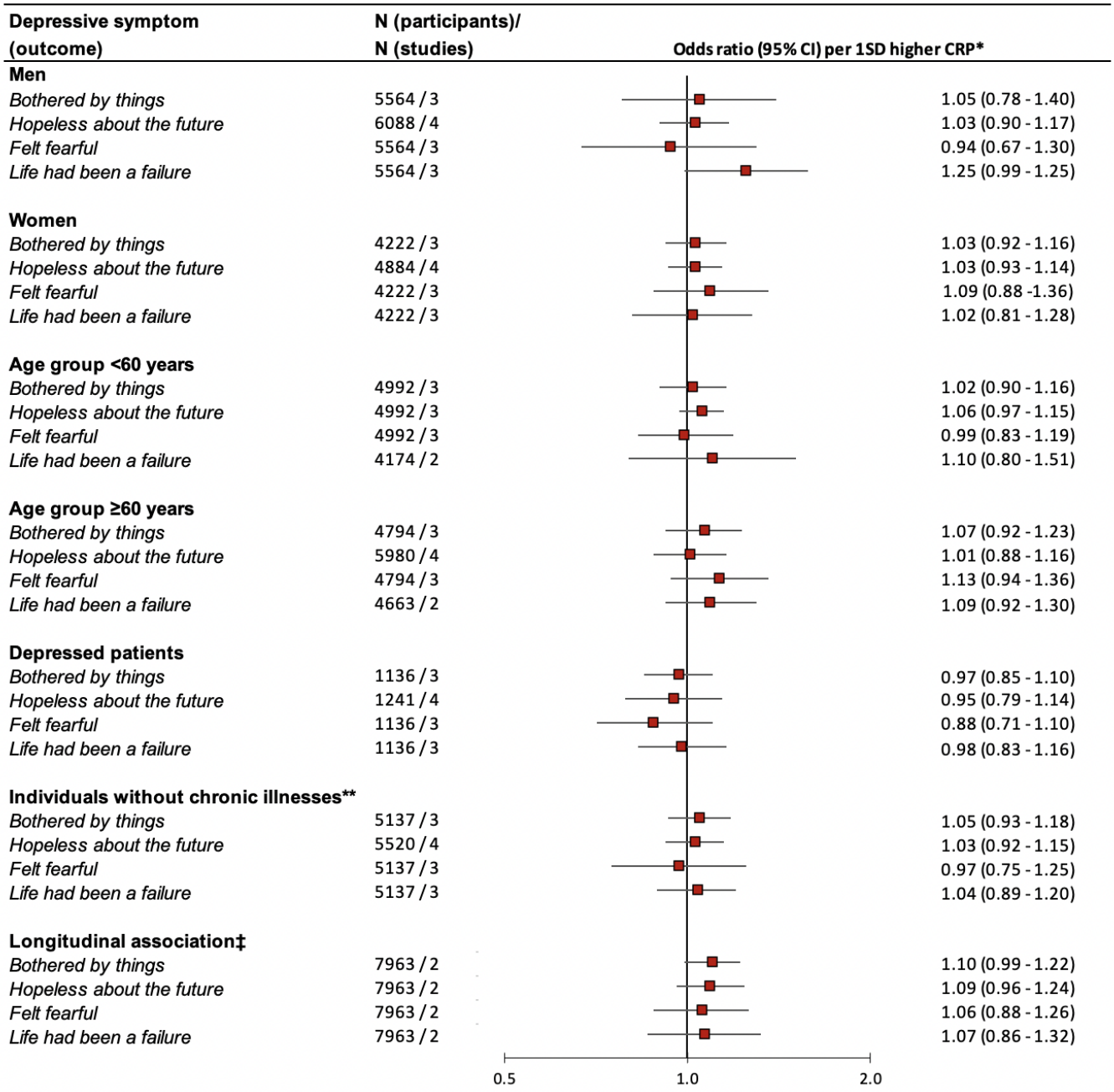
**FIGURE S9. Unadjusted and serially adjusted cross-sectional association between C-reactive protein (CRP) and, depression status, symptom domains, and 24 symptoms of depression (random-effects meta-analysis)**

| Outcome | N (participants)/ N (studies) | Odds ratio (95% CI) per 1SD higher CRP* | | | | | |
|---|---|---|---|---|---|---|---|
| | | Crude | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 |
| **Depression** | 56220 / 15 | | 1.18 (1.14 - 1.22) | 1.15 (1.11 - 1.18) | 1.16 (1.12 - 1.20) | 1.06 (1.03 - 1.10) | 1.05 (1.02 - 1.09) |
| **Symptom domains** | | | | | | | |
| ***Physical symptoms*** | | | 1.17 (1.12 -1.22) | 1.15 (1.10 - 1.20) | 1.15 (1.10 - 1.20) | 1.08 (1.05 - 1.11) | 1.08 (1.04 - 1.11) |
| *Had crying spells* | 9786 / 3 | | 1.24 (1.00 - 1.53) | 1.22 (0.98 - 1.51) | 1.22 (0.99 - 1.51) | 1.12 (0.92 - 1.36) | 1.10 (0.94 - 1.30) |
| *Changes in appetite* | 34615 / 10 | | 1.23 (1.18 - 1.27) | 1.20 (1.16 - 1.24) | 1.21 (1.17 - 1.26) | 1.12 (1.07 - 1.18) | 1.14 (1.09 - 1.19) |
| *Felt everything was an effort* | 27130 / 8 | | 1.23 (1.12 - 1.36) | 1.21 (1.11 - 1.32) | 1.21 (1.10 - 1.34) | 1.11 (1.04 - 1.19) | 1.12 (1.04 - 1.21) |
| *Could not get going* | 50736 / 14 | | 1.20 (1.16 - 1.24) | 1.18 (1.14 - 1.23) | 1.19 (1.14 - 1.23) | 1.09 (1.06 - 1.13) | 1.08 (1.05 - 1.12) |
| *Moving or speaking slowly or too fast* | 22420 / 5 | | 1.14 (1.07 - 1.22) | 1.11 (1.04 - 1.19) | 1.11 (1.04 - 1.20) | 1.06 (0.98 - 1.13) | 1.04 (0.97 - 1.11) |
| *Sleep problems* | 55165 / 14 | | 1.13 (1.09 - 1.17) | 1.11 (1.07 - 1.15) | 1.11 (1.08 - 1.15) | 1.06 (1.02 - 1.10) | 1.05 (1.01 - 1.09) |
| *Talked less than usual* | 9786 / 3 | | 1.06 (0.99 - 1.15) | 1.05 (0.98 - 1.14) | 1.06 (0.98 - 1.15) | 1.00 (0.92 - 1.09) | 1.00 (0.92 - 1.09) |
| ***Cognitive symptoms*** | | | 1.17 (1.11 - 1.23) | 1.14 (1.09 - 1.20) | 1.15 (1.10 - 1.21) | 1.08 (1.05 - 1.12) | 1.08 (1.04 - 1.12) |
| *Little insterest in doing things* | 31000 / 6 | | 1.21 (1.16 - 1.26) | 1.18 (1.13 - 1.23) | 1.19 (1.14 - 1.24) | 1.10 (1.05 - 1.15) | 1.09 (1.04 - 1.14) |
| *People were unfriendly* | 12195 / 5 | | 1.15 (0.97 - 1.36) | 1.11 (0.95 - 1.31) | 1.14 (0.96 - 1.35) | 1.07 (0.90 - 1.27) | 1.03 (0.85 - 1.24) |
| *Trouble concentrating* | 37821 / 9 | | 1.12 (1.07 - 1.18) | 1.11 (1.05 - 1.16) | 1.11 (1.06 - 1.16) | 1.07 (1.02 - 1.11) | 1.07 (1.01 - 1.13) |
| ***Self-perception-related symptoms*** | | | 1.13 (1.06 - 1.20) | 1.10 (1.03 - 1.17) | 1.12 (1.07 - 1.19) | 1.04 (1.00 - 1.09) | 1.02 (0.99 - 1.07) |
| *Feeling bad about yourself* | 22420 / 5 | | 1.18 (1.12 - 1.24) | 1.15 (1.09 - 1.21) | 1.15 (1.09 - 1.20) | 1.05 (0.99 - 1.11) | 1.03 (0.97 - 1.09) |
| *Could not shake off the blues* | 9786 / 3 | | 1.16 (1.04 - 1.29) | 1.14 (1.04 - 1.26) | 1.16 (1.04 - 1.29) | 1.03 (0.91 - 1.16) | 1.03 (0.91 - 1.15) |
| *People dislike me* | 11593 / 4 | | 1.12 (0.90 - 1.39) | 1.09 (0.88 - 1.35) | 1.11 (0.90 - 1.35) | 0.99 (0.78 - 1.25) | 0.98 (0.78 - 1.22) |
| *Felt worse than others* | 9786 / 3 | | 1.05 (0.97 - 1.13) | 1.02 (0.96 - 1.10) | 1.05 (0.96 - 1.15) | 1.03 (0.95 - 1.12) | 1.02 (0.95 - 1.10) |
| ***Emotional symptoms*** | | | 1.10 (1.07 - 1.13) | 1.08 (1.05 - 1.10) | 1.08 (1.05 - 1.11) | 1.02 (0.99 - 1.05) | 1.02 (0.99 - 1.05) |
| *Life had been a failure* | 9786 / 3 | | 1.15 (0.95 - 1.38) | 1.14 (0.95 - 1.35) | 1.15 (0.96 - 1.39) | 1.06 (0.91 - 1.25) | 1.07 (0.92 - 1.23) |
| *Felt lonely* | 27130 / 8 | | 1.13 (1.09 - 1.17) | 1.10 (1.06 - 1.14) | 1.12 (1.08 - 1.16) | 1.05 (0.99 - 1.11) | 1.04 (0.99 - 1.09) |
| *Felt depressed* | 54563 / 13 | | 1.13 (1.09 - 1.18) | 1.10 (1.06 - 1.14) | 1.11 (1.06 - 1.16) | 1.03 (1.00 - 1.07) | 1.02 (0.98 - 1.06) |
| *Felt unhappy* | 33329 / 9 | | 1.11 (1.04 - 1.18) | 1.09 (1.03 - 1.17) | 1.10 (1.02 - 1.18) | 1.05 (0.97 - 1.13) | 1.04 (0.96 - 1.12) |
| *Did not enjoy life* | 33329 / 9 | | 1.10 (1.04 - 1.15) | 1.08 (1.02 - 1.14) | 1.08 (1.03 - 1.14) | 1.03 (0.97 - 1.09) | 1.02 (0.97 - 1.08) |
| *Felt sad* | 26528 / 7 | | 1.07 (1.01 - 1.12) | 1.05 (1.01 - 1.10) | 1.05 (1.01 - 1.10) | 0.99 (0.94 - 1.05) | 1.00 (0.95 - 1.04) |
| *Bothered by things* | 9786 / 3 | | 1.05 (0.94 - 1.16) | 1.04 (0.95 - 1.15) | 1.05 (0.95 - 1.16) | 0.96 (0.85 - 1.09) | 0.96 (0.86 - 1.08) |
| *Felt hopeless about the future* | 10972 / 4 | | 1.04 (0.97 - 1.11) | 1.02 (0.95 - 1.10) | 1.04 (0.98 - 1.10) | 1.00 (0.92 - 1.09) | 1.00 (0.92 - 1.09) |
| *Felt fearful* | 9786 / 3 | | 1.03 (0.87 - 1.23) | 1.03 (0.86 - 1.22) | 1.02 (0.84 - 1.25) | 0.97 (0.77 - 1.22) | 0.97 (0.76 - 1.23) |




*Model 1: adjusted for age and sex; Model 2: as Model 1 and additionally adjusted for education; Model 2: as Model 1 and additionally adjusted for health-related factors; Model 4: as Model 1 and additionally adjusted for behavioural factors; Model 5: adjusted for all of the above covariates.

**FIGURE S10. Association between C-reactive protein (CRP) and 4 depression symptoms in subgroups, after additional adjustments and longitudinally (random-effects meta-analysis)**




*Adjusted for age and sex as appropriate

† Adjusted for age, sex and adverse childhood experiences

‡ Adjusted for age, sex and depressive symptom at baseline

** Note: These analyses excluded individuals with a self-reported history of coronary heart disease, stroke, cancer, hypertension, and/or diabetes.

**TABLE S7. Random-effects meta-analysis of the cross-sectional associations between CRP and 6 individual symptoms of depression, stratified by time of exposure and outcome ascertainment**

| Symptom | Studies with no time lag | | | Studies with time lag | | |
|---|---|---|---|---|---|---|
| | OR | LCI | UCI | OR | LCI | UCI |
| Changes in appetite | 1.23 | 1.18 | 1.28 | 1.23 | 1.1 | 1.37 |
| Could not get going | 1.19 | 1.14 | 1.23 | 1.21 | 1.11 | 1.33 |
| Felt everything was an effort | 1.18 | 0.98 | 1.42 | 1.26 | 1.13 | 1.41 |
| Little insterest in doing things | 1.2 | 1.14 | 1.27 | 1.23 | 1.18 | 1.29 |
| Sleep problems | 1.16 | 1.11 | 1.21 | 1.1 | 1.03 | 1.16 |
| Trouble concentrating | 1.17 | 1.12 | 1.23 | 1.05 | 0.99 | 1.12 |

Effect estimates adjusted for age & sex

**TABLE S8. Age- and sex-adjusted random-effects meta-analysis of the cross-sectional association between CRP and individual symptoms of depression in people with an overall elevated level of depressive symptoms**

| | Model 1 | | | N (Sample /Studies) |
|---|---|---|---|---|
| **Symptom** | **OR** | **LCI** | **UCI** | |
| Had crying spells | 1.13 | 0.93 | 1.37 | 1136 / 3 |
| Changes in appetite | 1.11 | 1.02 | 1.2 | 3573 / 10 |
| Felt everything was an effort | 1.15 | 0.99 | 1.34 | 3864 / 8 |
| Thought you would be better off dead | 1.07 | 0.93 | 1.21 | 1896 / 5 |
| Little insterest in doing things | 1.11 | 1.04 | 1.19 | 3145 / 6 |
| Could not get going | 1.17 | 1.1 | 1.25 | 5864 / 14 |
| Feeling bad about yourself | 1.05 | 0.97 | 1.14 | 1896 / 5 |
| Could not shake off the blues | 1.03 | 0.89 | 1.19 | 1136 / 3 |
| People were unfriendly | 1.04 | 0.89 | 1.22 | 1677 / 5 |
| Life had been a failure | 0.98 | 0.83 | 1.16 | 1136 / 3 |
| Moving or speaking slowly or too fast | 0.97 | 0.87 | 1.08 | 1896 / 5 |
| Felt lonely | 1.05 | 0.96 | 1.14 | 3864 / 8 |
| Sleep problems | 1.08 | 1.02 | 1.14 | 6709 / 14 |
| Felt depressed | 1.02 | 0.96 | 1.08 | 6603 / 13 |
| Trouble concentrating | 1.03 | 0.95 | 1.13 | 3981 / 9 |
| People dislike me | 1.03 | 0.8 | 1.33 | 1571 / 4 |
| Felt unhappy | 0.99 | 0.91 | 1.07 | 4812 / 9 |
| Did not enjoy life | 0.99 | 0.89 | 1.09 | 4812 / 9 |
| Felt sad | 0.96 | 0.87 | 1.05 | 3758 / 7 |
| Talked less than usual | 0.87 | 0.7 | 1.08 | 1136 / 3 |
| Felt worse than others | 1.03 | 0.91 | 1.16 | 1136 / 3 |
| Bothered by things | 0.97 | 0.85 | 1.1 | 1136 / 3 |
| Felt hoopeless about the future | 0.95 | 0.79 | 1.14 | 1241 / 4 |
| Felt fearful | 0.88 | 0.71 | 1.1 | 1136 / 3 |

Model 1: effect estimates adjusted for age and sex

## Appendix 5. Statistical Code

### Statistical Code R: Random-effects analysis of the cross-sectional associations between C-reactive protein and individual symptoms of depression (RStudio)

```r

### Preparation meta-analysis
library(meta)
library(metafor)
CRPmeta<- read.csv("Meta-analysis_CRP_DEP.csv") #read csv file with simple model results
# log_transform effect size data
CRPmeta$OR <- log(CRPmeta$OR)
CRPmeta$lower <- log(CRPmeta$lower)
CRPmeta$upper <- log(CRPmeta$upper)
# Calculate standard error seTE
CRPmeta$seTE <- (CRPmeta$upper - CRPmeta$lower)/3.92
# metagen function - to reconvert effect sizes to original scale
m <- metagen(OR,seTE, studlab = paste(Study), method.tau = "", sm = "OR", data = CRPmeta)
# Forest plot
forest(m,rightlabs = c("OR","95% CI","weight"),leftlabs = c("Symptoms"),layout = "JAMA",digits.sd = 2)
## subgroups
forest.subgroup<-update.meta(m,byvar=Symptom,comb.random = TRUE,comb.fixed = FALSE)
forest.subgroup
forest(forest.subgroup, study.results = TRUE, bysort = FALSE,print.subgroup.labels = TRUE,
       print.byvar = FALSE,print.Rb = TRUE,print.Rb.ci = TRUE,
       leftcols = c("studlab", "N", "Cases"),
       smlab = "CRP - crude model", pooled.totals = TRUE,comb.random = TRUE,
       comb.fixed = FALSE, text.random = "Overall effect",print.tau2 = TRUE, col.square = "grey",
       colgap = "10mm", col.square.lines = "blue",col.diamond = "blue",
       col.diamond.lines = "black",col.inside = "black", col.predict = "green",
       print.I2.ci = TRUE,overall = FALSE, hetstat = TRUE, overall.hetstat = FALSE,
       calcwidth.hetstat = TRUE, label.right = "Increased risk", col.label.right = "darkblue",
       label.left = "Decreased risk", col.label.left = "darkblue",
       digits.sd = 4)
```

## Statistical Code STATA: Loop for multivariate logistic regression analyses (example)

The following code is an example syntax (i.e., loop) used to calculate the odds ratios and accompanying 95% confidence intervals for the cross-sectional association between C-reactive protein and individual depression symptoms in Whitehall II.

*** Loop TILDA data cross-sectional ***
**********

```
** Loop
capture program drop prog_getpred
program define prog_getpred
    args row outcome title

    matrix B=r(table)

    local b=round(B[1,1],.01)
    local lci=round(B[5,1],.01)
    local uci=round(B[6,1],.01)
    local string "`b' (`lci',`uci')"

    putexcel A`row'="`outcome'"
    putexcel B`row'="`title'"
    putexcel C`row'="`string'"
    putexcel D`row'="`b'"
    putexcel E`row'="`lci'"
    putexcel F`row'="`uci'"
end


putexcel set "TILDA_data_CRP_cross_cov.xlsx", modify sheet("Sheet1", replace)

local options       , nolog or
local extras
local if            if codcrp==1
local outcomes      w1bothbi w1appbi w1bluesbi w1goodbi w1concbi ///
                    w1depbi w1effbi w1hpebi w1failbi w1fearbi ///
                    w1slpebi w1hpybi w1tlkbi w1lonebi w1unfrbi w1enjoybi ///
                    w1crybi w1sadbi w1dislbi w1nmuchbi w1deptotbi

local exposure      w1crpLog



local row=0
local num=0


foreach outcome of local outcomes{
//  local baseline: subinstr local outcome "8" "6"
//  local num=`num'+1
//  local baseline: word `num' of `baselines'

    local row=`row'+1
    logistic `outcome' `exposure' `if' `options'
    prog_getpred `row' `outcome'  "Baseline"
    forval i=1/5{
        if `i'==1   local extras    w1age i.w1sex
        if `i'==2   local extras    w1age i.w1sex i.edu1
        if `i'==3   local extras    w1age i.w1sex bmi1 i.smoked1 i.nopa1 i.alcc1
        if `i'==4   local extras    w1age i.w1sex i.chd1 i.stroke1 i.cancer1 sbp1 dbp1 i.diab1
        if `i'==5   local extras    w1age i.w1sex i.edu1 bmi1 i.smoked1 i.nopa1 i.alcc1 i.chd1 i.stroke1 i.cancer1 sbp1 dbp1 i.diab1


        local row=`row'+1
        logistic `outcome' `exposure' `extras' `if' `options'
        prog_getpred `row' `outcome' "`extras'"
        foreach var of local extras{
            local row=`row'+1
            logistic `outcome' `exposure' `var'  `if' `options'
            prog_getpred `row' `outcome' "`var'"
            }
        }
}

import excel using "TILDA_data_CRP_cross_cov.xlsx", sheet(Sheet1) clear
reshape wide C, i(B) j(A) string
rename C* *
rename B extra
```

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