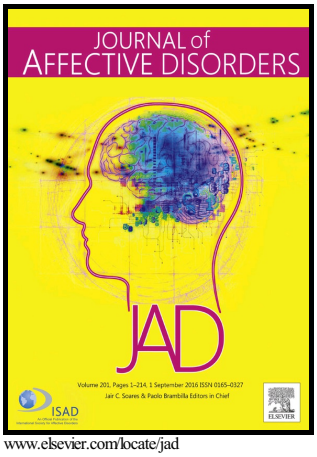

www.elsevier.com/locate/jad

Pathways to depression by age 16 years: examining trajectories for self-reported psychological and somatic phenotypes across adolescence

Scott Jan, Tracey A. Davenport, Richard Parker, Daniel F. Hermens, Penelope A. Lind, Sarah E. Medland, Margaret J. Wright, Nicholas G. Martin, Nathan A. Gillespie, Ian B. Hickie

PII: S0165-0327(17)31556-2
DOI: https://doi.org/10.1016/j.jad.2017.12.007
Reference: JAD9414

To appear in: *Journal of Affective Disorders*

Received date: 26 July 2017
Revised date: 16 October 2017
Accepted date: 3 December 2017

Cite this article as: Scott Jan, Tracey A. Davenport, Richard Parker, Daniel F. Hermens, Penelope A. Lind, Sarah E. Medland, Margaret J. Wright, Nicholas G. Martin, Nathan A. Gillespie and Ian B. Hickie, Pathways to depression by age 16 years: examining trajectories for self-reported psychological and somatic phenotypes across adolescence, *Journal of Affective Disorders,* https://doi.org/10.1016/j.jad.2017.12.007

Pathways to depression by age 16 years: examining trajectories for self-reported psychological and somatic phenotypes across adolescence.

Authors:

Scott Jan[1]; Tracey A. Davenport[2]; Richard Parker[3]; Daniel F. Hermens[2]; Penelope A. Lind[4;] Sarah E. Medland[5]; Margaret J. Wright[4,5]; Nicholas G. Martin[4]; Nathan A. Gillespie[5,6]; Ian B. Hickie[2.]

1: Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK.

2. Brain & Mind Centre, University of Sydney, Sydney, Australia.

3. QIMR Berghofer Medical Research Institute, Brisbane, Australia.

4. Queensland Brain Institute, the University of Queensland, Brisbane, Australia.

5. Centre for Advanced Imaging, the University of Queensland, Brisbane, Australia.

6: Virginia Institute for Psychiatric and Behavioral Genetics, VCU, Richmond, Virginia, USA.

Correspondence- Professor Jan Scott, Academic Psychiatry, Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK.
Email: jan.scott@newcastle.c.uk

Abstract: 249 words
Main text: 3540 words (excluding abstract, tables and references)
Tables: 3
Figures: 1
Online supplementary material: 3 Appendices
References: 32

ABSTRACT

Background: Sex differences in rates of depression emerge during adolescence. However, it is unclear whether symptom patterns and trajectories differ significantly according to gender in youth. Barriers to research include the fact that most self-report tools are weighted towards psychological rather than somatic symptoms.

Methods: Data were collected on symptoms of depression in about 1800 individuals at ages 12, 14 and 16 years. Odds ratios and 95% confidence intervals were used to examine the trajectory of psychological and somatic phenotypes and self-reported depression caseness over time.

Results: At age 12, 24% of participants met criteria for self-reported depression caseness. Although there was only a small incremental increase in the prevalence over time (about 5%), 57% of participants met criteria for self-reported depression caseness at least once. Generic symptoms at age 12 were associated with depression longitudinally, although early transition to caseness was reported in females only. Categorization as a psychological phenotype at age 12 predicted depression at age 14 and/or 16 years, especially in females. The somatic phenotype was more common in males, but showed a weaker association with self-reported depression caseness over time.

Limitations: Depression was assessed by self-report; only 30% of participants had ratings for age 12, 14 and 16.

Conclusions: Although sub-threshold psychological and somatic syndromes often co-occur in cases of self-reported depression in adolescence, longitudinally they may represent independent symptom trajectories. However, it is important to remember that self-reported depression is indicative of, but not confirmation of a depressive episode that meets diagnostic criteria.

Key words: depression, psychological, somatic, phenotypes, trajectories, gender, self-report, sub-threshold, longitudinal.

INTRODUCTION

A recent systematic review by Musliner et al (2016) identified that trajectories of depressive symptoms in the general population are heterogeneous and that symptom patterns may vary in terms of severity (low, medium, and high) and stability (stable, increasing, and decreasing). The review confirmed that female gender, peer relationships and socio-economic status were associated with patterns of depression, and it was noted that over time: (i) stability of depressive symptoms was more common than instability; (ii) most individuals reported no depressive symptoms or minimal symptoms; and (iii) chronic mild-moderate level symptoms can be quite common, but chronic severe depressive symptoms were rare. The review is one of the first to offer insights regarding trajectories and symptom patterns. However, it did not explore whether particular types of symptoms or sub-threshold phenotypes were more likely to be associated with depression caseness at follow-up. Another potential limitation was that less than a third of the eligible studies examined samples of children or adolescents (7 of 25 studies) and those that were included all came from North America (USA=5; Canada=2). Given that depression is ranked worldwide as the most burdensome condition in individuals aged less than 25 years (Gore et al, 2011), we decided to examine trajectories of self-reported depression in a community-based cohort of adolescents recruited to a long-term study in Australia.

The importance of identifying depression and understanding its trajectories in adolescents cannot be overstated as depression onsets prior to the age of 17 years are associated with increased risk of adult mental disorders, reduced response to standard therapeutic strategies as adults, adverse social and clinical outcomes, high levels of morbidity and all-cause mortality (Zisook et al, 2007; Substance Abuse and Mental Health Services Administration [SAMHSA], 2014). Furthermore, Carrellas et al (2017) demonstrated that sub-threshold syndromes are also associated with significant morbidity and social impairment. Longitudinal cohort studies identify that rates of depression are higher in females as

compared to males (e.g. Essau et al, 2010; Patton et al, 2014), that the sex differences become most apparent post-puberty and that these differences are a consequence of both a higher risk of incident cases and a higher prevalence of recurrent or chronic depressions. However, there is limited information about the prevalence of sub-threshold risk syndromes for depression caseness in this age group (e.g. Dekker et al, 2007).

One of the significant barriers to exploring clinical phenotypes associated with depression in youth relates to the nature of the assessment instruments employed (Angold et al, 2002; Cole et al, 2011). The burden on young study participants means that there is reluctance to employ the extensive structured assessments used with adults. There is evidence that alternative tools can be valid and that self-report diagnosis has been previously reported as an adequate proxy measure for clinician diagnosis of depression, when compared to the Structured Clinical Interview for DSM-IV (Sanchez-Villegas et al., 2008). However, the potential issue in using some of the most widely employed screening tools for depression is that they may introduce unexpected biases in case identification according to sex. For example, two of the most widely used assessments for depression (and other common mental disorders in adolescents), the Short Mood and Feelings Questionnaire and the Strengths and Difficulties Questionnaire, are weighted towards the psychological and cognitive-emotional features rather than somatic symptoms (Kent et al, 1997). This might lead to an under-estimation of the risk of depression in young males and some (but not all) studies of depressive symptoms in adolescents suggest that, compared to females, depressed males may self-report more morning fatigue, anhedonia or somatic symptoms and that these may be precursors to, or symptoms of depressive episodes (e.g. van Beck et al, 2012). Overall, prospective observation of somatic and psychological profiles separately and together could shed light on variations in illness trajectories according to these sub-threshold phenotypes, gender and the stability or severity of depressive symptoms over time.

This report from the Brisbane Longitudinal Twin Study (BLTS) describes the use of an established 12-item self-rating scale, called the Somatic and Psychological HEalth REport (SPHERE-12; Hickie et al, 2001), to:

(a) determine the proportion of males and females who meet SPHERE-12 criteria for psychological or somatic phenotypes or self-rated depression caseness at ages 12, 14 and 16 years, and

(b) evaluate trajectories of self-reported depression in terms of severity and stability over time.

METHODS

Sample

The population sample was derived from >1800 adolescent and young adults who were all participating in three linked BLTS studies; the same recruitment and assessment procedures were used for identifying and following the cohort (for details see online material, Appendix 1). Ethical approval was obtained from the Human Research Ethics Committee at the Queensland Institute of Medical Research for all BTLS research projects, and written informed consent was obtained from a parent or guardian for all individuals aged less than 18 years.

A detailed description of the study protocol and procedures, recruitment strategies and populations included in the BLTS is given elsewhere (Wright & Martin, 2004). The present study included those individuals with data available on basic demographic information who participated in prospective monitoring and completed at least two SPHERE-12 self-assessments (as we wished to examine the inter-relationships between different symptom profiles and trajectories in the same individual over time). Individuals eligible for inclusion comprised of three sub-samples: 600 individuals with SPHERE-12 self-assessments at three specified time points (ages 12,14, and 16); 714 individuals with self-assessments at ages 12 and 16, and 750 with self-assessments at ages 14 and 16.

Measures

a) Demographics: Sex and age at each assessment were recorded.

b) Symptom ratings: We used the SPHERE-12 to obtain ratings of generic symptoms, somatic and psychological sub-types and of self-reported depression caseness (identified by a pre-specified combination of somatic and psychological symptoms) at ages 12, 14 and 16.

The SPHERE was originally designed for use in community, primary care and general medical settings where somatic symptoms (such as fatigue) often overlap with psychological complaints of depression and anxiety (Hickie et al, 2001; McFarlane et al, 2008). For the12-item version of the SPHERE, participants indicate if they had been troubled by symptoms over the past few weeks (e.g. psychological

items include: Feeling unhappy and depressed, Everything getting on top of you; whilst somatic items include: Prolonged tiredness after activity, Waking up tired), and individuals are required to make one of three response choices to each item: 0= "never or some of the time"; 1= "a good part of the time"; or, 2= "most of the time". Item ratings were summed to obtain scores on two subscales (each consisting of six items) that best describe the likely presence of somatic symptoms such as fatigue ('SOMA') or of common symptoms of depression and anxiety ('PSYCH'); simultaneous high scores on both scales are an indicator of likely depression caseness. The total score on the SPHERE-12 can be used as a continuous measure of symptoms, but usually the SPHERE subscale scores are used to create (i) two broadly defined or self-rated sub-threshold presentations: PSYCH (PSYCH score>=2 and SOMA<3) or SOMA (SOMA>=3 and PSYCH<2), and (ii) narrowly defined self-rated depression caseness (PSYCH score>=2 and SOMA>=3).

The scale has high internal consistency (PSYCH .9; SOMA .8) and test-retest reliability (PSYCH .81; SOMA .8) (Hickie et al, 2001). In a study of over 800 young adults, McFarlane et al (2008) noted that the PSYCH scale compared favorably with the Hospital Anxiety and Depression Scale (.67-.73) and that the Receiver Operating Curve (ROC) for the PSYCH was .73 and for the SOMA was .72. As expected the subthreshold and threshold caseness ratings show contrasting sensitivity and specificity profiles, with the PSYCH and SOMA cutoffs having high levels of sensitivity (93%), whilst the more narrowly defined depression caseness has a higher level of specificity (72%). In a sub-sample of cases, we confirmed a similar adequate level accuracy of the SPHERE-12 for identifying cases of major depression in this study (see online material, Appendix 2).

Definitions of trajectories

Ratings on the SPHERE-12 were used to evaluate self-reported trajectories of depressive symptoms using Musliner et al's (2016) approach that focused on severity (low, medium, high) and stability (stable, increasing, decreasing):

a) Severity: the lowest level of severity was defined by the total score on the SPHERE-12 at baseline assessment (analysed as a continuous measure). Medium severity was defined by a score above the cut-off for either the PSYCH or SOMA sub-threshold phenotype at any time point. A high level of severity was defined as meeting SPHERE-12 criteria for depression caseness at any time point.

b) Stability: we assessed fluctuations in 'caseness' (PSYCH, SOMA or depression) over the study period. A stable trajectory indicated that SPHERE-12 self-ratings did not change over time. Trajectories were defined as unstable if the SPHERE-12 ratings fluctuated between assessment points, with an increasing trajectory identified by a change from self-rated sub-threshold phenotypes to depression caseness and a decreasing trajectory identified by a change from self-rated depression caseness to subthreshold phenotypes.

Statistical analysis

All statistical analyses utilized the Statistical Package for the Social Sciences version 22 (SPSS, Chicago, USA). As the subgroups included in each analysis included variable proportions of twins and non-twin siblings, all cases were considered as singletons.

Prior to undertaking the main analyses, we examined whether the sub-samples included in different analyses were representative of the total sample. We used chi-squared tests to compare each selected sub-sample with the original larger samples of the same age group and evaluated the prevalence and gender distributions of subthreshold syndromes (PSYCH or SOMA) and depression caseness (i.e. the age 12 sub-sample of included cases vs. all age12 data, etc.). The analyses demonstrated that individuals included in this study are representative of the BLTS population from which they were selected (for details see Table S1 in the online supplementary material).

The main analyses proceeded in several pre-defined steps:

1) Prevalence by age and gender: We calculated prevalence of different levels of caseness (non-case; PSYCH, SOMA, or depression case) at ages 12, 14 and 16 for males and females and report adjusted odds ratios (AOR) and 95% confidence intervals (CI) for the comparison of rates by sex.

2) Baseline ratings versus outcomes at 14 and 16 years: we explored whether symptom ratings obtained at age12 predicted outcomes at each follow-up. First, we analysed any changes from the lowest level of severity at age 12 (generic SPHERE symptoms) to the highest level of severity

(depression caseness) at age 14 or 16. The OR and AOR indicate the likelihood and speed of transition and any gender differences. Second, we calculated the odds that individuals meeting criteria for moderate severity (PSYCH or SOMA subtype) or high severity (self-reported case of depression) at age 12 or at 14 years would be classified as a self-rated depression case at age 16. 3) In the sub-sample of 600 cases with ratings at each time point, we examined individual trajectories over time and estimated the number of different patterns of sub-threshold and threshold syndromes and report the prevalence for each different trajectory for self-reported depression caseness. Odds ratios and AOR were calculated to determine whether meeting criteria for a PSYCH or SOMA phenotype was associated with a a course characterized by mostly being a depression case or ostly a non-case.

RESULTS

As shown in Table 1, 24% of the total cohort had already reached our threshold for self-rated depression caseness by age 12, rising to 30% by age 16, with most of the increase being accounted for by a bigger rise in the number of female (24% to 33%) compared to male cases (23% to 26%). Subthreshold syndromes showed slightly different patterns, with the number of SOMA only cases increasing in males between ages 12 and 14 (16% to 28%), and then stabilizing. The prevalence of PSYCH only cases showed relative stability over time, although rates were higher in females aged 14 and 16.

Table 1 about here

The AOR reported in Table 1 highlight that cross-sectional analysis of rates of self-rated subthreshold and threshold levels of caseness demonstrated no sex differences at age 12, but a significantly greater likelihood for both self-rated depression and PSYCH caseness in females compared to males at ages 14 and 16. In contrast, SOMA only caseness was significantly more common in males compared to females at ages 14 and 16.

Next, we examined any associations between different levels of severity at baseline assessment and future outcomes. Using the SPHERE-12 symptom score at 12 years (sample mean=3.26; standard deviation=2.84), we examined whether the overall level of generic depressive symptoms predicted future depression caseness. It was found that the odds for transition to the highest level (self-rated depression caseness) at follow-up was only significant for females at age 14 (AOR=1.86; 95% CI: 1.26, 2.75), but was significant for both males and females at age 16 (OR=1.22; 95% CI: (1.14, 1.29).

Table 2 about here

We then examined whether moderate or high severity at age 12 or 14 was associated with outcome at age 16 years. As shown in Table 2, longitudinal analyses demonstrated that the odds of being a self-rated depression case at age 16 were increased in individuals (and especially in females) who met criteria for PSYCH only caseness at ages 12 or 14. However, SOMA only caseness at age 12 or 14 did not predict self-rated depression caseness at age 16. Likewise, there were sex differences in changes from depression caseness at age 12 to sub-threshold syndromes (i.e. PSYCH only or SOMA only) at age 14 or 16. Females who met criteria for self-rated depression caseness at age 12 were significantly more likely than males to meet criteria for PSYCH caseness at age 14 (AOR=1.75; 95% CI: 1.21, 2.95) and 16 (AOR=2.32; 95% CI: 1.19, 2.64). However, males were significantly more likely to be a SOMA case at age 16 compared to females (AOR=.58; 95% CI: 0.38, 0.87).

Table 3 about here

Figure 1 about here

Figure 1 provides a schematic representation of self-rated depression caseness in the 600 individuals assessed at three consecutive time points. The diagram demonstrates that, although there is only a five percent incremental increase in the proportion of the total subsample who met criteria for self-rated

depression caseness at age 12 and16 (a shift from 23% to 28%), individual trajectories could be classified on one of eight different pathways. Over the four-year observation period, 57% of the cohort was classified as a self-rated depression case on at least one occasion. As shown, the two most stable trajectories (no change over time) comprised of 43% of the sample (258 individuals) who never met criteria for self-rated depression caseness (category 'NNN'), and one percent (8 individuals) who met criteria for self-rated depression caseness at every time point (category 'CCC'). Between 4% and 17% of the sample followed each of the other trajectories (see Figure 1). We estimated that the odds were low (OR 0.49 95% CI: 0.34, 0.72) that individuals who met criteria for any level of caseness (PSYCH, SOMA, self-rated depression) at age 12 would never be a case at follow-up (i.e. would be classified as 'mostly a non-case' or a 'consecutive non-case'). In contrast, threshold or sub-threshold caseness at age 12 was significantly associated with an increased likelihood of self-rated depression caseness on two or more occasions during the four-year follow-up period (OR 1.91; 95% CI 1.31, 4.29).

DISCUSSION

This study identified that about a quarter of young people completing the SPHERE-12 met criteria for self-rated depression caseness at age 12, and that self-rated caseness increased to nearly a third by age 16, with a greater rise in young females compared to males. These findings are in keeping with previous longitudinal studies that re-assess youth throughout adolescence and suggest that depression, however defined, increases significantly from puberty up to age 16, especially in females (Essau et al, 2010; Costello et al, 2011; Patton et al, 2014). Several of these prospective studies have addressed transitions to self- or observer-rated depression caseness in individuals presenting with lower levels of depression severity (e.g. Kim-Cohen et al, 2003; Dekker et al, 2007; Hill et al, 2014). However, as demonstrated by Musliner et al (2016), fewer studies have examined individual trajectories of self-rated depression in terms of levels of severity or stability over time. Furthermore, it is unclear whether sub-threshold phenotypes are more strongly associated with different self-rated outcomes in males and females (e.g. McLeod et al, 2016; Salk et al, 2016). As such our paper is an important addition to the existing literature.

There are three key findings in the present study. First, although the absolute increase in prevalence of self-rated depression was modest (a change of about 5% over four years), this result masked significant variations in the self-rated pathways to caseness by age 16. As suggested by Musliner and colleagues (2016), the most common pattern was a stable state of minimal or no symptoms (in our study, 43% were stable non-cases), but it was notable that other individuals showed variable trajectories. Overall, 57% of individuals met our criteria for the most severe level of depression (self-reported caseness) at least once during the follow-up period. Second, our lowest level of severity, namely non-specific symptom load, identified that females with a higher number of generic SPHERE-12 symptoms at age 12 were likely to make an earlier transition to self-rated depression caseness (by age 14) than males. Third, we report novel findings in relation to our medium level of severity (self-rated subthreshold PSYCH or SOMA clinical phenotypes), with our results offering provisional support for the notion that there may be different types of symptom pathways experienced during the critical period of 12-16 years. In one pathway, a sub-threshold PSYCH syndrome may predate or follow-on from self-rated depressive caseness. This is consistent with the hypothesis that these phenotypic expressions are intrinsically-linked, more typically seen in females rather than males and represent common experiences of symptoms of depression and anxiety (Simms et al, 2012). In contrast, the sub-threshold SOMA syndrome behaves largely independently, being significantly associated with male sex and relatively stable over time.

In previous BLTS publications, such as Hickie and Rodgers (2011), it was hypothesized that the sub-threshold PSYCH syndrome represents a common anxiety-depression diathesis underpinned by different neurobiological phenomena (e.g. high arousal, excessive sympathetic nervous system reactivity) than the sub-threshold SOMA syndrome, which may represent a (hypo)mania-fatigue dimension (possibly linked neurobiologically to circadian rhythm disturbance). Hansell et al (2012) have also demonstrated modest but significant heritability (h^2) for SPHERE psychological symptoms (h^2=0.38) and somatic symptoms (h^2=0.43). Future follow-ups of the cohort will address these issues in detail and establish whether the PSYCH and SOMA phenotypes delineate different trajectories such as observer-

rated recurrent depression, bipolarity or other heterotypic outcomes (Hickie et al, 2013; Scott et al, 2016). As the putative genetic and environmental risks underpinning the observed sex differences in changes in psychological and somatic symptoms, are still not well understood (e.g. Fowler et al, 2006); more exhaustive, genetically informative longitudinal designs will enable us to model any observed changes over time (Hickie et al, 1999; Gillespie et al, 2000).

There are several limitations to the study. First, as highlighted, although about 1800 individuals completed at least one SPHERE assessment, which allowed cross-sectional comparison of self-rated depression and subthreshold syndromes by sex at each time point, only about 30% of study participants completed three consecutive assessments over four years. However, we are encouraged that there were no significant differences in the clinical characteristics of the individuals who were included or excluded from the trajectory analysis. Second, whilst the SPHERE questionnaire can be used to screen for depression caseness, the psychological and somatic items were originally selected to also detect anxiety and fatigue symptoms, so it is not purely a screen for depression, but also for other common mental disorders such anxiety, etc. (Hickie et al, 2001; McFarlane et al, 2008). Third, and most important, we were not able to combine findings of SPHERE self-ratings with data from structured assessment interviews at each time point. As noted in this paper (see methods and Appendix 2), the overall the accuracy of the SPHERE (compared to the Composite International Diagnostic Interview) was about 60%. Further, whilst we can report that the prevalence of self-rated depression caseness exceeded that of major depression caseness diagnosed according to the DSM-IV diagnostic criteria (experienced by about 20% of the sample) (Covey-Duchesne et al, 2016), we cannot confirm whether specific individual trajectories associated with self-rated depression caseness will also reliably predict clinical depression. Fourth, we cannot be certain that youth completing repeated SPHERE assessments were rating current symptoms only (as required by the SPHERE) or whether they rated current and past symptoms. Lastly, we did not compare the trajectories of SPHERE symptoms with any other clinical outcomes, such as evolution to DSM-5 mood or psychotic disorders, etc. However, further research is planned on this cohort, including any associations between symptom and illness trajectories with social and environmental predictors and dimensional approaches, such as structural equational or growth

modelling and network analysis. These approaches may also allow exploration of the centrality of specific symptoms to different outcomes according to sex (e.g. Cramer et al, 2016).

In summary, the use of a screening tool that allows self-ratings of both psychological and somatic symptoms that are commonly associated with depression, but that overlap with other common mental health problems, provided valuable insights into the symptom trajectories as experienced in youth. The study offered evidence that supports the findings of the systematic review by Musliner et al (2016) regarding patterns or severity and stability of symptoms but extends the knowledge-base by demonstrating differences in self-rated sub-threshold symptom phenotypes in males and females. The next step involves assessment of these self-rated trajectories against structured clinical assessments and more sophisticated modelling of gender-specific pathways to major depression in a larger sample followed more intensively over a longer period. Using these approaches may provide a better understanding of the trajectories of self- or observer-rated depression, or fatigue or other syndromes, within a developmental framework and may help to further modify the intervention programmes being offered.

Acknowledgements:

we thanks the participants and their families for engagement with this longitudinal study.

Declaration of Interests:
Funding:
The BLTS studies have been supported by NHMRC project grants 1031119 and 1049911 (CI: Martin).

TD, RP, PL, SM, MW, and NG have no declarations in relation to this submission.

JS is a visiting professor at the Brain & Mind Centre at The University of Sydney. JS has received UK grant funding from the Medical Research Council (including for projects on actigraphy and bipolar disorders) and from the Research for Patient Benefit programme (PB-PG-0609-16166: Early identification and intervention in young people at risk of mood disorders).

DH has received honoraria for educational seminars from Janssen-Cilag and Eli Lilly. DH has received grant funding from the NSW Health, Mental Health and Drug & Alcohol Office.

IH is a Commissioner in Australia's National Mental Health Commission; a Member of the Medical Advisory Panel for Medibank; a Board Member of Psychosis Australia Trust. IH has received honoraria for presentations of his own work at educational seminars supported by several non-government organisations and by the pharmaceutical industry (including Servier, Pfizer, AstraZeneca and Eli Lilly). The University of Sydney (Principal Investigator: IH) received funding from Servier for a study of major depression and sleep disturbance in primary care settings. Other relevant funding for IH in relation to this study includes 'Testing and delivering early interventions for young people with depression' (APP ID: 1046899).

Contributors:
The original studies from which the sample were drawn was developed by Wright, Martin, and Gillespie. Several key studies have already been published by Parker, Lind, and Medland. Hickie was especially involved in the design and organization of collection of data on somatic and psychological phenotypes. Davenport undertaken most of the analyses. Scott undertook additional analyses and wrote the first draft. Hermens and all authors contributed to the redrafting of the manuscript and approved it for final submission.

Role of Funding:
The BLTS studies have been supported by NHMRC project grants 1031119 and 1049911 (CI: Martin).

REFERENCES

Angold A, Erkanli A, Silberg J, Eaves L, Costello EJ. (2002) Depression scale scores in 8-17-year olds: effects of age and gender. J Child Psychol Psychiatry; 43:1052–63.

Carrellas N.W., Biederman J., Uchida M. (2017) How prevalent and morbid are subthreshold manifestations of major depression in adolescents? A literature review. J Affect Disord. 210: 166-173.

Cole DA, Cai L, Martin NC, Findling RL, Youngstrom EA, Garber J, et al (2011) Structure and measurement of depression in youths: applying item response theory to clinical data. Psychol Assess. Dec;23(4):819-33.

Couvey-Duchesne B, O'Callaghan V, Parker R, Mills N, Kirk K, Scott J, et al. (2016) Cohort profile: The nineteen and up study, mapping neurobiological change across mental health stages. (Paper under review).

Cramer AO, van Borkulo CD, Giltay EJ, van der Maas HL, Kendler KS, Scheffer M, Borsboom D. Major Depression as a Complex Dynamic System. PLoS One. 2016 Dec 8;11(12):e0167490.

Dekker MC, Ferdinand RF, van Lang ND, Bongers IL, van der Ende J, Verhulst FC. (2007) Developmental trajectories of depressive symptoms from early childhood to late adolescence: gender differences and adult outcome. J Child Psychol Psychiatry. Jul;48(7):657-66.

Essau CA, Lewinsohn PM, Seeley JR, Sasagawa S. (2010) Gender differences in the developmental course of depression. J Affect Disord. Dec;127(1-3):185-90.

Fowler TA, Rice F, Thapar A, Farmer A. (2006) Relationship between disabling fatigue and depression in children: genetic study. Br J Psychiatry. Sep; 189:247-53.

Gillespie NA, Zhu G, Heath AC, Hickie IB, Martin NG (2000) The genetic aetiology of somatic distress. Psychol Med 30:1051-1061.

Gore FM, Bloem PJ, Patton GC, Ferguson J, Joseph V, Coffey C, Sawyer SM, Mathers CD. (2011) Global burden of disease in young people aged 10-24 years: a systematic analysis. Lancet. Jun 18;377(9783):2093-102.

Hansell NK, Wright MJ, Medland SE, Davenport TA, Wray NR, Martin NG, Hickie IB. (2012) Genetic co-morbidity between neuroticism, anxiety/depression and somatic distress in a population sample of adolescent and young adult twins. Psychol Med. Jun;42(6):1249-60.

Hickie IB. (2014) Evidence for separate inheritance of mania and depression challenges current concepts of bipolar mood disorder. Mol Psychiatry.19: 153-5.

Hickie IB, Hermens DF, Naismith SL, Guastella AJ, Glozier N, Scott J, Scott EM. (2013) Evaluating differential developmental trajectories to adolescent-onset mood and psychotic disorders. BMC Psychiatry. Nov 12;13:303.

Hickie I, Bennett B, Lloyd A, Heath A, Martin N (1999) Complex genetic and environmental relationships between psychological distress, fatigue and immune functioning: a twin study. Psychol Med 29:269-277

Hickie IB, Davenport TA, Naismith SL, Scott EM on behalf of the SPHERE National Secretariat (2001) SPHERE: a national depression project. Med J Aust 175 Suppl: S4-5.

Hickie IB, Rogers NL (2011) Novel melatonin-based therapies: potential advances in the treatment of major depression. Lancet 378:621-63.

Hill RM, Pettit JW, Lewinsohn PM, Seeley JR, Klein DN. (2014) Escalation to Major Depressive Disorder among adolescents with subthreshold depressive symptoms: evidence of distinct subgroups at risk. J Affect Disord. Apr; 158:133-8.

Kent L, Vostanis P, Feehan C. (1997) Detection of major and minor depression in children and adolescents: evaluation of the Mood and Feelings Questionnaire. J Child Psychol Psychiatry 38:565–73.

Kim-Cohen J, Caspi A, Moffitt TE, Harrington H, Milne BJ, Poulton R. (2003) Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. Arch Gen Psychiatry. Jul;60(7):709-17.

McLeod GF, Horwood LJ, Fergusson DM. (2016) Adolescent depression, adult mental health and psychosocial outcomes at 30 and 35 years. Psychol Med. May;46(7):1401-12.

McFarlane AC, McKenzie DP, Van Hooff M, Browne D. (2008) Somatic and psychological dimensions of screening for psychiatric morbidity: a community validation of the SPHERE Questionnaire. J Psychosom Res. Oct; 65(4): 337-45.

Musliner KL, Munk-Olsen T, Eaton WW, Zandi PP. (2016) Heterogeneity in long-term trajectories of depressive symptoms: Patterns, predictors and outcomes. J Affect Disord. Mar 1; 192:199-211.

Patton GC, Coffey C, Romaniuk H, Mackinnon A, Carlin JB, Degenhardt L, Olsson CA, Moran P. (2014) The prognosis of common mental disorders in adolescents: a 14-year prospective cohort study. Lancet. Apr 19; 383(9926):1404-11.

Salk RH, Petersen JL, Abramson LY, Hyde JS. The contemporary face of gender differences and similarities in depression throughout adolescence: Development and chronicity. J Affect Disord. 2016 Nov 15; 205:28-35.

Sanchez-Villegas A, Schlatter J, Ortuno F, Lahortiga F, Pla J, Benito S, Martinez-Gonzalez M. (2008) Validity of a self-reported diagnosis of depression among participants in a cohort study using the structured clinical interview for DSM-IV (SCID-I). BMC Psychiatry. *8:1–8.*

Scott J, Marwaha S, Ratheesh A, Morriss R, MacMillan I, Yung A, Hickie I, Bechdolf A. (2016) Bipolar at-risk criteria: an examination of which clinical features have optimal utility for identifying youth at risk of early transition from depression to bipolar disorders. Schizophrenia Bulletin. In press.

Silverstein B, Edwards T, Gamma A, Ajdacic-Gross V, Rossler W, Angst J. The role played by depression associated with somatic symptomatology in accounting for the gender difference in the prevalence of depression. Soc Psychiatry Psychiatr Epidemiol. 2013 Feb;48(2):257-63.

Simms L, Prisciandaro J, Krueger R, & Goldberg D. (2012). The structure of depression, anxiety and somatic symptoms in primary care. Psychological Medicine, 42, 15-28.

Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. (September 4, 2014). The NSDUH Report: Substance Use and Mental Health Estimates from the 2013 National Survey on Drug Use and Health: Overview of Findings. Rockville, MD.

Wright MJ, Martin NG (2004) Brisbane Adolescent Twin Study: outline of study methods and research projects. Aust J Psychology 56:65-78.

Van Beek Y, Hessen D, Hutteman R, Verhup E, van Leuven M. Age and gender differences in depression across adolescence: real or bias? Journal of Child Psychol Psych. 2012. 53 (9): 973-85.

Zisook S, Lesser I, Stewart JW, Wisniewski SR, Balasubramani GK, Fava M, et al (2007) Effect of age at onset on the course of major depressive disorder. Am J Psychiatry. Oct;164(10):1539-46.

Figure 1: Schematic diagram representing the different trajectories between depression caseness (C) and non-caseness (N) for 600 individuals who completed three consecutive SPHERE assessments at 12, 14 and 16 years (see text for details).

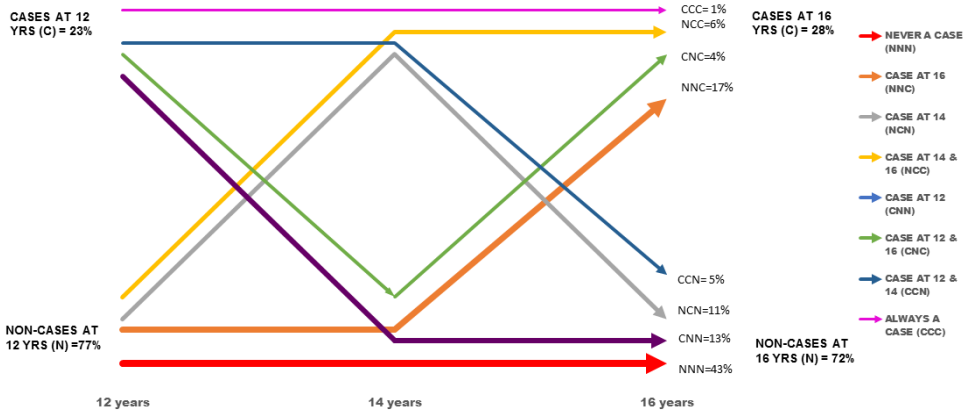

Table 1: Cross-sectional SPHERE-12 caseness and adjusted odds in females *vs* males at ages 12, 14 and 16.

	MALES n (%)	FEMALES n (%)	ALL n (%)	AOR 95% CI
AGE 12 †‡	282	318	600	
DEPRESSION CASENESS	66 (23)	73 (24)	139 (24)	1.04 (0.71, 1.53)
PSYCH	23 (8)	32 (8)	55 (8)	1.26 (0.72, 2.02)
SOMA	46 (16)	59 (19)	105 (18)	1.16 (0.77, 1.79)
NON-CASE	147 (52)	154 (48)	301 (50)	0.86 (0.63, 1.19)
AGE 14 ‡	355	395	750	
DEPRESSION CASENESS	84 (24)	121 (30)	205 (27)	1.43 (1.03, 1.97)
PSYCH	15 (4)	44 (11)	59 (8)	2.85 (1.55, 5.20)
SOMA	99 (28)	81 (21)	180 (24)	0.67 (0.48, 0.95)
NON-CASE	157 (44)	149 (38)	306 (41)	0.76 (0.52, 1.02)
AGE 16 †	337	377	714	
DEPRESSION CASENESS	88 (26)	125 (33)	213 (30)	1.41 (1.02, 1.94)
PSYCH	16 (5)	35 (9)	51 (7)	2.05 (1.11, 3.78)
SOMA	89 (26)	64 (17)	153 (22)	0.57 (0.39, 0.82)
NON-CASE	144 (43)	153 (41)	297 (42)	0.92 (0.68, 1.23)

Notes: n = number, % = Percentage rounded to nearest whole number. AOR = Adjusted Odds Ratio (reference = male); 95% CI = 95% confidence intervals.

SPHERE-12 ratings = DEPRESSION caseness (SOMA≥3 and PSYCH≥2); PSYCH (SOMA<3 and PSYCH≥2); SOMA (SOMA≥3 and PSYCH<2).
‡† Sample includes individuals with ratings at ages 12, 14 and 16; ‡ Sample includes individuals with ratings at ages 14 and 16;
† Sample includes individuals with ratings at ages 12 and 16. Bolded numbers are statistically significant.

Table 2: Longitudinal analysis of likelihood of self-rated DEPRESSION caseness at age 16 according to level of SPHERE-12 casesness at ages 12 or 14.

	DEPRESSION CASENESS AT AGE 16	
	OR (95% CI)	AOR (95% CI)
AGE 12 (n=714)		
DEPRESSION CASENESS	1.33 (1.05, 1.68)	1.68 (1.22, 2.32)
PSYCH	1.44 (1.00, 2.07)	1.57 (1.02, 2.04)
SOMA	1.43 (0.91, 2.25)	0.97 (0.68, 1.39)
AGE 14 (n=750)		
DEPRESSION CASENESS	1.26 (1.03, 1.97)	1.88 (1.32, 2.63)
PSYCH	1.31 (1.01, 1.70)	1.58 (1.11, 2.25)
SOMA	0.95 (0.78, 1.16)	0.72 (0.41, 1.24)

Notes: OR = Odds Ratio (reference = males); AOR = Adjusted Odds Ratio (reference = males);
95% CI = 95% confidence intervals. SPHERE-12 ratings = DEPRESSION caseness (SOMA≥3 and PSYCH≥2);
PSYCH (SOMA<3 and PSYCH≥2); SOMA (SOMA≥3 and PSYCH<2).
Bolded numbers are statistically significant.

HIGHLIGHTS

- Assessment of adolescent depression uses tools weighted towards psychological symptoms.
- We employed a depression screening tool that also identified sub-threshold psychological and somatic phenotypes.
- 57% of youth met criteria for self-reported depression caseness at least once.
- There were sex differences in rates of sub-threshold psychological and somatic phenotypes.
- Illness trajectories were variable over time, and eight different patterns were identified.