plete with examples of the youthful hero or heroine's journey from adversity and despair to triumph and success, supporting the empirical evidence that the path to resilience is paved with protective relationships and resources. What is lacking from many trauma-focused interventions is an acknowledgement that PACEs are powerful elements of everyday life that already exist, or can be engineered to occur routinely and frequently, and can be leveraged to support treatment goals and activities.

Our research indicates that adults can benefit from current PACEs as well as previous experiences from childhood. We have created an Adult PACEs Plan that encourages adults to choose one or two PACEs to work on each month with a group of adults. As with PACEs for children of different ages, adult PACEs focus on relationships and enriching experiences[2]. Anecdotally, we have found that individuals benefit from focusing on simple activities that strengthen relationships and impose structure and routine.

In summary, PACEs are often overlooked but powerful tools, that can support therapeutic interventions and mental health throughout the life course.

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Clearing the air: clarifying the causal role of smoking in mental illness

Decades of observational research have identified a vast range of risk factors which may contribute to the onset of various mental health conditions. A recent review published in this journal[1] brought together data from 380 meta-analyses on this topic, finding over 1,000 different associations for even just non-genetic factors which may influence the risk of mental disorders. Examples of well-established risk factors include adversity/abuse in childhood and stressful employment circumstances in adulthood[1]. Additionally, a more recent body of research has strongly implicated a range of physical health conditions/behaviors – such as diabetes, physical inactivity and obesity – as being associated with an increased risk of mental illness[1,2].

Within this framework, tobacco smoking has emerged as holding particularly strong associations with the onset of mental health conditions. Meta-analyses of longitudinal studies have found strong evidence for a prospective association between smoking and mental disorders, particularly major depression, psychotic disorders and opioid use disorder[1,2]. However, findings from these traditional observational studies may be subject to bias from reverse causation (for example, through unmeasured prodromal symptoms leading individuals to initiate smoking) and residual confounding (for example, through other unmeasured behaviors that influence both smoking and mental health).

Mendelian randomization (MR) is an increasingly applied epidemiological methodology which can address these biases, by using genetic variants known to predispose individuals to certain behaviors/outcomes (e.g., initiating smoking, or smoking heavily), and examining their associations with other outcomes (e.g., mental health diagnoses)[3,4]. In MR, the genetic variants act as instrumental variables, inherited at random and fixed at conception, thus reducing bias from confounding and reverse causation[3]. A number of MR studies on smoking and mental health have already been conducted to examine causal relations, and a recent systematic review of this literature identified high-quality evidence for an effect of smoking on depression, schizophrenia and bipolar disorder[4].

However, there are several limitations of these studies that must be considered[3]. First, although MR studies suggest that smoking behaviors are causal for some mental health outcomes, there is a high degree of bidirectionality, with strong evidence for reverse effects also apparent for depression and schizophrenia[2,4]. This presents the possibility of a vicious cycle, whereby symptoms of mental illness increase smoking and dependence, while smoking increases the risk and severity of mental health conditions. Second, we do not fully understand as yet the biological mechanisms underlying the majority of smoking genetic instruments used in MR analyses. Therefore, the strongest evidence for causal effects of smoking on mental illness will ultimately come from triangulating results across different research methodologies.

The gold standard approach to determine causality would be to conduct a randomized controlled trial (RCT), but it would be unethical to test the effects of tobacco smoking as an experimental exposure directly in this way (due to the addictive potential, and known effects on physical health). Nonetheless, the mental health outcomes of smoking cessation interventions in RCTs can instead be used to infer causal relations. Indeed, a 2021 Cochrane review of 102 studies on this topic consistently showed that people who quit smoking, on average, experienced an improvement in all mental health outcomes examined[5].

Importantly, the observed effects: a) were robust to multiple sensitivity analyses; b) persisted when adjusting for a broad range of socio-demographic, behavioral and clinical covariates; and c) were evident across the 56 RCTs, collectively showing improved mental health outcomes from smoking cessation among participants who had decided to quit smoking *before* being randomized to smoking cessation vs. control interventions (thus eliminating

the potential of reverse causality)[5].

Despite the growing causal evidence, the neurobiological pathways through which smoking adversely affects mental health have yet to be ascertained. One plausible mechanism is related to neuroadaptations in nicotinic pathways in the brain[6] which are associated with psychological withdrawal symptoms, such as depressed mood, agitation and anxiety. Withdrawal symptoms are alleviated by smoking but return when blood levels of nicotine decline at around 20 min after smoking, resulting in repeated changes in a smoker's psychological state throughout the day[6], and perhaps also supporting the "self-medication hypothesis" around smoking and mental health. The fluctuations in mood state experienced by smokers could worsen mental health over time, and the associated biological effects of withdrawal-induced psychological symptoms could increase the risk of developing mental illness[6].

Another potential biological pathway relates to inflammation and oxidative stress, which are both implicated in a range of mental health conditions. A large cohort study in 2021 confirmed that current smoking was associated with increased oxidative stress biomarkers, in a dose-response fashion[7]. Alongside this, the observation that those who had quit smoking for >10 years had similar oxidative stress biomarker levels as never smokers indicates that the biological effects relevant to mental health are reversible[7], which is also consistent with the aforementioned evidence from RCTs showing that cessation improves mental health status in smokers[5].

Continued research into the mechanistic pathways involved in the effects of smoking on mental health will serve to both confirm the nature of indicated causal relations, and increase our understanding of how cessation or other strategies can improve neurological and psychological outcomes in smokers (with or without diagnosed mental illness). Relatedly, the recent adoption of e-cigarettes across society calls for more research on how their use impacts mental health.

While studies in psychiatric settings have suggested that e-cigarettes may be a beneficial tool for helping people with mental illness to reduce tobacco use[8], and thus the adverse physical and mental health effects of smoking, other research in the general population has indicated that nicotine consumption in e-cigarette form may still impact adversely on psychological well-being[9]. Further research is needed to establish a clear evidence base and consensus around the use of e-cigarettes with regards to mental health, in the general population as well as in psychiatric settings.

Meanwhile, as the literature around the magnitude and mechanisms of the psychiatric effects of nicotine and tobacco smoking continues to evolve, promoting smoking cessation in populations with or at-risk for mental illness should be considered as an urgent priority anyway. In recent decades, public health initiatives in many Western societies have successfully reduced tobacco smoking across the general population. However, these initiatives have failed to reach some of most vulnerable members of society, resulting in disparities in tobacco smoking among mental health populations becoming even more apparent than ever. People with mental illness now smoke >40% of all cigarettes sold, and account for around half of all smoking-related deaths across the population, making this single health behavior a key driver of the premature mortality observed in people with severe mental illness[8].

In summary, there is an increasingly strong triangulation of evidence from various study designs and populations that smoking adversely impacts on mental health, in terms of both enhancing the risk of mental illness, and increasing psychiatric symptoms in those with and without diagnosed conditions. While the research priorities lie with elucidating the causal mechanisms for the effects, the clinical priorities pertain more immediately to establishing and disseminating effective smoking cessation interventions within mental health care, in order to protect both the physical and mental health of smokers treated for mental illness.

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A clinically useful model of psychopathology must account for interpersonal dynamics

A useful taxonomy of psychopathology should not only describe variations in mental disorder, but also explain how they occur and point to therapeutic solutions. Contemporary diagnostic models based on a system of polythetic disorder categories do not validly capture the covariation of disorders and symptoms across people, introducing both disorder comorbidity and heterogeneity. As a result, significant advances in explaining discrete categories of psychopathology or deriving disorder-specific therapeutic solutions have not been forthcoming.

These failures have led to new approaches to psychiatric tax-