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**Title:** Twenty-year outcomes in adolescents who self-harm: a population-based cohort study

**Authors:**

**Rohan Borschmann, PhD** (corresponding author)

Centre for Adolescent Health; Murdoch Children's Research Institute  
Royal Children's Hospital  
50 Flemington Road 3052  
Melbourne, AUSTRALIA  
(tel): +61 (0) 410 903 337  
[rohan.borschmann@mcri.edu.au](mailto:rohan.borschmann@mcri.edu.au)

**Denise Becker, MBiostatistics**

Centre for Adolescent Health; Murdoch Children's Research Institute  
Royal Children's Hospital  
50 Flemington Road 3052  
Melbourne, AUSTRALIA  
[denise.becker@mcri.edu.au](mailto:denise.becker@mcri.edu.au)

**Carolyn Coffey, PhD**

Centre for Adolescent Health; Murdoch Children's Research Institute  
Royal Children's Hospital  
50 Flemington Road 3052  
Melbourne, AUSTRALIA  
[ccoffey@bigpond.com](mailto:ccoffey@bigpond.com)

**Elizabeth Spry, MSc**

Centre for Adolescent Health; Murdoch Children's Research Institute  
Royal Children's Hospital  
50 Flemington Road 3052  
Melbourne, AUSTRALIA  
[elizabeth.spry@mcri.edu.au](mailto:elizabeth.spry@mcri.edu.au)

**Margarita Moreno Betancur, PhD**

Clinical Epidemiology and Biostatistics Unit; Murdoch Children's Research Institute  
Royal Children's Hospital  
50 Flemington Road 3052

Melbourne, AUSTRALIA  
[margarita.moreno@mcri.edu.au](mailto:margarita.moreno@mcri.edu.au)

**Paul Moran, MRCPsych** (\*joint senior author)  
Centre for Academic Mental Health  
School of Social & Community Medicine  
University of Bristol  
Oakfield House  
Oakfield Grove  
Clifton, Bristol BS8 2BN  
[paul.moran@bristol.ac.uk](mailto:paul.moran@bristol.ac.uk)

**George Patton, MRCPsych** (\*joint senior author)  
Centre for Adolescent Health; Murdoch Children's Research Institute  
Royal Children's Hospital  
50 Flemington Road 3052  
Melbourne, AUSTRALIA  
[george.patton@rch.org.au](mailto:george.patton@rch.org.au)

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## ABSTRACT

**Importance:** Little is known about the longer-term psychosocial outcomes associated with adolescent self-harm. **Objective:** To determine whether adolescents who self-harm are at increased risk of adverse psychosocial outcomes in the fourth decade of life, using data from the Victorian Adolescent Health Cohort Study. **Design, Setting and Participants:** A stratified, random sample of 1943 adolescents was recruited from 44 schools across the state of Victoria, Australia, commencing in August 1992. We obtained data relating to self-harm from questionnaires and telephone interviews at eight waves of follow-up, commencing at mean age 15.9 years (SD 0.5) and ending at mean age 35.1 years (SD 0.6). **Main Outcome and Measure(s):** Substance use, common mental disorder and five measures of social disadvantage (divorced or separated, not in a relationship, not earning money, receipt of government welfare, and experiencing financial hardship) were measured at age 35 years. **Results:** At 35 years, social disadvantage, anxiety, and licit and illicit substance use were all more common in participants who had reported self-harm during the adolescent phase of the study. Adjustment for socio-demographic factors made little difference to these associations but adjustment for adolescent common mental disorder substantially attenuated most associations, with the exception of daily smoking (adjusted odds ratio, aOR: 1.7; 95% CI: 1.1, 2.8), any illicit drug use (aOR: 1.7; 1.1, 2.8) and weekly cannabis use (aOR 3.2; 1.6, 6.4). Further adjustment for adolescent risky substance use and antisocial behaviour attenuated the remaining associations, with the exception of weekly cannabis use at age 35, which remained independently associated with adolescent self-harm (OR 2.3, 95%CI 1.1–4.7). **Conclusions and Relevance:** Adolescents who self-harm are more likely to experience a wide range of psychosocial problems later in life. With the notable exception of heavy cannabis use, these problems appear to be largely accounted for by concurrent adolescent mental health and substance use. Complex interventions addressing the domains of mental state, behaviour and substance use, are likely to be more successful in helping this vulnerable group adjust to adult life.

## **INTRODUCTION**

Self-harm and suicide are major global health problems (1, 2). Self-harm is one of the strongest predictors of subsequent suicide (3, 4) and, globally, self-inflicted injuries result in the deaths of more females aged 15-19 than any other cause (5). Although the great majority of adolescents who self-harm cease doing so as they enter their adult years, we know little about how these individuals fare later in life (6, 7).

Recent evidence from longitudinal cohort studies of the general population shows that self-harming during adolescence is associated with mental and substance use disorders in early adulthood, independent of measured confounders (8, 9). However, the longer-term psychosocial outcomes associated with adolescent self-harm have yet to be fully described. To date, most follow-up studies have been based on small, selected clinical samples (10, 11); however, given that only a minority of young people who self-harm require medical attention and present to clinical services (12), such studies do not provide a clear picture of the long term natural history of self-harm.

Using data from the Victorian Adolescent Health Cohort Study (VAHCS) (13), we sought to examine the health and social outcomes in adulthood of a sample of community-dwelling participants with a history of self-harm during adolescence. We had two main aims:

- 1) To document the prevalence of social difficulties, mental and substance use disorders at the age of 35 years in participants who had reported having self-harmed during adolescence compared to those who had not; and
- 2) To examine the extent to which poor outcomes at 35 years might be explained by other health risks known to be associated with adolescent self-harm.

## **METHODS**

The Victorian Adolescent Health Cohort Study (VAHCS) is a 10-wave longitudinal cohort study of the health across the second to the fourth decade in the state of Victoria, Australia, conducted between August 1992 and September 2013. At baseline, a representative sample of mid-secondary school adolescents was selected with a two-stage cluster sampling

procedure. At stage one, 45 schools were chosen at random from a stratified frame of government, Catholic and independent schools, with a probability proportional to the number of Year 9 (aged 14-15 years) students in the schools in each stratum. At stage two, a single intact class was selected at random from each participating school. One class entered the study in the latter part of the ninth school year (wave 1) and the second class six months later (wave 2). School retention rates to Year 9 in the year of sampling were 98%. One school did not continue beyond wave 1, with a loss of 13 participants, leaving 44 schools. Participants were subsequently reviewed at four six-month intervals between the ages of 15-18 years (waves 3-6) with four follow-up waves in adulthood, aged 20-21 years (wave 7), 24-25 years (wave 8), 28-29 years (wave 9) and 34-35 years (wave 10). Figure 1 displays the flow of participants through the study. The present paper concerns data collected in waves 3-6 and wave 10. In wave 10 (mean age 35.1 years), 1348 participants completed the full interview, 95 participants (willing to participate, but with limited time) completed a partial survey, 340 participants refused, 140 participants were lost to follow-up, and 20 had died. Of the total 1943 adolescent participants, 1341 (69%) completed at least one wave in waves 3-6, had full background data, and completed wave 10.

## **INSERT FIGURE 1 ABOUT HERE**

### **Measurements**

**Background factors:** These included sex, age, participant and parental completion of secondary education, and parental divorce or separation up to and including wave 6.

### **Adolescent measures**

The following measures were summarised across adolescence by identifying any occurrence in waves 3-6 for self-harm and the remaining adolescent measures (with the response assumed to be negative or “no occurrence” when missing):

**Self-harm:** This was assessed at each wave from waves 3-6, using the following question: “*In the last [reference period] have you ever deliberately hurt yourself or done anything that you knew might have harmed you or even killed you?*” The reference period was one year for wave 3 and six months for all remaining waves. Participants who responded positively to the main question were then asked to describe the nature and timing of each self-harm event.

These detailed responses were then coded into five sub-types of self-harm by GCP and confirmed by PM. A dichotomous (yes/no) variable was created for each subtype: cutting or burning; self-poisoning; deliberate and potentially life-threatening risk-taking; self-battery; and other (including attempted self-drowning, hanging, intentional electrocution and suffocating). Participants could report more than one category of self-harm within a wave or in different waves. They were classified with “any self-harm” by wave if they were identified to have reported one or more of these individual categories.

**Common mental disorders:** Symptoms of depression and anxiety were assessed at each wave using the revised Clinical Interview Schedule (CIS-R) (14). The total scores on the CIS-R were dichotomized at a cut-off point of >11 to delineate a mixed depression-anxiety state at a lower threshold than syndromes of major depression and anxiety disorder but where clinical intervention would still be appropriate (15, 16).

**Antisocial behaviour:** This was assessed using ten items from the Self Report of Early Delinquency Scale (17) relating to property damage, interpersonal conflict, and theft in the previous six months. To distinguish participants with multiple antisocial behavioural problems, antisocial behaviour was categorised according to whether two or more behaviours were reported as having occurred more than once at any wave.

**Substance use:** Participants who consumed alcohol in the past week completed a seven-day retrospective diary of drinking days, with detailed beverage and quantity specific reports. We calculated the number of alcohol units (1 unit=10g of alcohol) consumed each day of the diary week. Very high risk alcohol use was defined according to Australian guidelines (18) as having drunk >20 units for males and >11 units for females on any day in the week prior to interview. Participants reporting smoking on six or seven days in the week prior to survey were classified as daily smokers. Those reporting using cannabis at least weekly as well as those using any amphetamines were identified.

### **Outcome measures at age 35**

**Social measures:** Participants were assessed on five measures of social disadvantage: (1) ever divorced or separated from a long term partner (cohabitation of >2 years), (2) not

currently in a relationship, (3) not earning money, (4) being in receipt of government welfare and (5) experiencing financial hardship (i.e. those with a positive response to one or more of the following statements: unable to pay gas, electricity or telephone bills on time; unable to pay mortgage or rent on time; could not afford a night out once a fortnight; and/or afford a holiday away for at least one week a year). Multiple social disadvantage was identified in participants reporting two or more measures of social disadvantage.

**Mental health:** For participants who completed the full wave 10 survey, two measures of depression and anxiety were obtained from computer-assisted telephone interviews using the Composite International Diagnostic Interview (CIDI): major depressive disorder (MDD) and anxiety disorder (AD) were both defined according to ICD-10 criteria, with MDD assessed using the CIDI-Auto (19) and AD using the CIDI-Short Form (20). Participants were classified with AD if they were diagnosed with generalised anxiety disorder, social phobia, agoraphobia or panic disorder. Participants who did the short interview in wave 10 completed the General Health Questionnaire (21). Any participant with a diagnosis of MDD, AD, or with a GHQ score of >2 (short interview only) was classified with **common mental disorder** (22).

**Cigarette smoking and nicotine dependence:** Participants who reported smoking on six or seven days in the week prior to survey were classified as daily smokers. Nicotine dependence was assessed at using the Fagerstrom Test for Nicotine Dependence (23). Nicotine dependence was defined at a cut-off point of >3 which corresponds with a cut-off point of >6 on the Fagerstrom Tolerance Questionnaire (24).

**Alcohol use and dependence:** Alcohol use was assessed using a beverage- and quantity-specific diary for Friday, Saturday, Sunday, and the most proximal weekday in the week prior to interview. Very high risk alcohol use was calculated in the same way as the equivalent adolescent measure (i.e. having consumed >20 units for males and >11 units for females on any day in the week prior to interview). Alcohol dependence (according to DSM-IV criteria) in the past year was assessed using the CIDI 12-month version (25).

**Cannabis use and dependence:** Cannabis use at least weekly in the past year was identified. We administered the computerised CIDI to generate the DSM-IV criteria for a diagnosis of cannabis dependence in participants reporting at least weekly cannabis use in the past 12



months. We applied this filter to minimise respondent fatigue as we considered that a diagnosis of cannabis dependence was only consistent with regular cannabis use, given the DSM-IV description of substance dependence as occurring with a “pattern of repeated (substance) self-administration” (26).

***Other illicit substances:*** Any use of amphetamines, cocaine, and ecstasy/designer drugs in the past 12 months was identified.

***Any illicit drug use:*** This included any use in the past year of either cannabis, amphetamines, ecstasy/designer drugs, and/or cocaine.

***Any substance dependence syndrome:*** This was identified from any of the three measures of dependence (nicotine, alcohol, and cannabis).

## **Analysis**

We first used logistic regression to estimate the sex- and age-adjusted associations between adolescent self-harm and background factors, mental health, and health risk behaviours during adolescence. We then assessed the associations between adolescent self-harm and the outcome measures at wave 10 (35 years) using logistic regression models, with progressive adjustment: (1) adjusted for sex and age (2); further adjustment for background social factors (3); additional adjustment for common mental disorder in adolescence (4); and final additional adjustment for adolescent antisocial behaviour and substance use measures. Effect modification by sex was tested using the Wald chi-square test. All analyses were conducted in Stata version 14.0 (27).

From the total cohort of 1943 participants, 1802 participants were assessed for self-harm between waves 3 and 6 (6). Of these, 74% were assessed at all four waves, 14% missed one wave, 6% missed two, and 6% missed three waves. Of the 1802, 16 (0.9%) had died by wave 10. A further 115 participants were missing covariate data (83 with no educational outcome due to missing all adult waves [7 to 10], 16 missing parental education, and 16 missing one or more adolescent measure), leaving 1671 participants in the analysis sample. Of these 1671, a total of 330 were missing all wave 10 data, and a further 118 had at least one wave 10 outcome missing. To minimise the effects of attrition bias due to missing wave 10 data, we used multiple imputation to impute these outcomes. We imputed the missing data so as

to produce 50 completed datasets for the 1671 participants. Imputation was performed separately for men and women, with multivariate imputation by chained equations. The imputation model for each wave 10 variable included all background analysis variables, three auxiliary background variables associated with incomplete participation (at least one parent smokes cigarettes most days [ $p=0.010$ ], no parent drinks alcohol most days [ $p=0.002$ ], and having attended a metropolitan school [ $p=0.009$ ]), and the wave 8 variables most closely associated with the wave 10 outcome. We imputed age with linear regression and all other variables with logistic regression. The final estimates were obtained by averaging results across the 50 imputed datasets using Rubin's rules for multiple imputation inference (28). We found no statistical evidence of effect modification by gender of the association between adolescent self-harm and outcomes. We conducted a sensitivity analysis including the 1341 participants who had data for adolescent self-harm, background and adolescent covariates, and at least one outcome measure at wave 10.

### **Ethical approval**

Data collection protocols were approved by the Ethics in Human Research Committee of the Royal Children's Hospital, Melbourne. Informed parental consent was obtained before inclusion in the study. In the adult phase, all participants were informed of the study in writing and gave verbal consent before being interviewed.

### **RESULTS**

One hundred and thirty five of the 1671 participants (8.1%; 95CI% 6.9-9.5) in the analysis sample reported having self-harmed at least once during waves 3-6, comprising 85 girls (9.5%; 95%CI 7.7-11.5) and 50 boys (6.5%; 95%CI 5.0-8.4). Of these, 101 (6.0%), 26 (1.6%) and 8 (0.5%) reported self-harming at one, two, and three waves respectively (none reported self-harm at all four waves). The frequency of self-harm was greatest at wave 3 (mean age 15.9 years) for both girls (51; 6.0%; 95%CI 4.6-7.9) and boys (29; 4.0%; 95%CI 2.8-5.7). At wave 6 (mean age 17.4 years), 2 boys (0.3%; 95%CI 0.1-1.1) and 21 girls (2.5%; 95%CI 1.7-3.8) reported self-harm.

Table 1 shows the frequency of background and adolescent measures in the sample by adolescent self-harm and their association with adolescent self-harm, adjusted for sex and

age. Participants who reported having self-harmed during adolescence were more likely to report parental divorce, common mental disorder and antisocial behaviour during adolescence than those who did not report having self-harmed. They were also more likely during the adolescent waves to be daily smokers, and to report high risk alcohol use, weekly cannabis use and amphetamine use.

### ***Outcomes at age 35***

Table 2 shows the proportion of adverse social adjustment, substance use, mental and substance use disorders at age 35 years in participants who reported having self-harmed during adolescence compared with those who did not. There were clear differences in the proportions of participants in the two groups reporting financial hardship at age 35 (34% in the self-harm group [95%CI 25-43] vs. 22% in the no self-harm group [95%CI 20-24]), daily smoking (26% [95%CI 18-34] vs. 15% [95%CI 13-17]), and weekly cannabis use (12% [95%CI 6-17] vs. 4% [95%CI 3-5]).

Other differences between the two groups were also apparent at 35 years, including the proportion of participants reporting a history of divorce or separation (35% [95%CI 26-44] vs. 24% [95%CI 22-26]), multiple social disadvantage (30% [95%CI 21-38] vs. 20% [95%CI 17-22]), and common mental disorder (26% [95%CI 18-34] vs. 17% [95%CI 15-19]).

### ***Adjusted associations between adolescent self-harm and outcomes at age 35***

Table 3 displays results from a series of predictive models examining the associations between self-harm during adolescence and outcomes at 35 years, with progressive adjustment for background factors and adolescent measures associated with self-harm. After adjusting for sex and age, adolescent self-harm was associated with the occurrence of divorce/ separation (OR 1.7, 95%CI 1.1-2.5), financial hardship (OR 1.8, 95%CI 1.2-2.8), multiple social disadvantage (OR 1.6, 95%CI 1.1-2.5), anxiety (OR 1.8, 95%CI 1.1-3.1), common mental disorder (OR 1.7, 95%CI 1.1-2.6), daily smoking (OR 2.1, 95%CI 1.4-3.3), weekly cannabis use (OR 3.8, 95%CI 2.0-7.1), use of ecstasy (OR 2.1, 95%CI 1.0-4.3), use of any illicit drug use (OR 1.9, 95%CI 1.2-3.0), cannabis dependence (OR 3.0, 95%CI 1.3-7.0), and any substance dependence syndrome (OR 1.9, 95%CI 1.1-3.3). Although the estimates were less precise, there was also some evidence of association between adolescent self-

harm and several other outcomes at age 35, including depression (OR 1.6, 95%CI 0.94-2.7), receiving government welfare (OR 1.8, 95%CI 0.91-3.5), and nicotine dependence (OR 1.8, 95%CI 0.94-3.5).

Adjustment for the participant's history of parental divorce, level of parental education and level of participant education had little impact on these associations. However further adjustment for adolescent mental health status, substance use and antisocial behaviour, attenuated all of these associations. The association between adolescent self-harm and weekly cannabis at age 35 persisted after adjustment for all background and adolescent measures (OR 2.3, 95%CI 1.1–4.7).

The sensitivity analysis of observed data showed similar findings, confirming the pattern of results obtained with imputed data (see Appendix 1).

## **DISCUSSION**

In this population-based cohort study, adolescents who self-harmed were more likely to experience a wide range of other health and social problems during adolescence. These included common mental disorder, antisocial behaviour and both licit and illicit substance use (6, 8). These problems appeared to persist into the mid-thirties, as participants who reported having self-harmed during adolescence reported greater financial hardship, daily smoking, and weekly cannabis use at 35 years, prior to adjustment for known confounders. Even allowing for baseline differences in sex and age, participants with a history of adolescent self-harm were much more likely to encounter serious social problems in their thirties, including higher rates of divorce or separation, greater financial hardship, and multiple social disadvantages. Furthermore, those who had self-harmed during adolescence had poorer mental health, with an excess prevalence of anxiety disorders, antisocial behaviour and substance use. The associations with adolescent self-harm were only marginally reduced after adjustment for adolescent social factors. Further adjustment for adolescent common mental disorders substantially reduced many of the associations, but did not fully attenuate the increased odds of smoking, or use of cannabis and ecstasy at age 35. After adjusting for all adolescent health and social risks, adolescent self-harm remained independently associated with a more than two-fold increase in the odds of using cannabis on a weekly basis at age 35 years.

Previous research examining the longer-term outcomes of adolescent self-harm in non-treatment-seeking samples is scarce. Using data from the Avon Longitudinal Study of Parents And Children [ALSPAC; (29)] cohort, Mars and colleagues (9) examined short-term health and social outcomes between the ages of 16-21 years of 4,799 community-dwelling adolescents, of whom 19% reported having self-harmed by the age of 16. In that study, participants reporting adolescent self-harm were more likely to have mental and substance use disorders at age 18 and less likely to be in education, employment or training at age 19, compared with those who had not self-harmed (9). We have previously reported the outcomes of adolescent self-harm in the third decade of life (8). In this further follow-up, we have found that the psychosocial sequelae of adolescent self-harm persist into the fourth decade. Our findings suggest that individuals who self-harm earlier in life are more likely to use cannabis heavily later in life, an association which may be mediated by the occurrence of emotional distress (30, 31).

Risky behaviours such as harmful drinking and antisocial behaviour tend to cluster during the adolescent years (32). These risky behaviours can compromise teenage health and jeopardize the successful transition into adulthood (33). Our findings indicate that self-harm in adolescence is clearly part of this cluster of risk behaviours that have potential to disrupt normal social development. There are several possible explanations for the clustering of these behaviours. First, adolescence is the period when sensation-seeking is at an all-time high (34), yet the neurodevelopment and underlying brain circuitry implicated in the inhibition of inappropriate desires, emotions and actions in favour of appropriate ones continues to develop well into young adulthood (35, 36). Second, both self-harm (31) and substance use (30, 37) are used to regulate emotion in young people, and it is possible that the same psychosocial risk factors underlie the two behaviours (32). Third, social influences, such as the influence of deviant peer group (38) feature heavily in the development and maintenance of both substance use (39) and self-harm (40).

There is some evidence of effectiveness for several therapeutic interventions aimed at reducing self-harm during the adolescent years. In a recent systematic review and meta-analysis of 19 randomised controlled trials (41), the interventions with the largest effect sizes were dialectical behaviour therapy (DBT), cognitive-behavioural therapy (CBT), and mentalization-based therapy (MBT). However, the evidence base is small. There is an urgent

need for larger pragmatic trials and independent replication of these findings, and this should be considered a research priority. Future research should also seek to examine the impact of sustained intervention, beyond the time at which self-harm ceases, on the health and social outcomes for this population.

Our study is noteworthy for its large, close to representative sample, high retention rates and multiple waves of follow-up over a 20-year period from mid-adolescence to the mid-thirties. However, our findings need to be considered in light of certain methodological limitations. First, we used a broad definition of self-harm that encompassed behaviours with and without suicidal intent, and did not have the capacity to examine individual subtypes of self-harm. We deliberately adopted this approach because a substantial overlap exists between suicidal and non-suicidal self-harm during adolescence and behavioural intention with respect to suicide is changeable (42, 43). Second, we relied exclusively on self-reported self-harm and we did not check the validity of these reports against other sources, such as hospital records. Recent UK research has highlighted discrepancies between self-reported accounts of self-harm and those assessed by hospital admissions or emergency department presentations, with approximately 20% of those resulting in a hospital admission not being disclosed by participants during self-report surveys (44). Additionally, many adolescents in this UK sample provided inconsistent accounts of their self-harm histories on different assessment dates, and these adolescents were less likely to be depressed or to have self-harmed with suicidal intent. It is possible, therefore, that self-harm events were under-ascertained in our cohort, possibly resulting in conservative estimates of association. Third, some of the fully adjusted models were underpowered, resulting in poor precision of some estimates with large confidence intervals. Fourth, despite our high retention rates, it is possible that attrition bias may have affected our findings. For example, participants with complicated or chaotic lives may have been more likely to refuse participation, or to be absent from survey at individual waves. We addressed possible attrition bias by using multiple imputation for wave 10 missing data to obtain least biased estimates of associations. Fifth, we cannot rule out the possibility that some of the detected findings may have arisen due to chance, given the fact that multiple outcomes were investigated. However, the associations we report are consistent with the literature and are clinically intuitive; as such, we are confident in reporting them with appropriate confidence intervals.

Finally, due to resource availability, we were unable to link participant data to national health, education, social or justice datasets to obtain a more informed picture of non-respondents.

## **Conclusions**

Self-harm during adolescence is part of a cluster of other adolescent mental and behavioural problems and, for some adolescents, may be associated with substantial psychosocial difficulties later in life. Adolescent self-harm should be viewed neither in isolation nor as merely a passing phase (45). Rather, it is a marker for a range of risk behaviours that, in turn, pose hazards for social and emotional development through young adulthood. In light of this, interventions addressing other key individual-level risk domains (particularly substance use, mental health, and antisocial behaviour) are likely to be more successful in helping this vulnerable group of young people as they make their way through life (32, 33, 46). Further research currently underway using these data will help us to better understand the pathway between adolescent self-harm and later psychosocial adversity, and this will be essential to inform the development of effective individual-level interventions. Coherent policy approaches should focus on reducing the prevalence of common underlying population-based risk factors (46, 47) and, to maximise the effectiveness of such policies, a response from multiple sectors, including the education, health, and community sectors, is required (48).

## **RESEARCH IN CONTEXT PANEL**

### **Evidence before this study**

We sought to identify relevant studies that have examined prospective associations between adolescent self-harm and future mental health and social adjustment, in a non-treatment-seeking sample of adults. We searched MEDLINE and PsycINFO from inception and Embase for studies written in English published from database inception (1974) until April 3, 2017, using the following search terms: “self-harm”, “self-injury”, “longitudinal study”, “cohort study”, “community”, and “mental health”. The Avon Longitudinal Study of Parents and Children (ALSPAC) has reported a range of short-term, prospective, clinical and social outcomes associated with self-harm at age 16 years in a community sample. The

ALSPAC findings showed that any history of self-harm at age 16 was associated with poorer outcomes in relation to mental and substance use disorders, education attainment, and employment. However, self-harm was measured on one occasion only and the outcomes were short-term in nature (i.e. <5 years); as such, the longer-term outcomes remain unclear. To our knowledge, no published studies have reported on the long-term outcomes of adolescent self-harm in a non-treatment-seeking sample with repeated measures of self-harm in the adolescent and young adult period.

### **Added value of this study**

In this population-based, longitudinal study, we not only examined on six occasions during the adolescent years, but we also captured rich data relating to clinical and psychosocial outcomes up to 20 years later. Self-harm during adolescence was linked to increased rates of social disadvantage, anxiety, and licit and illicit substance use. Whilst adjusting for socio-demographic factors, adolescent substance use and adolescent antisocial behaviour attenuated several of these associations, weekly cannabis use at age 35 remained independently associated with adolescent self-harm. Our findings suggest that adolescent self-harm should be viewed as a conspicuous marker of emotional and behavioural problems that are predictive of poor life outcomes.

### **Implications of all the available evidence**

Self-harm during adolescence is common in the general population and is associated with a distinct cross-sectional pattern of social and health-related disadvantage. Over time, individuals who have self-harmed have worse mental health and poorer psychosocial outcomes than those with no history of self-harm. Our findings suggest that interventions addressing multiple risk domains are likely to be more successful in helping this vulnerable group adjust to adult life.

### **Contributors**

GCP is the principle investigator and data custodian of the Victoria Health Cohort Study. GCP, PM and RB conceived the idea for this study. GCP, PM, CC, DB, MMB and RB developed the analysis plan. Data were analysed by DB. RB led the writing of the paper and DB, PM, CC, ES, MMB and GCP all contributed to the writing of the paper.

### **Conflicts of interest**



RB, DB, CC, PM, ES, MMB and GCP declare that they have no conflicts of interest.

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