Associations between peer victimization, depressive symptoms, and suicidal ideation: investigating biological underpinnings

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ABSTRACT

Peer victimization has consistently been linked to depression and suicidal ideation in adolescence with persisting associations in adulthood. Peer victimization has been defined as harm caused by peers outside the norms of appropriate conduct (e.g., being insulted, harassed, robbed, or hit). This thesis is based on three manuscripts (henceforth referred to as Chapters 1, 2, & 3), and aimed to fill specific gaps in the literature regarding the associations between peer victimization with depressive symptoms and suicidal ideation by using two population-based cohorts; Quebec Longitudinal Study of Child Development (QLSCD) and the 1958 British Birth Cohort (1958BBC). Firstly, it is unclear whether a newer form of peer victimization expressed through electronic devices; cybervictimization, is similarly associated to suicidal ideation, compared to face-to-face peer victimization. Using the QLSCD, Chapter 1 showed that both face-to-face and cybervictimization were cross-sectionally associated to suicidal ideation throughout adolescence, but the magnitude of association was stronger for cybervictimization. Being cybervictimized only or in combination with face-to-face victimization was linked to a higher risk of reporting suicidal ideation, compared to being face-to-face victimized only. However, while face-to-face victimization predicted suicidal ideation 2 years later, cybervictimization was not a predictor after adjusting for baseline suicidal ideation. Secondly, little is known about the biological mechanisms behind the associations between peer victimization with depressive symptoms and suicidal ideation. Several biomarkers, including genetic variants and DNA methylation sites, have been studied in association with peer victimization, depressive symptoms, and suicidal ideation, independently. However, the literature is largely inconsistent, and lacking in the context of peer victimization. Building on Chapter 1 as well as prior findings with QLSCD showing that peer victimization was also associated to depressive symptoms, we sought to further understand who is more at-risk. In Chapter 2, we used a novel marker of genetic vulnerability for depression, the

polygenic risk score for depression (PRS-depression), and test whether it influenced the associations between peer victimization, depressive symptoms, and suicidal ideation in adolescence. Chapter 2 results showed that PRS-depression was associated with depressive symptoms in adolescence but did not interact with peer victimization in predicting depressive symptoms or suicidal ideation. Another potential mechanism at the interface between the environment and genetics; epigenetics, was explored using epigenetic indices of biological aging (Horvath, Skin & Blood, and PedBE clocks), epigenetic pace of aging (DunedinPACE), and stress response reactivity (Epistress score). Thirdly, some studies have investigated Horvath epigenetic age in association with early life adversity, depressive symptoms, and suicidal ideation, with inconsistent findings. In addition, few have explored whether epigenetic age partly explained the associations of peer victimization with depressive symptoms and suicidal ideation. Chapter 3 used a two-cohort design using the QLSCD and the 1958BBC with information on depressive symptoms and suicidal ideation in adolescence and adulthood. Our findings unraveled some associations between epigenetic aging, as well as the DunedinPACE score, and depressive symptoms. However, no association was found between epigenetic indices and peer victimization, or suicidal ideation, hence there was no evidence of epigenetic mediation. Overall, this thesis has expanded on studies investigating peer victimization in association with depressive symptoms and suicidal ideation, specifically on potential underlying biological mechanisms, and clarifying the associations with cybervictimization.

RÉSUMÉ

La victimisation par les pairs a été liée à la dépression et aux idéations suicidaires à l'adolescence avec des effets qui persistent à l'âge adulte. La victimisation par les pairs a été définie comme un tort causé par des pairs qui agissent de façon hors normes comportementales (e.g., se faire insulter, harceler, voler, ou frapper). Cette thèse est basée sur trois manuscrits (Chapitres 1, 2, et 3) et vise à combler certaines lacunes de la littérature scientifique sur les associations entre la victimisation par les pairs et les symptômes dépressifs, ainsi que les idéations suicidaires, en utilisant deux cohortes de population générale ; Étude Longitudinale du Développement des Enfants du Québec (ELDEQ), et 1958 British Birth Cohort (1958BBC).

Premièrement, il n'a pas été déterminé si la cybervictimisation ; un nouveau type de victimisation ayant lieu sur des plateformes électroniques, est similairement associée à la victimisation traditionnelle. Le Chapitre 1 (ELDEQ) nous montre que la victimisation traditionnelle et la cybervictimisation sont associées de façon transversale avec les idéations suicidaires à travers l'adolescence, mais l'ampleur de l'association était plus importante pour la cybervictimisation. Cependant, la victimisation traditionnelle prédisait les idéations suicidaires 2 ans plus tard, mais ce n'était pas le cas pour la cybervictimisation après avoir contrôlé pour les idéations suicidaires concomitantes. Deuxièmement, les mécanismes biologiques derrière les associations entre la victimisation par les pairs, les symptômes dépressifs et les idéations suicidaires sont méconnus. Plusieurs marqueurs biologiques, incluant les variants génétiques, ont été indépendamment étudiés en association avec la victimisation par les pairs, les symptômes dépressifs, et les idéations suicidaires. Cependant, les études publiées manquent et présentent des résultats contradictoires, notamment dans le contexte de la victimisation par les pairs. Le Chapitre 2 (ELDEQ) nous montre qu'un marqueur de vulnérabilité génétique de la dépression ; un score polygénique de dépression (PRS-dépression) était associé avec les symptômes dépressifs à l'adolescence, mais n'interagissait

pas avec la victimisation par les pairs dans la prédiction des symptômes dépressifs ou des idéations suicidaires. Troisièmement, un autre mécanisme potentiel à l'interface entre l'environnement et la génétique ; l'épigénétique, a été exploré grâce à des indicateurs d'âge biologiques, de vitesse du vieillissement biologique, et de réactivité à la réponse au stress. Des études ont exploré l'âge épigénétique en relation avec l'adversité en début de vie, les symptômes dépressifs, et les idéations suicidaires, mais ont rapportés des résultats contradictoires. Le Chapitre 3 (ELDEQ, 1958BBC) montre des associations avec l'âge épigénétique et la vitesse de vieillissement épigénétique et les symptômes dépressifs. En revanche, aucune association n'a été trouvée entre nos scores épigénétiques et la victimisation par les pairs, ou les idéations suicidaires. Ainsi, il n'y a eu pas de preuve évidente d'une médiation par ces scores épigénétiques. Dans l'ensemble, cette thèse ajoute aux études sur la victimisation par les pairs, les symptômes dépressifs et les idéations suicidaires. Notamment sur les mécanismes biologiques potentiellement impliqués dans ces associations, ainsi que sur les associations uniques avec la cybervictimisation.

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CONTRIBUTION TO ORIGINAL KNOWLEDGE

1 in 5 children and adolescents experienced peer victimization in Canada in across the globe. Given the literature to date, we know that peer victimization can have deleterious effects on mental health in adolescence and adulthood. The development of depressive symptoms and suicidal ideation are known to be linked with prior experiences of peer victimization. We built on this well-established evidence to examine whether a specific type of peer victimization occurring on electronic platforms, cybervictimization, is similarly associated to suicidal ideation. In this project we confirmed that cybervictimization was associated to a higher risk of experiencing concurrent suicidal ideation. In more exploratory analyses we attempted to unravel biomarkers that influence or underlie the associations between peer victimization, depressive symptoms, and suicidal ideation. We built on prior evidence regarding biological markers of genetic vulnerability to depression and discovered that peer victimization predicted depressive symptoms and suicidal ideation beyond this genetic vulnerability. After further exploring markers based on biological aging, and the stress response, as biomarkers explaining the relationship between peer victimization, depressive symptoms, and suicidal ideation, the evidence did not support the hypothesis that peer victimization may leave a lasting mark on the biological systems of aging and stress. Future work into further characterizing these biomarkers is needed, as well as exploring other biomarkers which may be better candidates influencing or underlying these associations. Nonetheless, these novel explorations into these associations represent important first steps towards finding biomarkers to better understand what makes individuals at a greater risk of developing depressive symptoms and suicidal ideation after being peer victimized.

CONTRIBUTION OF AUTHORS

This thesis was written by Léa C. Perret and edited by Dr. Marie-Claude Geoffroy. The statistical analyses in Chapter 1 were conducted by Dr. Massimiliano Orri. The polygenic risk score for depression used in Chapter 2 was computed by Dr. Geneviève Morneau-Vaillancourt, and the imputation of the phenotypic data was done by Alain Girard. Horvath's pan-tissue clock, Horvath's skin and blood clock, Pediatric Buccal Cell epigenetic clock, Dunedin pace of aging, and the Epistress were computed by Emily Barr. All other data processing, statistical modelling and analyses were performed by Léa C. Perret.

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INTRODUCTION

Depression is a major contributor to the burden of disease worldwide, and suicide is a leading cause of mortality in youth (WHO, 2021). Depressive symptoms and suicidal ideation/attempts typically emerge in early adolescence and increase rapidly into young adulthood (Geoffroy, Bouchard, et al., 2022; Nock et al., 2013; Thapar, Collishaw, Pine, & Thapar, 2012). Environmental stressors are important risk factors of depression and suicidal ideation (Carballo et al., 2020; Thapar et al., 2012). This highlights the importance of studying modifiable environmental risk factors of depressive symptoms early in adolescence that could be targeted in prevention and intervention strategies.

Peer victimization is a well-documented modifiable risk factor for mental health symptoms across the life-course (Geoffroy et al., 2018a; McDougall & Vaillancourt, 2015), including depressive symptoms and suicidal ideation (Holt et al., 2015; Katsaras et al., 2018; Moore et al., 2017). However, there are several gaps in the literature which will be addressed in this thesis.

Firstly, a novel type of peer victimization; **cybervictimization**, has also been linked to depressive symptoms (Tran, Thai, Dang, Vo, & Duong, 2021) and suicidal ideation (Bonanno & Hymel, 2013; Buelga, Cava, Ruiz, & Ortega-Barón, 2022; Quintana-Orts, Rey, & Neto, 2022). Although its cross-sectional link with suicidal ideation has been reported in adolescence in some studies (Bonanno & Hymel, 2013; Buelga et al., 2022; Quintana-Orts et al., 2022), less is known about its longitudinal association with suicidal ideation in adolescence. Furthermore, there is a reported overlap whereby some individuals who experienced peer victimization in-person (i.e., face-to-face or traditional victimization) also experience it through electronic means (i.e., cybervictimization). However, most studies have attempted to explore the unique association of

cybervictimization with suicidal ideation in adolescence, without considering the overlap with in-person victimization.

Secondly, existing findings on the biological mechanisms behind the association between peer victimization, depressive symptoms and suicidal ideation are inconsistent. In other words, we have yet to identify a clear biological marker that may influence or partially explain one's susceptibility to developing depressive symptoms or suicidal ideation after being peer victimized. Prior studies have shown that variations within single genes, also called gene variants, influenced the association between peer victimization and depressive symptoms (Benjet, Thompson, & Gotlib, 2010; Sugden et al., 2010). However, depressive symptoms are known to involve many genes; they are polygenic. The **polygenic risk score** (PRS) for depression has been associated with depressive symptoms in adolescence (Halldorsdottir et al., 2019). Therefore, this measure of genetic vulnerability for depression would seem to be a suitable candidate for studying the potential influence of genes on the association between peer victimization and depressive symptoms. However, to date, there are no studies that have investigated the potential gene x environment interaction between peer victimization and PRS for depression in predicting depressive symptoms.

Lastly, the regulation of genes (epigenetics) has been explored in relation to environmental stressors. A specific type of epigenetic mechanism, DNA methylation, has been studied in the context of peer victimization (Marzi et al., 2018; Mulder et al., 2020), depressive symptoms (Nestler, 2014), and suicidal ideation (Dada, Adanty, et al., 2021). In addition, several studies have looked at the DNA methylation of candidate genes (i.e., serotonin transporter gene) as a moderator of the association between peer victimization and depressive symptoms (Benjet et al., 2010; Sugden et al., 2010). However, the most widely used approaches, including focusing on examining

the entire genome or single genes, contain limitations. Like the polygenic approach, more specific cumulative scores across several genomic regions related to stressors, such as peer victimization, as well as depressive symptoms, and suicidal ideation are likely more suitable. Recently, biological aging research has yielded new measures of epigenetic aging, which not only predicts chronological age but can estimate one's biological age based on an aggregate score of selected sites across the genome. Biological aging, including **epigenetic age**, has been investigated in the context of social stress, including peer victimization (Guarneri-White, Arana, Boyd, & Jensen-Campbell, 2018; Manczak & Gotlib, 2020; Shalev et al., 2013), depressive symptoms (Talarowska, 2020), and suicidal ideation (Dada et al., 2020; Han et al., 2019). However, studies are inconsistent and largely lacking. Additionally, the concept of pace of aging will be tested with the DunedinPACE epigenetic biomarkers in relation to peer victimization, depressive symptoms, and suicidal ideation. **Epigenetic pace of aging** has been associated with several types of victimization (e.g., abuse, neglect, peer victimization) (Bourassa et al., 2021), however it is a novel biomarker thus studies are lacking. Finally, a polygenic index of epigenetic changes linked to the stress response has recently been computed (Provençal et al., 2020); the **Epistress**, which may be a candidate mechanism behind the associations between peer victimization, depressive symptoms, and suicidal ideation.

Using information collected from the Quebec Longitudinal Study of Child Development, a longitudinal population-based sample (Chapters 1, 2, 3) and the 1958 British Birth Cohort (Chapter 3), this thesis will focus on bridging the identified gaps mentioned above to; 1) examine the cross-sectional and longitudinal associations between **cybervictimization** and **suicidal ideation** beyond face-to-face victimization, throughout adolescence; 2) investigate whether **PRS for depression** moderates the association between peer victimization and depressive symptoms in

adolescence; and 3) test **epigenetic clocks, pace of aging** and **Epistress** as potential mediators in the associations between peer victimization, depressive symptoms and suicidal ideation in adolescence and adulthood. The overarching aim of this thesis was to further our current knowledge in identifying individuals at-risk of developing depressive symptoms or suicidal ideation in the context of peer victimization.

BACKGROUND

i. Definitions of bullying & peer victimization

The origin of the word "bully" has been traced back to the 1500s, but it was not until the late 1600s that its meaning evolved to "blusterer", "harasser of the weak" (Harper, 2022; Merriam-Webster, 2022). Bullying was first researched and attributed an academic definition in the 1970s by the late Dan Olweus, a world-renowned Swedish-Norwegian psychologist. Olweus characterized it as; 1) repeated acts of aggression over time, 2) intended to cause harm, and 3) including a power imbalance between the perpetrator and the victim (Olweus, 1993). Some experts have argued that this definition is too strict, as acts of aggression do not always have to be repeated to have damaging consequences on the victim (Monks & Coyne, 2011), and a power imbalance is difficult to assess by the victim and researchers (Finkelhor, Turner, & Hamby, 2012). Interestingly, one study has shown that neither victims, nor perpetrators, nor witnesses, considered the repetition aspect of bullying to be relevant when reporting (Cuadrado-Gordillo, 2012). Furthermore, victims did not take into account the power imbalance aspect of experiencing bullying when reporting its exposure (Cuadrado-Gordillo, 2012). Thus, unless these criteria are explicitly assessed when measuring bullying, it is possible that they will not all be reflected in the victim, perpetrator, or witnesses' reports of bullying. More recently, another term was proposed; peer victimization, which is defined as "harm caused by peers acting outside the norms of appropriate conduct" (Finkelhor et al., 2012). While bullying and peer victimization are often used interchangeably, peer victimization is an umbrella term that includes different types of peer victimization, not limited to bullying.

ii. Types of peer victimization

Historically, research on peer victimization took flight in the 1980s due to increased public and academic interest when 3 boys died by suicide in 1982 in Norway, after being severely bullied (Limber, Breivik, & Smith, 2021; Monks & Coyne, 2011). Early research specifically focused on one type of peer victimization; physical peer victimization (e.g., getting hit, pushed). Then, studies expanded to include other direct types of peer victimization such as verbal victimization (e.g., being insulted or teased) or property damage, as well as a more indirect type; relational peer victimization (e.g., rumor-spreading, social exclusion). When experienced in-person, these types of peer victimization can be referred to as face-to-face peer victimization (also known as traditional peer victimization). However, they can also be experienced through non-traditional means, as the use of electronic devices is widespread.

Over the last decade, research on non-traditional peer victimization has increased exponentially along with the development of technologies; cybervictimization (e.g., insulting texts or comments on social media). Indeed, Steeves (2015) reported that over 65% of Canadian adolescents owned a cell phone or a smart phone which makes the majority of adolescents likely to be exposed to cybervictimization, and rates are likely much higher now in 2022. Additionally, in 2017 it was estimated that 20% of adolescents in Ontario spent five hours or more on social media per day (Boak, Hamilton, Adlaf, Henderson, & Mann, 2018). Although children and adolescents can experience different types of peer victimization, there is a known overlap between them. For example, a meta-analysis of 135 studies over 17 countries reported a strong correlation (average Pearson's *r* coefficient = 0.70) between overt types of peer victimization such as physical or verbal, and relational peer victimization (Casper & Card, 2017). In addition, face-to-face victimization and cybervictimization have a known overlap; with 40-95% of cybervictimized

adolescents also reporting exposure to other types of peer victimization (Cosma et al., 2020; Waasdorp & Bradshaw, 2015). Sumter, Baumgartner, Valkenburg, and Peter (2012) have also shown that all adolescents that were chronically cybervictimized from 12 to 19 years, were also chronically peer victimized in person. Thus, it is important for studies to take this substantial overlap into consideration when studying a specific type of peer victimization.

iii. Prevalence of peer victimization

Prevalence rates of peer victimization vary greatly across studies as they are influenced by age, sex, type of peer victimization measured, and type of informant. The scientific literature reports varying prevalence rates of peer victimization, although there seems to be a general consensus that the prevalence is approximately 10-25%. To illustrate, a worldwide survey of adolescents in 40 countries indicated that 12.6% of 11- to 15-year-olds (middle schoolers) reported being exposed to bullying victimization in the past two months (Craig et al., 2009). However, rates varied considerably between 4.8 and 45.2% (Craig et al., 2009). A more recent review on peer victimization in adolescence reported a varying prevalence between 7% and 75% in 83 countries (Biswas et al., 2020). This international variation can be attributed to differences in defining "bullying" and "peer victimization", variations in methodology, as well as sociocultural factors (Biswas et al., 2020; Craig et al., 2009; Hong & Espelage, 2012). In Quebec (Canada), about 20% of youth are estimated to be victims of face-to-face peer victimization (INSPQ, 2016).

There are documented differences in peer victimization prevalence by age, with younger children experiencing higher peer victimization (Craig et al., 2009). For example, studies in the United Kingdom have reported a higher prevalence of peer victimization in elementary school (19-41%) compared to secondary school (4-24%) (McEachern, Kenny, Blake, & Aluede, 2005). In Canada, peer victimization scores have also been reported to decrease from elementary to

secondary school (Pellegrini & Long, 2002). In their meta-analysis, Craig et al. (2009) studied prevalence by age according to the type of peer victimization in six different countries, but their findings were mixed and a general conclusion on trends cannot be made. For example, in Canada, verbal peer victimization was found to increase from 11 to 15 years, while physical and relational peer victimization rates were unchanged (Craig et al., 2009). However, these trends were not replicated in five other countries: Israel, Italy, Luxembourg, Macedonia, or the United States of America. Some sex differences in traditional peer victimization prevalence rates have been reported. For example, Craig et al. (2009) found that boys report more peer victimization overall in all 40 countries (8.6-45.2%) compared to girls (4.8-35.8%) (Craig et al., 2009). However, in a 2012 report of 38 countries, more bullying in boys was only reported in 15 countries (Currie et al., 2012). Sex differences have also been reported across different types of traditional peer victimization, but are not consistent across countries, thus a general conclusion cannot be drawn (Craig et al., 2009).

A systematic review on cybervictimization has reported a prevalence ranging from 13.99%-57.5.5% across 63 studies (Zhu, Huang, Evans, & Zhang, 2021). The wide range has been attributed to the large rate variation to methodological differences in terms of definitions and measures used (Hamm et al., 2015; Zhu et al., 2021). Of note, it has also been reported that cybervictimization increases throughout adolescence (Patchin & Hinduja, 2011), thus prevalence rates may differ within the period of adolescence. Furthermore, Brochado, Soares, and Fraga (2017) hypothesized that the period of adolescence examined in studies varied from 12-18 years, 10-17 years, 12-15 years, which may have affected estimated rates of prevalence (Brochado et al., 2017). In terms of sex differences, recent reviews have found that girls reported more cybervictimization compared to boys (Brochado et al., 2017; Evangelio, Rodríguez-González,

Fernández-Río, & Gonzalez-Villora, 2022). However, not all individual studies have found sex differences in cybervictimization prevalence.

The variation in rates of peer victimization may also be attributed to the informant. Indeed, different informants have been used to report peer victimization such as parents, peers, teachers, and children themselves. Mother and father reports have been found to be highly correlated, and thus concordant (Shakoor et al., 2011). However, correlations between children, parents, peers, and teachers' reporting of peer victimization are generally moderate (Ladd & Kochenderfer-Ladd, 2002; Shakoor et al., 2011), which indicates some overlap but also a certain degree of divergence. Parent- and self-reports have been found to estimate higher prevalence of peer victimization compared to teacher- and peer-reports (Ladd & Kochenderfer-Ladd, 2002). In early childhood, between 5 and 7 years of age, self-reports and parent-reports have been found to be more reliable than peer-reports or teacher-reports, as the strength of the correlation was stronger between self-reports and parent-reports than any other informants (Ladd & Kochenderfer-Ladd, 2002). This is because teachers and peers are more likely to report peer victimization exposure in children exhibiting aggressive behaviors or social withdrawal which are two characteristics often attributed to victims of peer victimization (Ladd & Kochenderfer-Ladd, 2002). However, this may signify that different informants identify different victims; in which case peers and teachers would mostly identify aggressive and withdrawn victims. Several studies have agreed that rater perspectives are all valid overall, and can capture different subsets of peer victimized youth, with some overlap (Ladd & Kochenderfer-Ladd, 2002; Shakoor et al., 2011; Totura, Green, Karver, & Gesten, 2009). Furthermore, peer victimization rated by different informants is associated with similar mental health outcomes (Ladd & Kochenderfer-Ladd, 2002; Shakoor et al., 2011; Totura et al., 2009), as well as genetic and environmental correlates (Shakoor et al., 2011).

In sum, experiencing peer victimization is not uncommon in childhood and adolescence. Generally, traditional peer victimization is most prevalent in childhood and decreases in adolescence (Craig et al., 2009; McEachern et al., 2005; Pellegrini & Long, 2002), while cybervictimization increases in adolescence (Patchin & Hinduja, 2011). Interestingly, longitudinal studies have identified groups of victims that exhibit different profiles of peer victimization exposure according to severity and recurrence over time (i.e., developmental trajectories). In other words, peer victimization exposure trajectories can be determined in childhood with consistent levels throughout adolescence (low, moderate, or high). For example, youth that were severely peer victimized in childhood are likely to continue being severely victimized in adolescence (Adrian, Miller, McCauley, & Vander Stoep, 2016; Geoffroy et al., 2018a; Pepler, Jiang, Craig, & Connolly, 2008). Research on peer victimization prevalence is constantly evolving, as definitions are being refined and diverse types of peer victimization are being explored. Inconsistent prevalence rates may reflect different study methodologies, as well as differences between generations, ages, samples, and countries. Furthermore, peer victimization prevalence is likely to have been impacted by the covid-19 pandemic, as distance learning and social distancing were implemented in Canada, the UK, and other countries around the world. For example, one study on a Canadian sample reported lower rates of face-to-face peer victimization and cybervictimization during the pandemic (Vaillancourt et al., 2021). However, future studies are needed to determine if this trend will be transient or not.

iv. Depressive symptoms, suicidal ideation, and peer victimization

Around the world, mental health disorders have received more attention as the global burden of disease study from 1990 to 2019 is placing depression amongst the top 3 contributing factors of disability (Ferrari et al., 2022). Moreover, the prevalence of a major depressive episode

among Canadian youth aged 15-24 years in 2012 was 11%, which is the highest depression prevalence of all age groups (Findlay, 2017). Another Canadian study reported that the prevalence of mood disorders, which include depression, increases from early adolescence to young adulthood (Wiens et al., 2020). Furthermore, suicide is the leading cause of death in this age group (Findlay, 2017). Nock et al. (2013) has reported a 12% prevalence of serious suicidal ideation in the US National Comorbidity survey. More recently, Orri, Scardera, et al. (2020) estimated prevalence rates of serious suicidal ideation at 13, 15, and 17 years in Canadian adolescents, 3.3%, 3.9%, 5.8%, respectively. Both depressive symptoms and suicidal ideation are more prevalent in females than males (Eid, Gobinath, & Galea, 2019; Ivey-Stephenson et al., 2020; Orri, Scardera, et al., 2020), and depression in adolescence is associated with poorer functioning in adulthood (Mullen, 2018). It is therefore of the outmost importance to study known risk factors for depression and suicidal ideation in childhood and adolescence, such as peer victimization.

Since the beginning of peer victimization research, a plethora of negative outcomes have been investigated; from socioeconomic factors (e.g., quality of life), to health habits (e.g., smoking) (McDougall & Vaillancourt, 2015), to physical health (e.g., nausea, sleep disturbances, obesity, inflammation) (Arseneault, 2018; Hager & Leadbeater, 2016), to biological markers (e.g., cortisol dysregulation) (Schacter, 2021), and mental health symptoms (e.g., depressive symptoms, suicidal ideation, psychiatric hospitalizations) (Arseneault, 2018). It is very important to note that the association between peer victimization, depressive symptoms, and suicidal ideation may be confounded by certain individual and familial factors (e.g., low socioeconomic status, family dysfunction, internalizing and externalizing symptoms (Bowes, Joinson, Wolke, & Lewis, 2015b; Geoffroy et al., 2018a; Martin-Storey et al., 2018; Oncioiu et al., 2021). This evidence signifies that these factors may lead to inflated effect sizes in these associations. It is therefore very

important to control for these factors occurring prior to peer victimization. This thesis will identify several gaps of knowledge which are introduced and discussed below.

v. Cybervictimization, depressive symptoms, and suicidal ideation

Much research has solidified evidence that peer victimization is associated to depressive symptoms, suicidal ideation, and suicide attempts longitudinally in adolescence (Geoffroy et al., 2018a; Geoffroy et al., 2016; McDougall & Vaillancourt, 2015) and in adulthood (Geoffroy, Arseneault, Girard, Ouellet-Morin, & Power, 2022; McDougall & Vaillancourt, 2015). These associations have included broad measures of peer victimization that encompassed different types, sometimes including cybervictimization. More recently, cybervictimization has also been linked to depressive symptoms (Tran et al., 2021), and suicidal ideation (Bonanno & Hymel, 2013; Van Geel, Vedder, & Tanilon, 2014) in adolescence. There has been an ongoing debate over whether cybervictimization may be linked to differential outcomes compared to face-to-face victimization, as it includes unique characteristics. Indeed, cybervictimization distinguishes itself from face-to-face victimization in several ways; 1) it can happen through electronic devices; 2) victims can be targeted anytime and anywhere; 3) it can be witnessed by a large audience; and 4) perpetrators may remain anonymous (Cosma et al., 2020; Waasdorp & Bradshaw, 2015). Furthermore, a meta-analysis by Van Geel et al. (2014), found that cybervictimization only was linked to a higher risk of reporting suicidal ideation compared to face-to-face victimization only. However, this was based on 3 studies only, which further indicates the need for more studies on the association between cybervictimization and suicidal ideation, beyond face-to-face victimization. Indeed, only few studies have looked at the unique associations of cybervictimization and face-to-face victimization with depressive symptoms and suicidal ideation (Tran et al., 2021; Van Geel et al., 2014). Since there is a significant overlap between cybervictimization and face-to-face peer

victimization as previously discussed, it is important to take into account face-to-face victimization and cybervictimization when studying the independent associations.

Of note a recent systematic review and meta-analysis including 17 cross-sectional and longitudinal studies reported 2.7 odds of reporting depressive symptoms in cybervictimized youth, compared to non-cybervictimized youth (Tran et al., 2021). Most, but not all the studies included, controlled for face-to-face victimization. Furthermore, other individual longitudinal studies have confirmed that cybervictimization was longitudinally linked to depressive symptoms 6 months to 3 years later in adolescence (Cole et al., 2016; Gámez-Guadix, Orue, Smith, & Calvete, 2013; Rose & Tynes, 2015). Indeed, an increasing number of studies have gathered evidence on the cross-sectional and longitudinal associations between cybervictimization and depressive symptoms. However, less is known about the cross-sectional and longitudinal associations between cybervictimization and suicidal ideation in adolescence, over and above the influence of other types of victimization. A meta-analysis by John et al. (2018b) included a sensitivity analysis with 6 cross-sectional studies that accounted for face-to-face victimization and found that cybervictims had 2.43 odds of reporting suicidal ideation. This meta-analysis concludes that longitudinal studies are needed in order to better control for prior confounders and investigate the directionality of association between cybervictimization and suicidal ideation.

Emphasizing our efforts to further understand this association is important because it may guide future research on whether to include this specific type (i.e., cybervictimization) in general peer victimization measures when studying its link to depressive symptoms as well as suicidal ideation, in the long term. Lastly, understanding cybervictimization is of particular importance on a societal level as media have reported on suicides being directly or vaguely linked to cyberbullying; “cyber-bullicide” (Umesh, Ali, Farzana, Bindal, & Aminath, 2018).

vi. Biological systems involved in peer victimization, depression, and suicidal ideation

Using techniques in genetics and endocrinology, neuroscience research has helped to identify several biological systems associated to peer victimization, depression, and suicidal ideation. Although these studies largely focus on each of these individually, there is evidence that similar systems are involved. Firstly, the neuroendocrinological system involved in the stress response, the Hypothalamic-Pituitary-Adrenal axis (HPA axis) has been linked to peer victimization (Kliewer, Sosnowski, Noh, McGuire, & Wright, 2019; Isabelle Ouellet-Morin et al., 2011; Isabelle; Ouellet-Morin et al., 2011; Ouellet-Morin et al., 2013; Ouellet-Morin et al., 2021; Vaillancourt et al., 2008), depression (Pariante & Lightman, 2008; Wasserman, Wasserman, & Sokolowski, 2010), as well as suicidal ideation (Berardelli et al., 2020; Melhem et al., 2017; O'Connor, Green, Ferguson, O'Carroll, & O'Connor, 2017; Rizk et al., 2018; Wasserman et al., 2010). Studies in humans mainly rely on measuring biological markers of the HPA axis in peripheral tissues, such as cortisol measurements in saliva or hair. The HPA axis can also be studied by focusing on genes known to be involved in the stress response, specifically the corticotrophin releasing hormone receptor 1 (CRHR1) and the serotonin transporter gene (5-HTT). Secondly, the immune system has also been linked, specifically using inflammatory markers, to peer victimization (Schacter, 2021), depression (Eyre & Baune, 2012), as well as suicidal ideation (Serafini et al., 2013). Lastly, accelerated cellular aging, also more generally called biological aging, has been studied using measures of telomere length and these studies have shown associations with depression (Darrow et al., 2016; Verhoeven, Revesz, Wolkowitz, & Penninx, 2014). However, its association with peer victimization and suicidal ideation is less clear. Some evidence has linked telomere length to psychosocial stress, including peer victimization (Bürgin et al., 2019; Guarneri-White et al., 2018; Manczak & Gotlib, 2020) and suicide (H. Kim, Cho, Yoo, Kim, & Ahn, 2019). Overall, few studies have tested these biological markers as potential

moderators or mediators in the associations between peer victimization, depression, and suicidal ideation. This thesis aimed to capture the complexity of various biological systems, by not including one single biological marker or gene, but an array of markers and genes, in order to better understand how they might influence (moderate) or partially explain (mediate) the association between peer victimization, depression, and suicidal ideation.

vii. Gene x environment interactions

As described above, it is well-established that peer victimization is associated with depressive symptoms in adolescence and adulthood. However, we have yet to fully understand why some individuals will develop these symptoms after being peer victimized, while others will not. Depression has one of the largest heritability rates of psychiatric diseases; around 30 to 50%, which is considered moderate (Kendall et al., 2021b). Therefore, it is reasonable to assume that genetic factors may play a role in the association between peer victimization and depression through a gene x environment interaction (GxE). However, few studies have looked at the moderating role of genetic vulnerability to developing depression in the context of peer victimization.

One candidate gene study on GxE found that girls that had been peer victimized and had the short/short allele combination of a polymorphism in the promoter region of 5-HTT, were more at-risk of developing depressive symptoms (Benjet et al., 2010). However, similarly to other candidate gene studies, this finding was not replicated. Aside from the lack of studies, there are limitations to the candidate gene approach. Generally in psychiatry, there have been a lack of replication of GxE candidate studies as reported by Duncan (2013). In addition, given the fact that it has become clear that depression is largely polygenic (N. Wray et al., 2012), a candidate gene approach can be shortsighted.

In order to conduct more exploratory research, some studies adopted a genome-wide approach and have managed to achieve a number of participants high enough to be able to detect significant polymorphisms associated to the depression phenotype (Cai et al., 2015; Howard et al., 2019; N. Wray et al., 2012). Since then, a novel measure of genetic vulnerability for depression has been developed; polygenic risk scores (PRSs). PRSs can be calculated by including specific genetic variants called single nucleotide polymorphisms (SNPs) which have been linked to a phenotype, such as depression, in genome-wide associations studies (GWAS). These identified SNPs are then attributed a weight according to their effect size in association to a given phenotype. PRS for depression has been used in a variety of studies; from predicting antidepressant response (Ward et al., 2018), to predicting severity and rate change of depressive symptoms (Kwong et al., 2021), as well as suicidal ideation (Colbert et al., 2022; Martínez-Levy et al., 2021; Martinez-Levy et al., 2021; Shen et al., 2020).

Although it is well-known that peer victimization is associated with depression and suicidal ideation in adolescence and adulthood (Bowes et al., 2015b; Geoffroy et al., 2018a; Geoffroy et al., 2016; McDougall & Vaillancourt, 2015; Ouellet-Morin et al., 2021; Takizawa, Maughan, & Arseneault, 2014), peer victimization does not invariably lead to these outcomes. The association could be partly explained by a certain genetic make-up which would make an individual more vulnerable to developing depression after peer victimization exposure. For example, some studies have tested the interaction between PRS for Major Depressive Disorder (PRS-MDD) and maltreatment in predicting depression in adult (Peyrot et al., 2018; Shao et al., 2021) and adolescent samples (Halldorsdottir et al., 2019). Overall, the results pointed towards a lack of a moderating effect (Halldorsdottir et al., 2019; Peyrot et al., 2018; Shao et al., 2021). However, some studies found evidence of an interaction indicating that trauma and higher PRS-MDD

predicted a higher risk of MDD in adulthood (Fang, Scott, Song, Burmeister, & Sen, 2020; Peyrot et al., 2014). Interestingly, Fang et al. (2020) also found a moderate gene-environment correlation (*r*GE) between PRS-MDD and trauma, which means that having a genetic vulnerability to depression is linked to a higher chance of reporting childhood trauma. In other words, a *r*GE may reflect a link between the genome and environmental exposures. Thus, when we are studying whether genes may influence the association between an environmental exposure and a phenotype such as depression, it is important to consider the possibility that the genes can also be linked with the environmental exposure itself. To date, no study has explored the potential moderating role of a PRS for depression and peer victimization in predicting depression. However, an association has previously been reported between PRS-MDD and self-reported peer victimization which points to a *r*GE, meaning that having a genetic vulnerability to depression may increase children's risk of experiencing peer victimization (Schoeler et al., 2019). PRSs take into account the polygenicity of depression and is one possible proxy for genetic vulnerability to depression. Studying PRS for depression as a moderator could help us understand how genetic vulnerability could play a role in the association between peer victimization and depressive symptoms and possibly suicidal ideation.

viii. Epigenetic mediation

Epigenetics refers to non-genetic factors that can regulate gene expression, such as DNA methylation. DNA methylation is the addition of a methyl group to a cytosine nucleotide, usually one that is paired with guanine (CpG), in DNA, thereby modifying gene expression. The presence of DNA methylation induces chromatin condensation which can prevent gene expression when it is present in gene promoter regions. Early research on DNA methylation adopted a candidate gene approach, whereby studies would measure methylation within specific genes of interest. DNA

methylation of candidate genes such as 5-HTT or glucocorticoid receptor gene (NR3C1) have been investigated in relation to peer victimization. Notably, one study based on 28 monozygotic twin pairs found increased methylation of 5-HTT in bullied twins (Ouellet-Morin et al., 2013) compared to non-bullied twins. Another study by Efstathopoulos et al. (2018) including 1149 participants found increased methylation in the NR3C1 in bullied adolescents. However, these findings have not been replicated in a larger study of 2232 twins (Marzi et al., 2018). An epigenome-wide study was performed Marzi et al. (2018) in order to take an exploratory approach, beyond candidate genes. Epigenome-wide approaches detect differentially methylated sites across the entire epigenome associated to a given phenotype, such as peer victimization. However, this study did not find differentially methylated sites in victimized children or adolescents (Marzi et al., 2018). A more recent study investigated changes of DNA methylation between two timepoints; 6 and 10 years in one cohort and 7.5 and 17 years in another cohort (Mulder et al., 2020). Small changes were noted on an epigenome-wide level at one CpG site. However, no marked evidence of an association between bullying and DNA methylation were noted (Mulder et al., 2020).

DNA methylation studies have pointed towards DNA methylation as a potential mediator of the association between childhood adverse experiences and depression. In particular, one study reported a partial mediation of DNA methylation by 37 CpG sites in the association between childhood adversity (0-7 years) and depression at 10-11 years (Smith et al., 2021). However, evidence on epigenome-wide associations with peer victimization in cohort studies currently points towards non-significant findings (Marzi et al., 2018; Mulder et al., 2020). As with GWAS, it is possible that having an epigenome-wide approach does not provide enough power to detect small changes in DNA methylation in relation to peer victimization. Peer victimization has been associated with other types of biological mechanisms, such as biological aging. Notably,

cumulative violence exposure, including peer victimization, was associated with accelerated telomere erosion (Shalev et al., 2013). Two other studies associated shorter telomere length with relational victimization (Guarneri-White et al., 2018; Manczak & Gotlib, 2020).

Another more recent marker of biological aging are epigenetic clocks. Epigenetic clocks are aggregate scores of CpG sites that are time dependent. Studies using epigenetic clocks estimate accelerated and decelerated aging when comparing epigenetic age to chronological age. Accelerated aging has been linked to adversity including exposure to threat in children and adolescents (Sumner, Colich, Uddin, Armstrong, & McLaughlin, 2019), prenatal anxiety (McGill et al., 2022), and childhood trauma (Palma-Gudiel, Fañanás, Horvath, & Zannas, 2020). However, no study has looked at epigenetic clocks and peer victimization specifically. Epigenetic clocks are plausible mediators in the association between peer victimization and depression. Firstly, research on other measures of childhood adversity, such as childhood trauma, has found an association with epigenetic aging (Palma-Gudiel et al., 2020). Secondly, epigenetic aging has been linked to depression (Tollenaar et al., 2021) and internalizing disorders in children (Dammering et al., 2021). In terms of suicidal ideation, one study found that DNA methylation of 1 CpG site mediated the association between perceived stress and suicidal behaviors in patients with schizophrenia (Dada, Adanty, et al., 2021). However, there is currently only one study that looked at epigenetic aging, which found a lack of association between epigenetic clocks and suicidal ideation in patients with schizophrenia (Dada et al., 2020). Overall, there is a gap in the literature on epigenetic aging as a potential mediator in the link between peer victimization and depression.

A promising novel biomarker as emerged in the last few years which introduces the idea of the pace aging, the Dunedin epigenetic pace of aging. Namely, the DunedinPACE and its predecessor, the DunedinPoAm (Belsky et al., 2020; Belsky et al., 2022). While epigenetic clocks

tell us what time it is, pace of aging can tell us how fast the clock is ticking. Emerging research is showing preliminary evidence that this concept may be more likely to relate to psychosocial factors and mental health symptoms compared to epigenetic clocks (Belsky et al., 2022). The Dunedin epigenetic pace of aging has been linked to polyvictimization (e.g., peer victimization, abuse and neglect) (Bourassa et al., 2021), however it has never been tested in association with peer victimization, or suicidal ideation. One prior study has linked the Dunedin pace of aging with concurrent depression in older adults aged above 50 years (McCrory et al., 2022).

One more potential candidate as a mediator is a recently-developed epigenetic score that has been created to reflect the glucocorticoid stress response; the epistress score (Provençal et al., 2020). Epistress score is a proxy for the HPA axis' reactivity to stress and has been linked to perinatal depressive symptoms (Provençal et al., 2020). Possible mechanisms behind peer victimization and depressive symptoms likely involve the stress response network and differential reactivity of the stress response through epigenetics; epigenetic clocks and epistress.

ix. Thesis aims

Aim 1: Determine independent associations of face-to-face and cybervictimization with suicidal ideation and suicide attempt cross-sectionally and throughout adolescence. This project will aid in estimating unique suicidal risk associated to cybervictimization and better inform prevention and intervention strategies.

Aim 2: Investigate whether PRS-depression moderates the association between peer victimization, depressive symptoms, and suicidal ideation in adolescence. This project will enable us to further understand whether genetic vulnerability to depression can heighten the risk to develop depressive symptoms after being peer victimized.

Aim 3: Examine whether epigenetic indices of biological aging, pace of aging, and the glucocorticoid stress response are associated with peer victimization, depressive symptoms, and suicidal ideation, as well as to determine their potential role as mediators of the associations between peer victimization, depressive symptoms, and suicidal ideation. This will allow us to determine whether epigenetic indices reflecting certain biological systems previously linked to these variables of interest can partially explain the association between peer victimization, depressive symptoms, and suicidal ideation in adolescence and adulthood.

CHAPTER 1: CYBERVICTIMIZATION IN ADOLESCENCE AND ITS ASSOCIATION WITH SUBSEQUENT SUICIDAL IDEATION/ATTEMPT BEYOND FACE-TO-FACE VICTIMIZATION: A LONGITUDINAL POPULATION-BASED STUDY

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1.1. Title Page

Cybervictimization in adolescence and its association with subsequent suicidal ideation/attempt beyond face-to-face victimization: a longitudinal population-based study

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1.2. Abstract

Background: Cross-sectional associations have been documented between cybervictimization and suicidal risk, however prospective associations remain unclear.

Methods: Participants were members of the Quebec Longitudinal Study of Child Development (QLSCD), a prospective birth cohort of 2,120 individuals followed from birth (1997/98) to age 17 years (2014/15)**.** Cybervictimization and face-to-face victimization experienced since the beginning of the school year, as well as serious suicidal ideation and/or suicide attempt were self-reported at ages 13, 15, and 17 years.

Results: In cross-sectional analyses at 13, 15 and 17 years, adolescents cybervictimized at least once had respectively 2.3 (95% CI=1.64-3.19), 4.2 (95% CI=3.27-5.41) and 3.5 (95% CI=2.57-4.66) higher odds of suicidal ideation/attempt after adjusting for confounders including face-to-face victimization, prior mental health symptoms, and family hardship. Sensitivity analyses suggested that cybervictimization only and both cyber- and face-to-face victimization were associated to a higher risk of suicidal ideation/attempt compared to face-to-face victimization only and no victimization; however, analyses were based on small n. In prospective analyses, cybervictimization was not associated with suicidal ideation/attempt 2 years later after accounting for baseline suicidal ideation/attempt and other confounders. In contrast, face-to-face victimization was associated with suicidal ideation/attempt 2 years later in the fully adjusted model, including cybervictimization.

Conclusions: The cross-sectional association between cybervictimization and suicidal ideation/attempt is independent from face-to-face victimization. The absence of a prospective association suggested short-term effects of cybervictimization on suicidal ideation/attempt.

Keywords: adolescence, longitudinal cohort, suicidal ideation, suicide attempt, QLSCD

1.3. Introduction

Peer victimization, including bullying, is a modifiable risk factor for suicidal ideation and attempt across the life-span(Klomek, Sourander, & Elonheimo, 2015b). To date, much of the research has focused on face-to-face victimization (i.e. intentional harm caused verbally, physically, and emotionally), however little is known about the role of a novel form of victimization, cybervictimization, on suicidal risk(Van Geel et al., 2014).

Cybervictimization is expressed through electronic forms of communication such as emails, texts, or social media. Common examples of cybervictimization include posting compromising material such as insulting comments, spreading rumours on social media, or harassing someone through instant messaging. Although there are overlaps between face-to-face and cybervictimization, the latter has unique features including 1) the absence of time and space boundaries leads to victims being targeted anytime anywhere, 2) a large audience witnessing victimization through live or shared content and (3) the perpetrator's anonymity making cybervictimization difficult to stop(Pingault & Schoeler, 2017). Thus far, research with varying age groups showed that 4-36% of girls, and 2-28% of boys reported having been cybervictimized in the last year(Brochado et al., 2017). Despite variation in estimates, the occurrence of at least one experience of cybervictimization is not uncommon.

Cybervictimization has attracted considerable attention with several mediatized high-profile cases of adolescent suicides reportedly linked to cybervictimization(Wolke, 2017). Cross-sectional studies indicated that adolescents who have been cybervictimized were more likely to report concurrent suicidal ideation(Bauman, Toomey, & Walker, 2013; Bonanno & Hymel, 2013; Elgar et al., 2014; Hay & Meldrum, 2010; Hinduja & Patchin, 2010; Hirschtritt, Ordóñez, Rico, & LeWinn, 2015; Kodish et al., 2016; Messias, Kindrick, & Castro, 2014; Sampasa-Kanyinga, Roumeliotis, & Xu, 2014; Schneider, O'donnell, Stueve, & Coulter, 2012), or to

attempt suicide(Elgar et al., 2014; Messias et al., 2014; Sampasa-Kanyinga et al., 2014; Schneider et al., 2012), even after controlling for other types of victimization. Additionally, two studies have reported stronger cross-sectional associations with suicide ideation for both cybervictimization and face-to-face victimization combined compared to cybervictimization only or face-to-face victimization only (Messias et al., 2014; Schneider et al., 2012). However, very few prospective studies have examined whether cybervictimization carried a suicidal risk in the longer term and the findings are unclear(Bannink, Broeren, van de Looij–Jansen, de Waart, & Raat, 2014; Wright, 2016). To the best of our knowledge, no study examined whether cybervictimization assessed throughout adolescence from 13 to 17 years is associated with suicidal ideation/attempt, both cross-sectionally and prospectively. This is important because this period is marked by increased suicidal ideation and attempt(Cha et al., 2017).

In the present study, we aimed to 1) describe the prevalence of cybervictimization from early to late adolescence in a representative population-based sample, 2) test whether cybervictimization was associated with suicidal ideation/attempt beyond face-to-face victimization and key confounders (e.g., pre-existing mental health and family problems) both cross-sectionally and prospectively.

1.4. Methods

1.4.1. Participants

Participants were members of the Quebec Longitudinal Study of Child Development (QLSCD), a representative population study of 2,120 individuals born in the Canadian province of Quebec in 1997/98 who were followed-up from birth to age 17 years. Further details about the cohort can be found online(https://jesuisjeserai.stat.gouv.qc.ca). The sample size available for cross-sectional and prospective analyses ranged from 1228-1426 and 1160-1192 participants, respectively, with measures of peer victimization and suicidal ideation/attempt, and representing

55-67% of the original cohort. We applied inverse probability weighting to account for potential selection bias that could arise from sample attrition. Weights were derived from a logistic regression model for the binary outcome of being included in the adolescent data collection at 13-17 years (versus missing at any time point) from the following predictors: sex, maternal depression at age 5 months, internalizing and externalizing behaviour at age 6 years. As shown in **Table S1.1**, our samples at 13, 15, and 17 years did not differ in terms of key characteristics.

The Ethics Committee of the Institut de la Statistique du Québec and the Research Ethics Board of the CHU Sainte-Justine Research Center approved each phase of the study, and informed consent was obtained.

1.4.2. Measures

Exposure to victimization was assessed at ages 12, 13, 15, and 17 years using a modified version of the Self-Report Victimization Scale (Cronbach's α=.88 to .91) (Ladd & Kochenderfer-Ladd, 2002) administered in the second half of the school year (February to June). Adolescents were asked about the frequencies ("never", "rarely", "sometimes" "often", "very often") since the beginning of the school year of 6 different victimization experiences (e.g. "a child at school pushed, hit or kicked you?") and a cybervictimization experience ("how many times were you the victim of cyberbullying (insults, threats, intimidation) on the internet or by cell phone"; "never", "once", "few times", "often", "very often"; see **Appendix)**.

In accordance with our previous work(Geoffroy et al., 2016), adolescents were considered victims of face-to-face victimization if they answered 'often' or 'very often' to at least 1 of 6 items reflecting face-to-face victimization. Since the prevalence of cybervictimization was low in the sample, adolescents who were "never" cybervictimized were distinguished from those cybervictimized either "once", "a few times", "often" or "very often". A similar approach of

coding cybervictimization has been used in other studies(Bannink et al., 2014; Elgar et al., 2014). Cybervictims additionally reported whether cyberbullying originated from "students attending their school", "students not attending their school", "unknown identity" or "other".

We measured suicidal ideation/suicide attempt in terms of having serious thoughts of wanting to die (as indicated by an affirmative answer to the question, "Did you ever seriously think of attempting suicide?"; "yes", "no") or making a suicide attempt (and if so, "How many attempts", "never", "once", "more than once") in the past 12 months. We combined suicidal ideation and suicide attempt given their respectively low prevalence as mutually exclusive groups (2.1-4.3% for suicidal ideation, 2.4-2.8% for suicidal attempt between 13 and 17 years).

As in our past publications(Geoffroy et al., 2018b; Geoffroy et al., 2016), we controlled for prior mental health and family hardship characteristics associated with victimization and suicidal ideation/attempt. *Depressive symptoms* in the past 2-weeks were self-reported using the Children Depression Inventory (CDI, short-form)(Allgaier et al., 2012) rated on a 3-point scale at age 10 and 12 years. Other mental health symptoms were assessed with the Behaviour Questionnaire (BQ), a validated scale used in the Canadian National Longitudinal Study of Children and Youth(*Statistics Canada and Human Resources Development Canada. National Longitudinal Survey of Children and Youth: Overview of Survey Instruments for 1994-1995 Data Collection Cycle 1*, 1995), which incorporates items from the Child Behaviour Checklist(Achenbach, Edelbrock, & Howell, 1987), the Ontario Child Health Study Scales(Offord, Boyle, & Racine, 1989), and the Preschool Behaviour Questionnaire(Tremblay, Desmarais-Gervais, Gagnon, & Charlebois, 1987). *Oppositional/defiance* was assessed with 4 items (α=.92 and .91) (e.g., "defiant/refused to comply") and *inattention/hyperactivity* with 9 items (α=.95 and .94) (e.g., "could not sit still") through teacher ratings at 6-12 years, and

anxiety symptoms with 3 items (α=.72 and .83) (e.g., "fearful/nervous") at 10 and 12 years through self-reports. All items were rated on a 3-point scale (0="never or not true"; 1="sometimes or somewhat true"; 2="often or very true"). *Family socioeconomic status* was measured as an aggregate of annual gross income, parental education level, and occupational prestige(Willms & Shields, 1996) at 6-12 years; *family functioning* (α=.84) (i.e. communication, problem resolution, and control of disruptive behaviour) was assessed with the McMaster Family Assessment(*Statistics Canada and Human Resources Development Canada. National Longitudinal Survey of Children and Youth: Overview of Survey Instruments for 1994-1995 Data Collection Cycle 1*, 1995) at 6-12 years; *family structure* (biological parents/blended/single) was reported at 12 years; and *hostile-reactive parenting* (α=.59) (e.g., corporal punishment, raising voice) was assessed with 4 items(Boivin et al., 2005) at 6-12 years.

1.4.3. Statistical analyses

We estimated cross-sectional associations between cybervictimization and suicidal ideation/attempt at ages 13, 15 and 17 years using logistic regressions. Model 1 adjusted for sex, Model 2 additionally adjusted for prior mental health symptoms (6-12 years) (depression, anxiety, oppositional/defiance and inattention/hyperactivity symptoms) and family hardship (socioeconomic status, family functioning and structure, hostile-reactive parenting), and Model 3 additionally adjusted for concurrent face-to-face victimization. The same analyses were conducted using face-to-face victimization as the exposure in order to compare the relative effects of both forms of victimization on suicidal ideation/attempt. Second, we estimated prospective associations between cybervictimization and suicidal ideation/attempt using logistic regressions with cybervictimization at either 13 or 15 years as the exposure and subsequent suicidal ideation/attempt 2 years later at 15 or 17 years as the outcome. In the prospective

analyses, Model 1 accounted for sex, Model 2 and 3 for mental health and family confounders, and face-to-face victimization, respectively, and Model 4 for baseline suicidal ideation/attempt (e.g. suicidal ideation/attempt at age 13 years for prospective association between cybervictimization at 13 years and suicidal ideation/attempt at 15 years). The prospective analyses were also conducted using face-to-face victimization as the exposure. We additionally tested statistical interactions between sex and cybervictimization in the cross-sectional and prospective logistic regressions. No significant sex-by-cybervictimization interaction was found (*Ps*>.05 across cross-sectional and prospective analyses), therefore our analyses combined both sexes.

In sensitivity analysis, we estimated both cross-sectional and prospective models using cybervictimization frequency entered as a continuous variable (scale ranging from 0 to 4), rather than binary (yes/no), to test dose-response associations. The results of this analysis in our cross-sectional and prospective models are reported as a p-value for trend. Lastly, we created a categorical variable with the following exclusive categories: face-to-face victimization only, cybervictimization only, cyber- and face-to-face victimization, and no victimization to estimate the single and combined role of the two different forms of victimization on suicidal ideation/attempt.

Missing data on confounding variables (<11% for all variables) were imputed using multiple imputation by chained equation(Azur, Stuart, Frangakis, & Leaf, 2011), thus all models were estimated across 50 imputed datasets and the results were pooled.

1.5. Results

1.5.1. Prevalence of cybervictimization and suicidal ideation/attempt

Most adolescents who reported being cybervictimized were victimized "once" (4.1-10.4%), and less than 1% were cybervictimized "often or very often" since the beginning of the school year (**Table 1.1**). Overall, 45.9%-53.1% of adolescents who were cybervictimized at least once (7.3%-15.9% of the entire sample) were also exposed to face-to-face victimization. Most adolescents reported being cybervictimized by students attending the same school (56.8-71.6%) or another school (19.7-25.5%), while 14.8-24.0% reported they never knew who cybervictimized them; **Table 1.1**. Cybervictimization was more common in girls than boys, except at 12 years (**Table 1.2**).

1.5.2. Cross-sectional associations between cybervictimization and suicidal ideation/attempt

Overall, prevalence of suicidal ideation/attempt increased from 3.4% (n=42), 3.5% (n=42), 5.8% (n=62) for those never cybervictimized at 13, 15 and 17 years, respectively, to 13.3% (n=14), 19.3% (n=44), 25.5% (n=22) for those exposed to cybervictimization in given school year. Cybervictimization, experienced at least once, was associated with suicidal ideation/attempt after adjustment for prior mental health symptoms and family hardship (Model 2, **Table 1.3**). The associations remained significant when face-to-face victimization was added to the model at 13 years (Model 3, Table 1.3; OR=2.29, 95% CI=1.64-3.19; *p*-trend for frequency of cybervictimization entered continuously<.001), 15 years (OR=4.20, 3.27-5.41; *p*-trend<.001), and 17 years, (OR=3.46, 2.57-4.66; *p*-trend<.001). In these same models, face-to-face victimization was also associated with suicidal ideation/attempt after adjustment for prior mental health symptoms, family hardship, and cybervictimization (OR=2.61, 1.92-3.56, at 13 years; OR=2.16, 1.67-2.81, at 15 years; OR=2.09; 1.54-2.84, at 17 years). However, at both 15 and 17

years the odds were significantly smaller for face-to-face victimization compared to cybervictimization p<.001 and p<.01, respectively).

Suicidal ideation/attempt prevalence by victimization exposure category was; 2.7% (n=24), 2.7% (n=28), and 4.6% (n=44) for no victimization at 13, 15, and 17 years; 9.9% (n=18), 10.7% (n=14), 12.6% (n=14) for face-to-face victimization only at 13, 15, and 17 years; 22.7%(n=22) and 40.6% (n=13) for cybervictimization only at 15 and 17 years; and 26.1% (n=12), 27.1% (n=22), 25.7% (n=9) for cybervictimization and face-to-face victimization combined at 13, 15, and 17 years. Figure 1 shows odds ratio (ORs) and 95% CIs at 15 and 17 years for face-to-face victimization only, cybervictimization only, cyber- and face-to-face victimization versus no victimization. We found that adolescents exposed to either cyber- and face-to-face victimization only or to both forms of victimization had higher risk of suicidal ideation/attempts than non-victim at both ages. Further comparisons showed that odds of suicidal ideation/attempt was higher for adolescents exposed to cybervictimization only (OR=2.00, 95% CI=1.37-2.90, and OR=2.02, 95% CI=1.31-3.10) and cyber- and face-to-face victimization combined (OR=1.68, 1.16, 2.43, and OR=1.74, 95% CI=1.11-2.71) than those exposed to face-to-face victimization only at 15 and 17 years respectively.

1.5.3. Prospective associations between cybervictimization and suicidal ideation/attempt

Cybervictimization at 13 and 15 years was prospectively associated with suicidal ideation/attempt 2 years later at 15 and 17 years (Table 1.4) after controlling for mental health symptoms, family hardship, and face-to-face victimization (Model 3, Table 1.4) (respectively, OR=1.79, 1.30-2.44; p-trend for frequency of cybervictimization entered continuously<.001, and OR=1.34, 1.01-1.78; p-trend=.12). However, these associations were no longer significant after baseline suicidal ideation/attempt was accounted for (Model 4, Table 1.4; Ps >.05). In contrast,

face-to-face victimization at age 13 and 15 years was associated to suicidal ideation/attempt 2 years later (OR=2.45, 1.82-3.29; OR=2.06, 1.56-2.72, respectively) even after accounting for childhood confounders and baseline cybervictimization and suicidal ideation/attempt (Model 4, Table 1.4).We re-estimated all models without inverse probability weighting; patterns of results were similar to ones based on multiple imputation alone (see **TableS1.2 and TableS1.3**).

1.6. Discussion

To our knowledge, this is the first population-based study examining the cross-sectional and prospective associations between cybervictimization and serious suicidal ideation/attempt across adolescence in the context of other forms of victimization and key confounders. We found that cybervictimization mostly occurred "once" in a given year and often co-occurred with face-to-face victimization. Additionally, we found that over and beyond co-occurring exposure to face-to-face victimization, being cybervictimized increased the risk of suicidal ideation/attempt cross-sectionally, but not prospectively. Suicidal ideation/attempt risk was higher among adolescents who were exposed to cybervictimization only, and cyber- and face-to-face victimization combined compared to adolescents who were exposed to no victimization or face-to-face victimization only.

In our sample, 6.9-15.9% of adolescents aged 12 to 17 years reported being cybervictimized at least once during the given school year. While some studies have reported highly heterogeneous cybervictimization prevalence rates, others reported prevalence estimates in adolescents consistent with the present study(Bannink et al., 2014; Bauman et al., 2013; Bonanno & Hymel, 2013; Kodish et al., 2016). As previously reported, the prevalence of cybervictimization tends to increase from 12 to 15 years(Messias et al., 2014; Schneider et al., 2012), which differs from face-to-face victimization which has been found to decrease(Geoffroy

et al., 2018b). Furthermore, the decreasing prevalence of cybervictimization after 15 years might reflect that later in adolescence youth might have learned more advanced perspective-taking skills and understand the effects of their aggressive acts on the internet. As reported previously, girls were more likely to be exposed to cybervictimization than boys(Messias et al., 2014; Sampasa-Kanyinga et al., 2014), which is opposite to what is observed for face-to-face victimization(Arseneault, 2018). This could be partly explained by some evidence showing that girls tend to use more indirect ways of aggression, through social media, for example (Waasdorp & Bradshaw, 2015) . We found that most victims can identify the perpetrators as students from the same school or other known peers (76.6%-91.8% between ages 12 and 17 years). The highest proportion of anonymous perpetrators was 24% at 12 years and decreased to 18% at 17 years. This is similar to a study showing that most students knew their perpetrator's identity(Waasdorp & Bradshaw, 2015), and another showing that 12.6% of cybervictimized high school students did not know the identity of their perpetrators(Ybarra, Diener-West, & Leaf, 2007). Although the range of reported perpetrator's anonymity seems to vary with age, this remains a unique feature of cybervictimization with perceived anonymity leading to more potential perpetration(Ybarra et al., 2007).

Our study documents a strong association between cybervictimization and cross-sectional suicidal ideation/attempt beyond face-to-face victimization while accounting for important confounders. Adjusted odds ratios indicated that cybervictimized adolescents had 2.29- to 4.20-folds higher odds to report suicidal ideation/attempt compared to non-victimized adolescents. This finding is in line with a recent meta-analysis of cross-sectional studies reporting odds ratios of 2.15 for suicidal ideation and 2.57 for suicidal attempt(John et al., 2018a). However, the

associations with suicidal attempt reported in the meta-analysis did not control for face-to-face victimization and other confounders.

Our analyses suggest a unique concurrent effect of cybervictimization regardless of whether it is experience alone or in combination with face-to-face victimization. Indeed, concurrent associations show that adolescents experiencing cybervictimization only and both cyber- and face-to-face victimization were at higher risk of suicidal ideation/attempt compared to adolescents experiencing no victimization and adolescent experiencing face-to-face victimization only. No study had reported higher odds for cyber- and face-to-face victimization combined compared to face-to-face victimization, or higher odds for cybervictimization only compared to face-to-face victimization only. For the first time, these findings indicate that cybervictimization, whether it is experienced alone or combined with face-to-face victimization, represents a higher concurrent risk for suicidal ideation/attempt compared to face-to-face victimization only. However these findings need to be interpret with caution given the low prevalence of suicidal ideation/attempt across subgroups and further studies are needed to replicate these results.

The prospective analyses in the current study showed that adolescents exposed to cybervictimization did not have a higher risk of showing suicidal ideation/attempt 2 years later, after adjusting for face-to-face victimization, prior mental health symptoms, family hardship, and baseline suicidal ideation/attempt. Conversely, adolescents exposed to face-to-face victimization had an increased risk of suicidal ideation/attempt 2 years later when similar confounders were controlled for including cybervictimization. Differential prospective associations between cyber- versus-face-to-face victimization may indicate that these 2 types of victimization have different developmental processes regarding suicidal ideation/attempt. One hypothesis is that cybervictimization may lead to an immediate suicidal risk, as shown by the cross-sectional

association in the current study, which might persist overtime. This may explain why the prospective associations were non-significant when baseline suicidal ideation/attempt was taken into account. In addition, cybervictimization may be less likely to be repeated while face-to-face victimization is more chronic(Geoffroy et al., 2018b), and potentially contributes to a stronger prospective association. This pattern is consistent with one prior study which found no association between cybervictimization and suicidal ideation from 12 to 14 years after adjusting for baseline suicidal ideation(Bannink et al., 2014).

Our study was conducted using a large representative birth cohort of children followed-up to 17 years of age, with repeated assessments of cybervictimization, face-to-face victimization, suicidal ideation/attempt and a range of childhood confounders. Despite these strengths, study limitations need to be acknowledged when interpreting the results. First, cybervictimization was based on a single item. This item gave similar examples of cybervictimization exposure; “insults, threats, intimidation by internet or by cell-phone”, to a well-known and widely used measure of cybervictimization in the Olweus Bully/Victim Questionnaire; “mean or hurtful messages, calls or pictures or other ways on my mobile phone or the internet” (Olweus, 1996). However our measure did not assess intention, repetition, and power imbalance as measured by the Olweus Bully/Victim Questionnaire. In addition, given the low frequencies of cybervictimization, we categorized adolescents as cybervictimized if they reported cybervictimization at least “once” while we categorized adolescents as having been victimized face-to-face if they reported face-to-face victimization “often/very often”. This must be taken into account when the two exposures are compared. Despite this limitation, stronger associations were seen for cybervictimization than face-to-face victimization in cross-sectional but not in prospective analyses. Our conclusions were further supported by the trend analyses using cybervictimization as a

continuous variable (i.e. “never” to “very often”) for cross-sectional associations. The trend analyses showed that the more often adolescents are exposed to cybervictimization the greater the risk of suicidal ideation/attempt. Additionally, the categorization is consistent with previous studies, thus increasing comparability between the available findings(Bannink et al., 2014; Elgar et al., 2014; Hirschtritt et al., 2015; Kodish et al., 2016; Messias et al., 2014; Sampasa-Kanyinga et al., 2014; Sinclair, Bauman, Poteat, Koenig, & Russell, 2012). Second, our victimization exposure was self-reported and may be influenced by current mental state, hence possibly inflating our effect sizes with suicidal ideation/attempt. Self-reported victimization is being used in most prior studies(John et al., 2018a) as most adolescents do not disclose to their teacher/parents if they have been victimized(Bowes, Joinson, Wolke, & Lewis, 2015a). Third, due to low statistical power we did not investigate whether cybervictimization was distinctively associated with suicidal ideation and suicide attempt. Some prior studies suggested that association of cybervictimization was stronger for suicide attempt than for suicidal ideation(S. Kim, Colwell, Kata, Boyle, & Georgiades, 2018; Schneider et al., 2012), but others showed the opposite finding(Kodish et al., 2016; Sinclair et al., 2012). Fourthly, the present study data did not include information on genetics, therefore the study could not account for genetic confounding. A prior study using a twin cohort has shown that victimized adolescents were more likely to report suicidal ideation even after accounting for genetic vulnerabilities (via a monozygotic twin design) and other pre-existing vulnerabilities, although the association with suicidal attempt was explained by genetic vulnerabilities(Baldwin et al., 2019).

Lastly, as in most longitudinal cohorts, attrition occurred overtime, especially amongst the most vulnerable participants, e.g., adolescents who were cybervictimized. However, the use of multiple imputations and weights reduced such selection bias.

1.7. Conclusion

Our findings indicate that cybervictimization is an important risk factor for concurrent serious suicidal ideation/attempt throughout adolescence that is independent from prior mental health symptoms, family hardship, and face-to-face victimization. A significant proportion (7-16%) of adolescents are victimized by their peers on electronic platforms and mostly targeted by other students attending the same or another school. Cybervictimization may be reduced through interventions, which may be highly cost-effective from a public health perspective. A recent review on school-based interventions against cybervictimization identified programs including educating youth on communication and social skills, empathy, coping, and responsible use of technology as effective targets in reducing its prevalence(Hutson, Kelly, & Militello, 2018). However, it is essential to examine whether prevention efforts against cybervictimization in adolescence translates into a measurable reduction of suicidal risk and cybervictimization. Future studies should also aim to investigate protective factors such as; family factors or peer support that could promote resilience to cybervictimization.

Keypoints

Cybervictimized adolescents (aged 13-17 years) were 2 to 4 times more likely to experience concurrent suicidal ideation/attempt regardless of exposure to face-to-face victimization and other key confounders including prior mental health symptoms and family hardship

Concurrent subgroup analyses showed that adolescents that were cybervictimized only, or exposed to both cyber- and face-to-face victimization were more at-risk for suicidal ideation/attempt compared to adolescents that were not victimized or victimized face-to-face only

Face-to-face victimization was associated with suicidal ideation/attempt 2 years later, however no longitudinal association was found for cybervictimization.

Cybervictimization is an important concurrent risk factor for serious suicidal ideation/attempt throughout adolescence and may be reduced through interventions, which may be highly cost-effective from a public health perspective

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1.8. Tables & Figures

Table 1.1: Frequencies of cybervictimization experiences since the beginning of the school year and the percentages of types of cybervictimization perpetrators from ages 12 to 17 years (y)[a, b, c]

Ages	**Frequency of cybervictimization n(%)**				**Cybervictimization originated from n(%)** [d]			
	Never	Once	A few times	Often/ Very often	Students at my school	Other young people who don't go at my school	I never knew whom	Other
12y	1248(93.2)	63(4.6)	26(1.8)	7(0.5)	50(56.8)	19(19.8)	23(24.0)	7(7.5)
13y	1119(90.2)	67(6.1)	30(2.5)	15(1.2)	72(71.6)	23(20.2)	17(14.8)	6(5.4)
15y	1211(84.0)	142(10.4)	63(4.3)	19(1.2)	146(66.5)	46(19.7)	34(15.2)	20(9.2)
17y	1137(92.8)	50(4.1)	32(2.6)	7(0.5)	51(58.8)	22(25.5)	17(18.1)	11(14.6)

a. Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998-2015), Québec Government, Institut de la Statistique du Québec

b. Sample sizes were 1344 at12y, 1231 at 13y, 1435 at 15y, and 1226 at 17y

c. Percentages are based on weighted data

d. Multiple responses were permitted

Table 1.2: Sex differences in the prevalence of having been cybervictimized at least once from ages 12 to 17 years (y) [a, b]

Ages	**Prevalence of cybervictimization**			
	All	Girls	Boys	Sex differences
	n(%)	n(%)	n(%)	p-values
12y	96(6.8)	54(7.1)	42(6.4)	.60
13y	112(9.8)	75(11.6)	37(6.8)	.005
15y	224(16.0)	152(19.3)	72(10.7)	.000
17y	89(7.2)	58(8.3)	31(5.3)	.044

a. Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998-2015), Québec Government, Québec Statistics Institute

b. Percentages are based on weighted data

Table 1.3**:** Odds ratios (ORs) and 95% confidence intervals (CIs) for concurrent associations between cyber versus face-to-face victimization and suicidal ideation/attempt from ages 13 to 17 years (y)[a, b, c]

	Suicidal ideation/attempt		
	Model 1	Model 2	Model 3
Cybervictimization			
13y	4.27 (3.16-5.76)	2.92 (2.12-4.03)	2.29 (1.64-3.19)
15y	6.00 (4.81-7.48)	5.40 (4.27-6.83)	4.20 (3.27-5.41)
17y	5.30 (4.09-6.87)	4.43 (3.35-5.86)	3.46 (2.57-4.66)
Face-to-face victimization			
13y	5.23 (3.98-6.86)	3.06 (2.27-4.13)	2.61 (1.92-3.56)
15y	4.13 (3.31-5.15)	3.52 (2.27-4.47)	2.16 (1.67-2.81)
17y	3.39 (2.26-4.40)	2.83 (2.14-3.74)	2.09 (1.54-2.84)

a. Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998-2015), Québec Government, Institut de la Statistique du Québec

b. Sample sizes were 1426 at 13y, 1245 at 15y, and 1245 at 17y

c. ORs and 95% CIs are based on weighted data

Model 1 adjusted for sex

Model 2 additionally adjusted for prior family socioeconomic status (6-12y), family structure (12y), family functioning (6-12y), hostile-reactive parenting (6-12y), depressive symptoms (10-12y), anxiety symptoms (10-12y), oppositional-defiant symptoms (6-12y), inattention/hyperactivity symptoms (6-12y). Multiple imputation by chained equation has been employed to impute missing information on childhood confounders

Model 3 additionally adjusted for face-to-face victimization or cybervictimization at each given age

Table 1.4**:** Odds ratios (ORs) and 95% confidence intervals (CIs) for prospective associations between cyber versus face-to-face victimization at 13 or 15 years and suicidal ideation/attempt 2 years later at 15 or 17 years (y) [a, b, c]

	Suicidal ideation/attempt			
	Model 1	Model 2	Model 3	Model 4
Cybervictimization				
13y	3.02 (2.28-4.00)	2.30 (1.70-3.12)	1.79 (1.30-2.44)	1.37 (0.97-1.93)
15y	2.23 (1.74-2.86)	1.82 (1.40-2.37)	1.34 (1.01-1.78)	0.98 (0.73-1.33)
Face-to-face victimization				
13y	4.26 (3.34-5.43)	3.08 (2.36-4.03)	2.78 (2.11-3.67)	2.45 (1.82-3.29)
15y	2.95 (2.33-3.73)	2.50 (1.94-3.23)	2.26 (1.72-2.97)	2.06 (1.56-2.72)

a. Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998-2015), Québec Government, Institut de la Statistique du Québec

b. Sample sizes were 1160 at 15y and 1192 at 17y

c. ORs and 95% CIs are based on weighted data

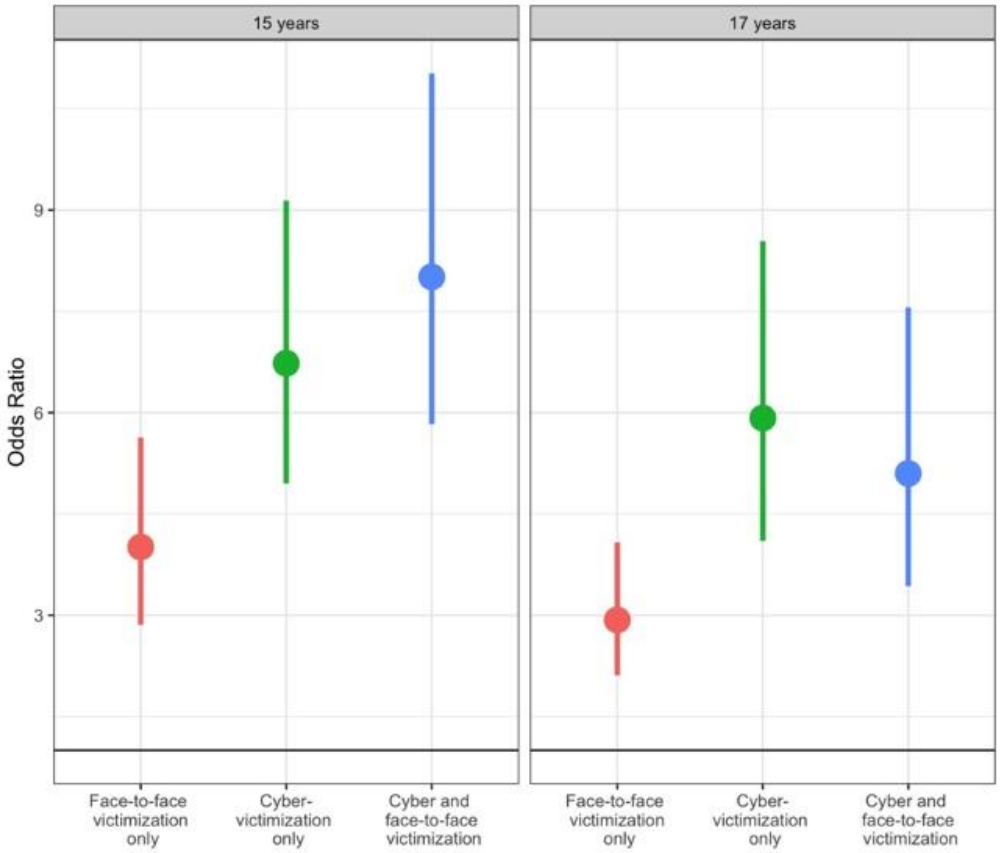
Model 1 adjusted for sex

Model 2 additionally adjusted for prior family socioeconomic status (6-12y), family structure (12y), family functioning (6-12y), hostile-reactive parenting (6-12y), depressive symptoms (10-12y), anxiety symptoms (10-12y), oppositional-defiant symptoms (6-12y), inattention/hyperactivity symptoms (6-12y). Multiple imputation by chained equation has been employed to impute missing information on childhood confounders.

Model 3 additionally adjusted for face-to-face victimization or cybervictimization at each given age

Model 4 additionally adjusted for suicidal ideation and attempt at baseline

Figure 1.1**:** Odds ratio and 95% confidence intervals for suicidal ideation/attempt by cybervictimization only, face-to-face victimization only, and cybervictimization with face-to-face victimization [a, b, c, d]



a. Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998-2015), Québec Government, Institut de la Statistique du Québec
b. Sample sizes were 1431 at 15y, and 1219 at 17y. Sample sizes for no victimization: 28 at 15y and 44 and 17y; for face-to-face victimization only: 14 at 15y and 14 at 17y; for cybervictimization only: 22 at 15y and 13 at 17y and for cybervictimization and face-to-face victimization combined: 22 at 15y and 9 at 17y. Estimates at 13 years were not available, because a cell was based on fewer than 5 participants.
c. Odds ratios (95% CI) for (1) face-to-face victimization only; (2) cybervictimization only; (3) both cyber- and face-to-face victimization compared to "no victimization"
d. The fully adjusted model included sex, prior family socioeconomic status (6-12y), family structure (12y), family functioning (6-12y), hostile-reactive parenting (6-12y), depressive symptoms (10-12y), anxiety symptoms (10-12y), oppositional-defiant symptoms (6-12y), inattention/hyperactivity symptoms (6-12y).

1.9. Supplementary Tables

Table S1.1**:** Descriptive statistics on key characteristics of participants by age in years (y)[a,b]

	Age, years (y)			
	13y	15y	17y	*p*-value
n (%)				
No. of participants, unweighted	1228	1426	1245	
Sex (female)	665 (62.5)	747 (61.1)	675 (63.0)	.55
Family structure at 12y				
Biological parents	757 (65.7)	843 (63.1)	750 (67.7)	.41
Single parent	224 (17.6)	232 (16.9)	204 (16.8)	.33
Blended	214 (16.7)	223 (16)	194 (15.5)	.36
Mean [SD][c]				
Socioeconomic status at 6-12y	-.002 [1.0]	.005 [1.0]	.035 [0.9]	.60
Hyperactivity/inattention at 6-12y	-.001 [0.8]	-.008 [0.8]	-.027 [0.8]	.70
Oppositional/defiance at 6-12y	-.001 [0.8]	-.007 [0.8]	-.022 [0.8]	.80
Depression at 10-12y	.005 [0.8]	.004 [0.8]	.007 [0.8]	.99
Anxiety at 10-12y	-.018 [0.8]	-.020 [0.8]	-.017 [1.0]	.99
Hostile-reactive parenting at 6-12y	-.001[0.8]	-.008 [0.8]	-.030 [0.8]	.61
Family functioning at 6-12y	.011 [0.8]	-.011 [0.8]	-.001 [0.8]	.78

a. Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998-2015), Québec Government, Institut de la Statistique du Québec
b. Estimates are based on weighted data
c. All continuous variables are Z-scores (Mean=0; SD=1)

Table S1.2**:** Odds ratios (ORs) and 95% confidence intervals (CIs) for cross-sectional associations between cyber versus face-to-face victimization and suicidal ideation/attempt from ages 12 to 17 years (y), unweighted [a, b]

	Suicidal ideation/attempt (multiple imputations only)		
	Model 1	Model 2	Model 3
Cybervictimization			
13y	3.52 (1.85-6.71)	2.46 (1.24-4.90)	1.84 (0.90-3.75)
15y	6.04 (3.82-9.55)	5.39 (3.32-8.74)	4.31 (2.57-7.22)
17y	5.44 (3.14-9.45)	4.49 (2.51-8.03)	3.87 (2.09-7.18)
Face-to-face victimization			
13y	5.22 (3.00-9.08)	3.16 (1.72-5.81)	2.80 (1.49-5.26)
15y	3.91 (2.47-6.19)	3.28 (2.02-5.35)	2.00 (1.17-3.42)
17y	2.69 (1.60-4.52)	2.20 (1.28-3.80)	1.54 (0.85-2.81)

a. Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998-2015), Québec Government, Institut de la Statistique du Québec

b. Sample sizes ranged from 1151-1228 at 13y, 1228-1426 at 15y, and 1068-1219 at 17y

Model 1 adjusted for sex

Model 2 additionally adjusted for prior family socioeconomic status (6-12y), family structure (12y), family functioning (6-12y), hostile-reactive parenting (6-12y), depressive symptoms (10-12y), anxiety symptoms (10-12y), oppositional-defiant symptoms (6-12y), inattention/hyperactivity symptoms (6-12y). Multiple imputation by chained equation has been employed to impute missing information on childhood confounders

Model 3 additionally adjusted for face-to-face victimization or cybervictimization at each given age

Table S1.3**:** Odds ratios (ORs) and 95% confidence intervals (CIs) for prospective associations between cyber versus face-to-face victimization at 13 and 15 years (y) and serious suicidal ideation/attempt 2 years later at 15 and 17 years (y), unweighted[a, b]

	Suicidal ideation/attempt (multiple imputations only)			
	Model 1	Model 2	Model 3	Model 4
Cybervictimization				
13y	2.62 (1.41-4.86)	2.01 (1.03-3.91)	1.57 (0.78-3.13)	1.29 (0.62-2.71)
15y	2.30 (1.35-3.90)	1.84 (1.06-3.22)	1.43 (0.78-2.61)	1.06 (0.56-2.02)
Face-to-face victimization				
13y	3.62 (2.17-6.03)	2.58 (1.47-4.54)	2.37 (1.32-4.25)	2.01 (1.08-3.75)
15y	2.73 (1.65-4.52)	2.24 (1.31-3.82)	1.98 (1.11-3.52)	1.85 (1.03-3.32)

a. Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998-2015), Québec Government, Institut de la Statistique du Québec
b. Sample sizes ranged from 1094-1160 at 15y and 1054-1192 at 17y
Model 1 adjusted for sex.
Model 2 additionally adjusted for prior family socioeconomic status (6-12y), family structure (12y), family functioning (6-12y), hostile-reactive parenting (6-12y), depressive symptoms (10-12y), anxiety symptoms (10-12y), oppositional-defiant symptoms (6-12y), inattention/hyperactivity symptoms (6-12y). Multiple imputation by chained equation has been employed to impute missing information on childhood confounders
Model 3 additionally adjusted for face-to-face victimization or cybervictimization at each given age
Model 4 additionally adjusted for suicidal ideation and attempt at baseline

1.10. Appendix

Modified Self-Report Victimization Scale at each given age (12y, 13y, 15y, 17y)

Since you started this school year, how many times did (never, rarely, sometimes, often, very often):

1. Another child in your school called you names, insulted you or said mean things to you?
2. A child at school didn't let you play with his or her group?
3. A child at school pushed, hit or kicked you?
4. Some children in your school said bad things about you to other children/students?
5. A child at school made fun of you, laughed at you?
6. A child in your school forced you to give him/her something that belonged to you?

Since the beginning of the school year*:

1. How many times were you the victim of cyberbullying (insults, threats, intimidation) on the internet or by cell phone? (never, once, few times, often, very often)
2. I was a victim of cyberbullying by internet or cell phone that originated from:
    a. students at my school
    b. other young people who don't go to my school
    c. I never knew by whom
    d. other.

*A definition of cybervictimization was provided to participants at 12y "Cyberbullying is when someone uses technology, such as a computer, cell phone, to deliberately harm someone. This allows an image (picture or video) or opinion to be distributed everywhere. The origin is often anonymous."

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From Chapter 1 to Chapter 2

In Chapter 1, we showed that cybervictimization and face-to-face victimization are both associated to suicidal ideation throughout adolescence. In this chapter, we investigate this association further by examining why some children may be more at risk of developing suicidal ideation, as well as depressive symptoms in adolescence after being peer victimized. The potential biological moderator tested in Chapter 2 is a partial measure of genetic vulnerability to depression, PRS-depression. We hypothesize that having a higher vulnerability to depression, as measured by the PRS-depression, will predict higher depressive symptoms and a higher risk of suicidal ideation. See section "Gene x Environment Interactions" in the Background for study rationale.

CHAPTER 2: POLYGENIC RISK SCORE AND PEER VICTIMIZATION INDEPENDENTLY PREDICT DEPRESSIVE SYMPTOMS IN ADOLESCENCE: RESULTS FROM THE QUEBEC LONGITUDINAL STUDY OF CHILD DEVELOPMENT

2.1. Title Page

Polygenic risk score and peer victimization independently predict depressive symptoms in adolescence: Results from the Quebec Longitudinal Study of Children Development

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2.2. Abstract

Background: Peer victimization has been associated with depressive symptoms during adolescence, however not all peer victimized adolescents will exhibit such symptoms. This study tested whether having a genetic predisposition to developing depression increased the risk of experiencing depressive symptoms in peer victimized youth. To date, no study has explored such gene-environment interaction using a polygenic risk score for depression (PRS-depression) in the context of peer victimization and depressive symptoms in adolescence.

Methods: The sample included 748 participants born in 1997/98 from the Quebec Longitudinal Study of Child Development with genotype data and prospectively collected information on peer victimization (12-13 years) obtained from both self- and teacher-reports, as well as self-reported depressive symptoms (15-17 years). The PRS-depression was based on the genome-wide association meta-analysis of broad depression by Howard et al. (2019).

Results: Self- and teacher-reported peer victimization in early adolescence were both associated with depressive symptoms in adolescence (β=0.34, p<.001; β=0.14, p=.001, respectively), and this association remained significant when accounting for PRS-depression (β=0.33, p<.001; β=0.13, p=.002, respectively). PRS-depression was independently associated with depressive symptoms, but there was no significant PRS-depression by peer victimization interaction (self-reported and teacher-reported). PRS-depression was correlated with self-reported, but not teacher-reported, peer victimization.

Conclusion: Our findings suggested that a partial measure of an individual's genetic predisposition to depression, as measured by PRS-depression, and being exposed to peer victimization (self- and teacher-reported) were independently associated with depressive symptoms in adolescence. Furthermore, PRS-depression did not exacerbate the risk of depressive

symptoms among adolescents who had been peer victimized. Lastly, we found evidence of a gene-environment correlation between PRS-depression and self-reported peer victimization. Future studies are needed to replicate this finding, and to further understand the role of genetic predispositions in experiencing depressive symptoms following peer victimization.

Keywords: peer victimization, depression, polygenic risk score, adolescence, longitudinal

2.3. Introduction

Peer victimization, a common experience among children and adolescents (Craig et al., 2009), is defined as physical, verbal, or psychological harm caused by peers acting outside the norms of appropriate conduct (Finkelhor et al., 2012). It has been associated with a range of mental health problems over the life course (see reviews : Arseneault (2018) and Moore et al. (2017)), including clinical depression (Arseneault, 2018), and depressive symptoms (Geoffroy et al., 2018a) after controlling for baseline mental health problems and family difficulties.

However, not all adolescents will experience depressive symptoms after being exposed to peer victimization. It has been suggested that peer victimization may be linked to a higher risk of depressive symptoms when it co-occurs with a genetic vulnerability to depression (Vaillancourt, Hymel, & McDougall, 2013). There is a strong genetic basis of depression, with heritability ranging from 30% to 50% (Kendall et al., 2021a). It is therefore important to consider the contribution of genetic vulnerability to depression when studying psychosocial risk factors, such as peer victimization. For example, Benjet et al. (2010) found evidence of an association between relational victimization (e.g., rumor spreading, social exclusion) and depressive symptoms in girls carrying the short/short allele combination of a polymorphism in the promoter region of the serotonin transporter gene (*5-HTTLPR*), but not in girls carrying the short/long or long/long allele combinations. This finding was replicated in boys and girls by Sugden et al. (2010). This points to an interaction between peer victimization and a measured candidate gene polymorphism, which together can explain a larger proportion of the association with depressive symptoms than if they were tested individually. However, these pioneer studies by Benjet et al. (2010) and Sugden et al. (2010) on the role of genetic vulnerability in depression, have focused on single genes with a candidate gene approach while depression is known to involve multiple genes; it is polygenic (N.

Wray et al., 2012). Thereby, a candidate gene approach would be limiting since the genetic etiology of depression is polygenic.

A polygenic approach has been made possible by the emergence of recent large genome-wide association studies (GWAS) detecting genetic variants associated with depression (Howard et al., 2019; N. R. Wray et al., 2018). Past GWAS had failed to uncover significant variants associated with a diagnosis of major depressive disorder (MDD) (Ripke et al., 2013), or had only discovered a few variants (Cai et al., 2015). More recent GWAS have considered a broader range of phenotypes in their inclusion criteria, departing from only comprising a clinical diagnosis of MDD to also including self-reported depressive symptoms. For example, N. R. Wray et al. (2018) discovered 44 variants associated with depression. Shortly after, a GWAS by Howard et al. (2019) identified 102 variants associated with a broader depression phenotype encompassing diagnosed MDD, depressive symptoms, as well as seeking help for depressive symptoms, from self-reports and medical reports.

From a methodological point of view, the inclusion of broader self-reported depression in these two GWAS has allowed the use of larger sample sizes, which are essential to detect more genetic variants with small effect sizes linked to broad depression phenotypes. Furthermore, using broader phenotyping of depression has been justified by several studies reporting a high genetic correlation between self-reported depressive symptoms and a clinical MDD diagnosis (Howard et al., 2018; N. R. Wray et al., 2018). As such, these GWAS are advantageously positioned to better understand the genetic etiology of a broader spectrum of depression phenotypes in clinical and community samples. GWAS further allow the computation of polygenic risk scores (PRS), which use GWAS statistics depicting the strength of association with depression across the genome at each single nucleotide polymorphisms (SNPs), while accounting for their individual weighted

effect sizes (Andlauer & Nöthen, 2020). The present study will use a community sample with self-reported depressive symptoms, and rely on the recent GWAS by Howard et al. (2019) to calculate a PRS for depression (PRS-depression) – in contrast to a PRS for MDD (PRS-MDD), based on GWAS solely comprising clinical and self-reported MDD cases, as in N. R. Wray et al. (2018) for example.

PRS-MDD has been used in prior studies to examine putative gene-environment interactions (G×E) in combination with adverse events such as childhood trauma (i.e., abuse and neglect) in predicting depression. A meta-analysis of nine cohorts of adults, using a retrospective measure of childhood trauma, showed that both trauma and PRS-MDD were independently associated with an increased risk of MDD (Peyrot et al., 2018), but failed to find evidence of a PRS-MDD and childhood trauma interaction. It is important to note that the studies from this meta-analysis did not use the more recent GWAS for depression by Howard et al. (2019) or PRS-MDD by N. R. Wray et al. (2018). A recent study based on the MDD GWAS by N. R. Wray et al. (2018) investigated G×E in clinical and epidemiological adolescent cohorts similarly found independent contributions of PRS-MDD and childhood abuse on depression, but no interaction (Halldorsdottir et al., 2019). In order words, childhood abuse did not influence the association between PRS-MDD and MDD. One study has investigated GxE between self-reported peer victimization in adolescence and PRS-depression using the depression GWAS by Howard et al. (2019) in predicting depressive symptoms in young adulthood, and found no interaction (Armitage, Wang, Davis, & Haworth, 2022).

Genome-wide research on G×E is still in its infancy, and more studies are needed to examine the contribution of PRS-depression in relation to environmental stressors known to be longitudinally associated with depression. To the best of our knowledge, no study has yet

examined the role of PRS-depression in the context of peer victimization and depressive symptoms in adolescence. Importantly, the present study included peer victimization assessed through both self- and teacher-reports. Prior studies found that self- and teacher-reported measures were linked to different correlates; psychological vs behavioral difficulties, respectively (Totura et al., 2009). Consequently, our study relied on both self- and teacher- reports to gain a broader and more complete overview of peer victimization. Furthermore, in light of previous and often inconsistent sex-specific G×E effects (Uher & McGuffin, 2008) we considered potential sex differences in our main analyses. The objectives of this prospective study were two-fold: (1) to test if peer victimization and PRS-depression independently predict depressive symptoms in adolescence, and (2) to investigate PRS-depression by peer victimization interaction, in other words if PRS-depression moderates the association between peer victimization and depressive symptoms.

2.4. Methods

2.4.1. Participants

Participants were members of the Quebec Longitudinal Study of Child Development (QLSCD; conducted by Institut de la Statistique du Québec) (Orri, Boivin, et al., 2020); an ongoing prospective birth cohort with biannual or annual data collection on 2,120 singletons born in the Canadian province of Quebec in 1997/98. The Ethics Committee of the Institut de la Statistique du Québec and the Research Ethics Board of the CHU Sainte-Justine Research Center approved each phase of the study, and informed consent was obtained at each time point. Further details about the cohort can be found online (https://jesuisjeserai.stat.gouv.qc.ca). At 10 years old, blood samples were collected from 992 participants and 978 were successfully genotyped, of which 816 passed quality control procedures (see **Supplement 2.1** for further details). The final sample size available was 748 participants, with measures of PRS-depression and depressive symptoms.

2.4.2. Measures

Peer Victimization (Self-reported and Teacher-reported)

Self and teacher-reported peer victimization were assessed twice at ages 12 and 13 years during the second half of the school year (February to June).

Self-reported peer victimization was assessed using a modified version of the Self-Report Victimization Scale (Ladd & Kochenderfer-Ladd, 2002). The six items reflect various types of victimization (physical, verbal, and relational): since the beginning of the school year, how many times has another student in school; 1) called you names/said mean things; 2) did not let you play in his/her group; 3) pushed/hit/kicked you; 4) said bad things behind your back; 5) teased you in a mean way; 6) made you pay them or give them something so they would leave you alone. These items were rated on a Likert scale "never", "few times" and "more often" at 12 years, and "never", "rarely", "often", and "very often" at 13 years.

Teacher-reported peer victimization was assessed using 3 items from the Behavior Questionnaire (Tremblay et al., 1987) reflecting physical, verbal, and relational victimization in the last 6 months: this child was 1) made fun of by other children, 2) hit or pushed by other children, 3) called names by other children. These items were all rated on a Likert scale; "never", "few times" and "more often" at 12 and 13 years.

The Cronbach alpha (α) was 0.82 at 12 years, and 0.81 at 13 years for self-reported peer victimization, and 0.77 at 12 years, and 0.85 at 13 years for teacher-reported peer victimization, indicating satisfactory internal consistency for all measures.

As self- and teacher- reported peer victimization measures had different ranges, we converted all scores to a 0-10 scale. The Pearson correlation of self-reported peer victimization at ages 12 and 13 years was .50, and for teacher-reported peer victimization it was .42 (*p*s<.001).

Depressive Symptoms

Depressive symptoms were self-reported at 15 and 17 years using the Mental Health and Social Inadaptation Assessment (MIA) (Côté et al., 2017; Geoffroy et al., 2018a). The MIA assessed eight DSM-V depression/dysthymia symptoms (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) (e.g., "I felt sad and unhappy") and their reported frequencies ("never", "sometimes", "often") in the past 12 months. Depression scores at 15 years (Cronbach α =0.85) and 17 years (Cronbach α =0.85) were averaged into a single score. The Pearson correlation of depressive symptoms at ages 15 and 17 years was .61 (p<.001).

PRS-depression

PRS-depression were created for 816 participants after quality control and imputation of genotyping data. Conceptually, PRS is a proxy of an individual's genetic propensity to a given disorder based on common genetic variation. Practically, PRS represent a count function of alleles at hundreds or thousands of SNPs across the genome, with each allele weighted by an associated effect size derived from an independent large scale GWAS of a phenotype of interest (Andlauer & Nöthen, 2020). To this end, the effect sizes from a GWAS are used as weights. In the present study, PRS were computed using PRSice v.2.2.11 (Euesden, Lewis, & O'Reilly, 2015) and based on the recent GWAS meta-analysis for depression (Howard et al., 2019). Autosomal SNPs were clumped for linkage disequilibrium (LD) with the following parameters to obtain independent SNPs LD: r^2 < 0.1 within 250 kb windows. Multiple PRS were computed, each based on a different number of SNPs (GWAS p-value thresholds were: 0.01; 0.10; 0.50; 1.00). To account for population stratification (described in **Supplement 2.1**), PRS were regressed on ten multidimensional scaling components calculated from the pairwise genetic relationship matrix. Standardized residuals (PRS-depression) were used in all analyses. PRS-depression used in the main analyses included

the most SNPs with a *p*-value threshold significance of p=1. Other PRS thresholds (p =0.01; p=0.10; p=0.50) were included in additional analyses.

Potential confounding factors

A set of known confounding factors (described in **Supplement 2.2**) in the association between peer victimization and depressive symptoms (Geoffroy et al., 2018a) were used in this study, including family factors at 10 years (socioeconomic status, family structure, family functioning, hostile-reactive parenting, maternal depressive symptoms, cognitive abilities), prior mental health symptoms in childhood at 8 years (oppositional/defiance symptoms, inattention/hyperactivity symptoms, depressive and anxiety symptoms).

2.4.3. Statistical Analyses

In **Table S2.1**, we described sociodemographic characteristics for the included vs excluded participant subsamples, and tested potential differences using t-tests and chi-squared tests. **Table 2.1** reports descriptive statistics of our variables of interest; peer victimization at 12-13 years (self- and teacher-reported), depressive symptoms at 15-17 years, and PRS-depression.

We then estimated associations between variables of interest **(Table 2.2)**. More specifically, sex-adjusted hierarchical linear regressions were conducted with depressive symptoms as the outcome by subsequently including peer victimization (step 1), PRS-depression (step 2), and the interaction term between peer victimization and PRS-depression (step 3) (**Table 2.2**). Analyses were performed separately for self- and teacher-reported measures. All variables were converted into standardized z-scores (mean=0, standard deviation=1) to facilitate interpretation.

We tested two-way interactions; sex by peer victimization (self- and teacher-reported), and sex by PRS-depression, as well as the three-way interaction; sex by peer victimization (self- and teacher-reported) by PRS-depression, in unadjusted models predicting depressive symptoms.

Unique variances (R^2) of peer victimization (self- and teacher-reported) and PRS-depression on depressive symptoms were also estimated independently (Harel, 2009).

In sensitivity analyses, we reported correlations between peer victimization, depressive symptoms, and potential confounders in **Table S2.2**. To further test the robustness of our findings, we then accounted for all these potential confounders in additional models testing the additional predictive value of the peer victimization and PRS on depressive symptoms and their interaction (**Table S2.3**). Similar patterns of findings suggest the robustness of the reported association between peer victimization, PRS-depression and depressive symptoms, and that these findings could not be accounted for by these potential confounders. Second, the main analyses included PRS-depression calculated on SNPs up to the significance threshold of p=1, but we re-estimated our main models using alternative PRS-depression thresholds; p<.01, p<.1, p<.5 (**Table 2.3**). These alternative PRS-depression thresholds were more conservative, hence included fewer SNPs when calculating the PRS-depression. These sensitivity analyses allowed us to confirm that our results were consistent across the different p-value thresholds used to calculate the PRS-depression.

Missing data were imputed using multiple imputation by chained equation (Azur et al., 2011) to avoid losing participants due to missing data on peer victimization (2.5% for self-report and 14.2%, for teacher report) and confounders (from 2.4% for socioeconomic status to 14.8% for maternal depressive symptoms).

2.5. Results

The descriptive statistics for the study participants versus participants who were not included are presented in **Table S2.1**. Participants included in the study subsample (vs non-included) were more likely to 1) be female, 2) have parents who graduated from high school, 3)

have a sufficient income, above the low-income cut-off, and 4) have a mother with less depressive symptoms when they were infants. **Table 2.1** presents descriptive statistics on the variables of interest; self-reported peer victimization, teacher-reported peer victimization, and depressive symptoms. Additional analyses showed that self-reported and teacher-reported peer victimization were moderately correlated with each other (Pearson r=0.39, p<.001). Furthermore, additional analyses showed that PRS-depression correlated with self-reported peer victimization (Pearson r=0.11; p=.002), but not with teacher-reported peer victimization.

Associations of peer victimization at 12-13 years and PRS-depression with depressive symptoms at 15-17 years are shown in **Table 2.2**. In sex-adjusted analyses, peer victimization (self- and teacher-reported) significantly predicted depressive symptoms (β=0.34, p<.001; and β=0.14, p=.001, respectively) (Step 1, **Table 2.2**). This association remained significant when PRS-depression was entered in the model (β=0.33, p=<.001; β=0.13, p=.002, respectively) (Step 2, **Table 2.2**). PRS-depression was associated with depressive symptoms in these models when accounting for peer victimization (β=0.07, p=.025; β=0.10, p=.002, respectively) (Step 2, **Table 2.2**). Furthermore, these associations remained significant after controlling for sex, childhood mental health symptoms at 8 years (oppositional/defiance symptoms, inattention/hyperactivity symptoms, depressive and anxiety symptoms) and family factors at 10 years (socioeconomic status, family structure, family functioning, hostile-reactive parenting, maternal depressive symptoms, cognitive abilities); see **Table S2.3**. However, the interaction term of PRS-depression and peer victimization (self- and teacher-reported) was not significant (β=0.04, p=.238; and β=-0.001, p=.986, respectively; Step 3, **Table 2.2**). In two separate regression models on either self-reported or teacher-reported peer victimization, the unique variance (based on R^2) of peer victimization in the prediction of depressive symptoms was 7.4% and less than 1%, respectively.

A third model showed that the PRS-depression uniquely predicted 1.2% of depressive symptoms' variance (based on R^2).

Finally, sex did not interact with either peer victimization (p=.788 for self-report, and p=.094 for teacher report), or PRS-depression (p=.190) to predict depressive symptoms. There was also no three-way interaction between peer victimization, PRS-depression, and sex (p=.600 for self-reported peer victimization; and p=.321 for teacher-reported peer victimization).

We additionally explored the possibility that the findings of the sex-adjusted analyses could be in part specific to the PRS p-value threshold we selected (p=1). The general pattern of findings for the main and interaction effects between peer victimization and depressive symptoms remained consistent across all analyzed PRS-depression thresholds (p<0.5; p<0.1; p<0.01; **Table 2.3**). The only exception was that PRS-depression did not predict depressive symptoms when more conservative PRS-depression thresholds were used (p<0.01 and p<0.1) in models with self-reported peer victimization.

2.6. Discussion

Previous studies showed that peer victimization is associated with depressive symptoms, but the role of genome-wide cumulative genetic vulnerability to depression as a moderator had not yet been examined. Using a longitudinal design, our findings indicate that adolescents who were victimized by their peers were more likely to experience higher levels of depressive symptoms up to five years later. This is in line with another study which found that teacher-, mother-, and self-reported peer victimization at 7-10 years were associated with depressive symptoms at 11-14 years (Zwierzynska, Wolke, & Lereya, 2013). Similar to our study, teacher and self-reported peer victimization were moderately correlated with each other (Ladd & Kochenderfer-Ladd, 2002).

Together, these findings suggest that teacher- and adolescent self-reports capture different perspectives of peer victimization, but they both predict depressive symptoms.

Furthermore, we showed that the association of peer victimization with depressive symptoms remained even after the genetic vulnerability to depression was taken into account, and the strength of this association did not vary as a function of PRS-depression. Our study is the first to show that peer victimization contributes to later depressive symptoms for all adolescents, regardless of their genetic vulnerabilities to depression partially captured by a recent PRS-depression. Similarly to our finding, one study in adolescents (Halldorsdottir et al., 2019) and a meta-analysis in adults (Peyrot et al., 2018) reported that the association between childhood trauma and depression was not affected by the genetic vulnerability to depression, as measured by PRS-MDD. Additionally, a more recent study using the same GWAS by Howard et al. (2019) as the present study, showed a lack of interaction between self-reported peer victimization and PRS-depression in predicting depressive symptoms in young adulthood (Armitage et al., 2022).

Our study showed that, as early as in adolescence, the PRS-depression was associated with depressive symptoms. This is consistent with one study previously reported an association between PRS-MDD and MDD, as well as depressive symptoms in adolescents (Halldorsdottir et al., 2019). Nonetheless, the effect size of the PRS-depression was rather small in magnitude, which points to the multifactorial nature of depressive symptoms' etiology, and calls for sustained effort in delineating the genetic underpinnings of depression. PRS-depression alone accounted for 1.2% of the variance in depressive symptoms in this study, which is similar to the 1.6% variance reported by Armitage et al. (2022) between PRS-depression and depressive symptoms in young adulthood. Additionally, Halldorsdottir et al. (2019) reported that PRS-MDD predicted a unique variance of

around 1% for depressive symptoms severity in a clinical sample and less than 1% in the epidemiological sample. These magnitudes are also consistent with a prior GWAS showing that PRS-MDD accounted for about 2% of the variance in MDD in adults (N. R. Wray et al., 2018). PRS-depression predicted depressive symptoms at the PRS thresholds p=1 and p=0.5. However, associations with depressive symptoms using more conservative PRS thresholds p=0.1 and p=0.01 were not significant, which may be the result of the more limited coverage of SNPs associated with depression at lower thresholds. Indeed, the advantage of using a higher (less conservative) p-value threshold is that we include a broader range of SNPs which each contribute in a small way to a genome-wide genetic vulnerability to depression. In addition, we found that associations of PRS-depression and peer victimization (self- and teacher-report) with depressive symptoms were similar in boys and in girls, and there was no sex difference in the PRS-depression by peer victimization (self- and teacher-report) interaction. Potential sex differences in terms of PRS-depression in relation to peer victimization and depressive symptoms had not been investigated prior to this study. More studies with larger samples are needed to investigate potential sex differences in more detail.

In addition, we found that PRS-depression was weakly correlated with self-reported but not with teacher-reported peer victimization. This is in line with findings from Schoeler et al. (2019) and Armitage et al. (2022) who found that self-reported peer victimization was associated with PRS-MDD and PRS-depression, respectively. One possible interpretation could be the presence of an evocative gene-environment correlation (*r*GE) between a genetic vulnerability to depression and self-reported peer victimization. In other words, having a genetic vulnerability to depression would increase the risk of experiencing depressive symptoms, which would in turn increase the risk of experiencing peer victimization. This *r*GE hypothesis is partly supported by a

meta-analysis showing that depressive symptoms are associated with later peer victimization in childhood (Christina, Magson, Kakar, & Rapee, 2021). We could further hypothesize that having a genetic vulnerability to depression is linked to certain social and interpersonal behaviors, such as social withdrawal and sadness, which increase one's risk of being peer victimized, as previously suggested (Luchetti & Rapee, 2014; Schlag et al., 2022). However, more studies are needed to replicate this *r*GE and to further investigate potential mechanisms behind it.

Lastly, one possible explanation for the inconsistent pattern of association between self-reported vs teacher-reported peer victimization and PRS-depression may be that self-reports of peer victimization may more readily capture a perception bias towards social relationships, which may co-occur with a genetic vulnerability to depression. In other words, individuals with a genetic vulnerability to depression may perceive more acutely or be more inclined to interpret behaviors by peers as victimization (Kellij, Lodder, van den Bedem, Güroğlu, & Veenstra, 2022; Lopez & DuBois, 2005; Orth, Robins, & Roberts, 2008). Alternatively, teacher-reports could be more limited in scope compared to self-reports of peer victimization as it included only 3 items. However, to strengthen their validity, these ratings were averaged over two years and included ratings of 2 different teachers across the 2 timepoints. Furthermore, the significant year-to-year stability of self-reported and teacher-reported peer victimization (r=.50, r=.42, respectively) in this study is comparable to a meta-analysis of 77 longitudinal studies reporting similar magnitudes (r=.49, r=.57, respectively) (Pouwels, Souren, Lansu, & Cillessen, 2016). Finally, to conclude on the *r*GE finding, as stressed by Christina et al. (2021), such reverse causality hypotheses should be handled with caution to avoid blaming to the victim, but rather to identify individual characteristics that may inform intervention research. Furthermore, more studies are needed to replicate this finding before further hypotheses can be made.

The study's strengths included the use a contemporary sample of adolescents from the general population followed from birth to age 17 years, with data on peer victimization assessed in early adolescence (12-13 years) from both the primary teachers and the adolescents themselves. This allowed us to compare associations of self-reported and non-self-reported measures with depressive symptoms, which is lacking in the literature. Our study also tested the contribution of PRS-depression in the association between peer victimization and depressive symptoms using PRS-depression derived from a recent GWAS meta-analysis on broad depression with one of the largest sample to date (Howard et al., 2019). Several more conservative PRS thresholds ($p<0.01$, $p<0.1$, $p<0.5$) were also included our analyses to confirm our results with PRS $p<1$.

However, our conclusions need to be interpreted in light of a number of limitations. First, teacher-reported peer victimization was measured using three items, while self-reported peer victimization had six items. Nevertheless, both scales assessed physical, verbal, and relational peer victimization and were associated with depressive symptoms. Second, no clinical measure of depression was available in the present study. Still, PRS-depression was associated with self-reported depressive symptoms in adolescence. Third, our results cannot be generalized to the initial QLSCD cohort as this study sample was limited to participants who provided DNA samples through blood collection at 10 years. The study participants were found to be more advantaged than non-included participants in terms of early-life factors such as socioeconomic (income) and family factors (maternal depression, parents' education).

2.7. Conclusion

In conclusion, being exposed to peer victimization in early adolescence was associated with higher depressive symptoms in middle to late adolescence. This association was not accounted for by a partial measure of genetic liability to depression (PRS-depression) nor by known confounding

factors (e.g., prior mental health symptoms) (Geoffroy et al., 2018a). PRS-depression weakly predicted depressive symptoms but did not influence the association between peer victimization and depressive symptoms. In other words, peer victimization predicted depressive symptoms for all levels of genetic vulnerability to depression. In light of a fast-evolving field, future studies are needed to replicate these findings. Particularly as different methods to calculate PRS are emerging and new GWAS are being published.

Keypoints

This study confirmed that both self-reported and teacher-reported peer victimization (aged 12-13 years) was associated with more depressive symptoms (15-17 years)

Genetic vulnerability to depression measured by a polygenic risk score for depression (PRS-depression) also predicted depressive symptoms at 15-17 years

PRS-depression did not moderate the association between peer victimization (self-reported and teacher-reported) and depressive symptoms (15-17 years)

Evidence for a gene-environment correlation between PRS-depression and self-reported peer victimization was uncovered

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2.9. Tables

Table 2.1**:** Descriptive statistics for peer victimization at 12-13 years, and depressive symptoms at 15-17 years in the study sample

	Self-reported peer victimization	**Teacher-reported peer victimization**	**Depressive symptoms**
N	729	642	748
Mean(±SD)	2.05(1.71)	1.06(1.72)	3.65(2.09)
Range	0-8.75	0-9.17	0-10

Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998–2015),

Table 2.2**:** Hierarchical linear regression predicting depressive symptoms (15-17 years) with peer victimization (12-13 years) and PRS-depression

	Hierarchical regression on depressive symptoms using either self-reported or teacher-reported peer victimization in independent models				
		Self-reported peer victimization		Teacher-reported peer victimization	
		Beta (SE)	**p-value**	**Beta (SE)**	**p-value**
Step 1	Peer victimization	0.339 (0.032)	<.001	0.136 (0.042)	.001
Step 2	Peer victimization	0.330 (0.032)	<.001	0.130 (0.041)	.002
	PRS-depression	0.071 (0.032)	.025	0.102 (0.034)	.002
Step 3 interaction	PRS-depression*peer victimization interaction	0.039 (0.033)	.238	-0.001 (0.038)	.986

Max N based on data available for PRS-depression and depressive symptoms, n=748.

Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998–2015), © Gouvernement du Québec, Institut de la Statistique du Québec

The residual score for PRS-depression calculated with p-value<1 threshold was used and included all 10 principal components.

All models were adjusted for sex.

Table 2.3**:** Hierarchical regression of depressive symptoms at 15-17 years on peer victimization at 12-13 years with different thresholds PRS-depression (p<.01, p<.1, p<.5)

	Hierarchical regression on depressive symptoms using self-reported peer victimization					
	P<0.01		**P<0.1**		**P<0.5**	
	Beta (SE)	***p*-value**	**Beta (SE)**	***p*-value**	**Beta (SE)**	***p*-value**
Step 1 : Self-reported peer victimization	0.339 (0.032)	<.001	0.339 (0.032)	<.001	0.339 (0.032)	<.001
Step 2 : Self-reported peer victimization	0.332 (0.032)	<.001	0.332 (0.032)	<.001	0.331 (0.032)	<.001
PRS-depression	0.052 (0.032)	.102	0.058 (0.032)	.067	0.072 (0.032)	.024
Step 3: interaction PRS-depression*Self-reported peer victimization interaction	0.016 (0.032)	.625	0.042 (0.032)	.194	0.038 (0.033)	.251
	Hierarchical regression on depressive symptoms using teacher-reported peer victimization					
	P<0.01		**P<0.1**		**P<0.5**	
	Beta (SE)	***p*-value**	**Beta (SE)**	***p*-value**	**Beta (SE)**	***p*-value**
Step 1 : Teacher-reported peer victimization	0.137 (0.042)	.001	0.137 (0.042)	.001	0.136 (0.042)	.001

Step 2 : Teacher-reported peer victimization	0.129 (0.042)	.002	0.129 (0.042)	.002	0.130 (0.041)	.002
PRS-depression	0.082 (0.033)	.014	0.086 (0.034)	.010	0.101 (0.033)	.003
Step 3: interaction PRS-depression*Teacher-reported peer victimization interaction	0.007 (0.036)	.848	0.014 (0.038)	.712	-0.004 (0.038)	.911

Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998–2015), © Gouvernement du Québec, Institut de la Statistique du Québec

Max N based on data available for PRS-depression and depressive symptoms, n=748

The residual score for PRS-depression, with p-value<1 threshold, was used and included all 10 principal components.

Models adjusted for sex

2.10. Supplemental Tables

Table S2.1: Sociodemographic characteristics[a] of the included participants in the study sample on early-life factors vs excluded participants

	Non-included subsample	**Included subsample**	***p*-value[b]**
Range *n* of participants	1323-1475	708-748	
Sex (female)	670 (45.4%)	415 (55.5%)	<.001
Maternal age at birth in mean(±SD) years	29.20 (±5.29)	29.45 (±5.06)	.299
Maternal depressive symptoms at 5 months in mean(±SD) scores	1.49 (±1.41)	1.23 (±1.21)	<.001
Insufficient income at 5 months	386 (26.8%)	139 (18.7%)	<.001
Mother's education at 5 months (less than high school)	284 (19.3%)	117 (15.6%)	.036
Father's education at 5 months (less than high school)	295 (22.3%)	125 (17.7%)	.014
Family structure at 5 months (single)	138 (9.4%)	36 (4.8%)	<.001

Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998–2015), © Gouvernement du Québec, Institut de la Statistique du Québec

[a] Maternal depressive symptoms scores were based on the short version of the Center for Epidemiologic Studies-Depression. Insufficient income was based on the Low Income Cut-Off calculated by Statistic Canada; defined as

having 20% or more household income than the average Canadian family used for food, shelter, and clothing. Mother's and father's education reflected proportions of mothers and fathers who did not receive a high school diploma. Family structure reflected the proportion of participants in a single parent family (vs blended, or both biological parents).

[b]p-value of a chi-squared test when measuring proportions in a categorical variable, or t-test when analyzing the mean (±SD) of a continuous variable.

Table S2.2: Correlations between variables of interest (self-reported and teacher-reported peer victimization at 12-13 years, depressive symptoms at 15-17 years) and potential confounders

	Self-reported peer victimization		**Teacher-reported peer victimization**		**Depressive symptoms**	
	Pearson correlation coefficient	*p*-value	Pearson correlation coefficient	*p*-value	Pearson correlation coefficient	p-value
Socioeconomic status at 10 years	-.089	.016	-.134	.001	-.030	.420
Family functioning at 10 years	.104	.008	.135	.001	.045	.260
Family structure at 10 years*	.010	.793	.015	.707	.014	.707
Hostile-reactive parenting at 10 years	.070	.063	.065	.106	-.056	.137
Maternal depressive symptoms at 10 years	.184	<.001	.156	<.001	.040	.315
Cognitive abilities at 10 years	.030	.415	-.004	.927	.009	.799
Oppositional/defiance symptoms at 8 years	.162	<.001	.134	.001	.114	.002
Inattention/hyperactivity symptoms at 8 years	.162	<.001	.264	<.001	.036	.333

Depressive and anxiety symptoms at 8 years	.092	.014	.121	.002	.098	.008

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*based on Spearman's rho non-parametric correlation.

Table S2.3: Hierarchical regression predicting depressive symptoms (15-17 years) with peer victimization (12-13 years) and PRS-depression, including all potential confounders

	Hierarchical regression on depressive symptoms using either self-reported or teacher-reported peer victimization in independent models			
	Self-reported peer victimization		Teacher-reported peer victimization	
	Beta(SE)	***p*-value**	**Beta(SE)**	***p*-value**
Step 1: Peer victimization	0.326(0.033)	<.001	.102(0.045)	.023
Step 2: Peer victimization	0.317(0.033)	<.001	0.098(0.045)	.028
PRS-depression	0.071(0.032)	.026	0.102(0.034)	.002
Step 3 : interaction PRS-depression*Peer	0.038(0.033)	.251	-0.001(0.038)	.981

victimization interaction				

Max N based on data available for PRS-depression and depressive symptoms, n=748

Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998–2015), © Gouvernement du Québec, Institut de la Statistique du Québec

The residual score for PRS-depression, with p-value<1 threshold, was used and included all 10 principal components.

All models adjusted for confounders (described in **Supplement 2.2**); sex, family factors at 10y (socioeconomic status, family structure, family functioning, hostile-reactive parenting, maternal depressive symptoms, cognitive abilities), prior mental health symptoms in childhood at 8y (oppositional/defiance symptoms, inattention/hyperactivity symptoms, depressive and anxiety symptoms).

2.11. Supplementary material

2.11.1. Supplement 2.1

Genotyping data

DNA collection and extraction

At 10 years old, 992 participants consented to having their blood drawn for genotyping. After DNA extraction (Qiagen FlexiGene DNA kit Cat#51206), DNA concentration and purity was tested by a PicoGreen DNA assay (Invitrogen Quant-iT™ PicoGreen™ dsDNA Assay Kit Cat#P7589). Normalizations of concentration were done according to requirements for SNP genotyping on microarrays.

Genotyping & Quality Control

978 participant DNA samples were genotyped by Génome Québec using a custom chip based on the Illumina Infinium PsychArray-24v1.1 Beadchip. Participants were excluded based on missing of data higher than 5% (12 participants), genetic duplicates (7 participants), sex mismatches (4 participants). SNPs with a minor allele frequency (MAF) less than 1%, or in deviation from Hardy-Weinberg equilibrium (HWE) ($p < 1\times10^{-6}$), or with ambiguous strand information were excluded.

Population stratification was estimated to address the potential bias due to genetic differences in the population. Population stratification was modeled using ten multidimensional scaling (MDS) components, calculated on the pairwise genetic identity-by-state matrix, for which SNPs with HWE test $p < 0.001$ or a MAF <5% were excluded. Remaining SNPs were pruned using windows of 200 variants, a step size of 100, and a linkage disequilibrium threshold of r^2<0.2. Population stratification identified 134 genetic outliers, these participants were

excluded. In addition, 5 individuals were removed as outliers due to high autosomal heterozygosity.

Imputation

Imputation leverages haplotypes from a reference panel to augment the number of SNPs in a smaller genotyped sample. To this end, we used the 1000 Genomes Phase 3 reference panel. Haplotypes were estimated using SHAPEIT2 (Delaneau, Marchini, & Zagury, 2012). SNPs were imputed using IMPUTE2 (Howie, Donnelly, & Marchini, 2009) in 5 mega-basepair chunks with 500 kilobase buffers, using all reference data. After imputation, only variants with a MAF ≥1% and an INFO metric ≥0.8 were retained. SNPs showing evidence for a deviation from HWE ($p < 1\times10^{-6}$) were excluded.

After quality control and imputation, 8 407 807 SNPs and 816 participants were included.

2.11.2. Supplement 2.2

Confounders at 8 and 10 years

As in our past publications (Geoffroy et al., 2018a; Geoffroy et al., 2016), we controlled for prior mental health and family hardship characteristics previously associated with peer victimization, and depressive symptoms.

Mental health symptoms were assessed with the Behaviour Questionnaire (BQ), a validated scale used in the Canadian National Longitudinal Study of Children and Youth(*Statistics Canada and Human Resources Development Canada. National Longitudinal Survey of Children and Youth: Overview of Survey Instruments for 1994-1995 Data Collection Cycle 1*, 1995), which incorporates items from the Child Behaviour Checklist (Achenbach et al., 1987), the Ontario Child Health Study Scales (Offord et al., 1989), and the Preschool Behaviour Questionnaire (Tremblay et al., 1987). *Oppositional/defiance* was assessed with 4 items (e.g.,

"defiant/refused to comply") and *hyperactivity-inattention/* with 9 items (e.g., "could not sit still"), and *anxiety symptoms* with 4 items (e.g., "fearful/nervous") at through mother-reports at 8 years. All items were rated on a 3-point scale (0="never or not true"; 1="sometimes or somewhat true"; 2="often or very true").

Family socioeconomic status was measured as an aggregate of annual gross income, parental education level, and occupational prestige (Willms & Shields, 1996) at 10 years; *family functioning* (i.e. communication, problem resolution, and control of disruptive behaviour) was assessed with the McMaster Family Assessment (*Statistics Canada and Human Resources Development Canada. National Longitudinal Survey of Children and Youth: Overview of Survey Instruments for 1994-1995 Data Collection Cycle 1*, 1995) at 10 years; *family structure* (0=biological parents/blended, 1=single) was reported at 10 years; and *hostile-reactive parenting* (e.g., corporal punishment, raising voice) was assessed with 4 items (Boivin et al., 2005) at 10 years.

Maternal depression at 10 years was assessed using a shortened version (12 items) of the Center for Epidemiologic Studies-Depression. Scores were standardized to range from 0-10, with higher scores indicating higher depressive symptoms.

C*ognitive ability* at 10 years was assessed using the Peabody Picture Vocabulary Test—Revised (PPVT-R) (Dunn, Thériault-Whalen, & Dunn, 1993). The PPVT-R assesses receptive verbal ability by tapping into the cognitive processes involved in matching a verbal cue to a picture, where no immediate memory or recall component is involved.

2.12. Supplementary Analyses

Supplemental Analyses Table 2.1.**:** Hierarchical linear regression predicting suicidal ideation (15-17 years) with peer victimization (12-13 years) and PRS-depression

	Logistical regression on depressive symptoms using either self-reported or teacher-reported peer victimization in independent models				
		Self-reported peer victimization		Teacher-reported peer victimization	
		OR(95% CI)	**p-value**	**OR(95% CI)**	**p-value**
Step 1	Peer victimization	1.76 (1.61-1.92)	<.001	1.44 (1.31-1.58)	<.001
Step 2	Peer victimization	1.73 (1.59-1.88)	<.001	1.44 (1.31-1.58)	<.001
	PRS-depression	1.22 (1.12-1.33)	.020	1.35 (1.24-1.48)	<.001
Step 3 interaction	PRS-depression*peer victimization interaction	0.98 (0.89-1.07)	.822	0.99 (0.94-1.05)	.928

Max N based on data available for PRS-depression and suicidal ideation, n=728

Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998–2015), © Gouvernement du Québec, Institut de la Statistique du Québec

The residual score for PRS-depression calculated with p-value<1 threshold was used and included all 10 principal components.

All models were adjusted for sex

Supplemental Analyses Table 2.2.**:** Hierarchical regression of depressive symptoms at 15-17 years on peer victimization at 12-13 years with different thresholds PRS-depression (p<.01, p<.1, p<.5)

	Logistical regression on suicidal ideation using self-reported peer victimization					
	P<0.01		**P<0.1**		**P<0.5**	
	OR(95% CI)	***p*-value**	**OR(95% CI)**	***p*-value**	**OR(95% CI)**	***p*-value**
Step 1 : Self-reported peer victimization	1.76 (1.61-1.91)	<.001	1.76 (1.61-1.91)	<.001	1.76 (1.61-1.92)	<.001
Step 2 : Self-reported peer victimization	1.73 (1.58-1.88)	<.001	1.73 (1.59-1.88)	<.001	1.73 (1.59-1.89)	<.001
PRS-depression	1.20 (1.10-1.31)	.029	1.19 (1.09-1.30)	.037	1.21 (1.11-1.31)	.027
Step 3: interaction PRS-depression*Self-reported peer victimization interaction	0.96 (0.89-1.05)	.679	0.95 (0.87-1.04)	.595	0.97 (0.88-1.06)	.717
	Logistical regression on suicidal ideation using teacher-reported peer victimization					
	P<0.01		**P<0.1**		**P<0.5**	
	OR(95% CI)	***p*-value**	**OR(95% CI)**	***p*-value**	**OR(95% CI)**	***p*-value**
Step 1 :	1.44 (1.31-1.58)	<.001	1.44 (1.31-1.58)	<.001	1.44 (1.31-1.58)	<.001

Teacher-reported peer victimization						
Step 2 : Teacher-reported peer victimization	1.42 (1.29-1.56)	<.001	1.42 (1.29-1.56)	<.001	1.43 (1.31-1.58)	<.001
PRS-depression	1.33 (1.22-1.46)	<.001	1.30 (1.19-1.41)	.003	1.33 (1.22-1.46)	.001
Step 3: interaction PRS-depression*Teacher-reported peer victimization interaction	1.01 (0.96-1.06)	.849	1.00 (0.94-1.05)	.935	0.99 (0.94-1.04)	.798

Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998–2015), © Gouvernement du Québec, Institut de la Statistique du Québec

Max N based on data available for PRS-depression and suicidal ideation, n=728

The residual score for PRS-depression, with p-value<1 threshold, was used and included all 10 principal components

Models adjusted for sex

From Chapter 2 to Chapter 3

In Chapter 2, we reported that having a genetic vulnerability to depression did not influence the association between peer victimization and depressive symptoms. In the published manuscript we did not include additional analyses with suicidal ideation. They are reported in the above section "**2.12. Supplementary Analyses**". Patterns of finding were similar; both depressive symptoms and suicidal ideation at 15-17 years were predicted by self- and teacher-reported peer victimization, beyond PRS-depression. PRS-depression predicted both depressive symptoms and suicidal ideation. However, no interaction was found between peer victimization (self- or teacher-reported) and PRS-depression in predicting depressive symptoms or suicidal ideation. In this chapter, we will investigate potential underlying mechanisms in the association between peer victimization, depressive symptoms, and suicidal ideation. More specifically we will test whether several epigenetic biomarkers mediate the association between peer victimization depressive symptoms, and suicidal ideation. We hypothesize that epigenetic aging (Horvath1, Horvath2, PedBE clocks), epigenetic pace of aging (DunedinPACE), and Epistress will associate to childhood peer victimization, depressive symptoms, and suicidal ideation. See section "Epigenetic Mediation" in the Background for study rationale.

CHAPTER 3: EPIGENETIC BIOMARKERS AND THEIR ASSOCIATIONS WITH PEER VICTIMIZATION, DEPRESSIVE SYMPTOMS, AND SUICIDAL IDEATION IN ADOLESCENCE AND ADULTHOOD: A STUDY OF TWO-POPULATION-BASED SAMPLES

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3.1. Title Page

Associations between epigenetic aging and childhood peer victimization, depression, and suicidal ideation in adolescence and adulthood: a study of two population-based samples

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3.2. Abstract

Background: Prior studies indicate that peer victimization (including bullying) is associated with higher risk for depression and suicidal ideation across the life course. However, neurophysiological and molecular mechanisms underlying these associations remain unclear. This two-cohort study proposes to test whether epigenetic aging and pace of aging, as well as a DNA methylation marker of responsive to glucocorticoids, are associated to childhood peer victimization and later depressive symptoms, or suicidal ideation.

Methods: Cohort 1: Epigenome-wide DNA methylation was measured in saliva collected at 10 years (EPIC array) in a subsample of the Quebec Longitudinal Study of Child Development (QLSCD, n=149 participants), with self-reported peer victimization at 6-8 years, depressive symptoms (mean symptoms, and dichotomized top 30% symptoms) and suicidal ideation at 15-17 years. Cohort 2: Epigenome-wide DNA methylation was measured in blood collected at 45 years (EPIC array) in a subsample of the 1958 British Birth cohort (1958BBC, n=238 participants) with information on mother-reported peer victimization at 7-11 years and self-reported depressive symptoms at 50 years and suicidal ideation at 45 years. Five epigenetic indices were derived: three indicators of epigenetic aging [Horvath's pan-tissue (Horvath1), Horvath's Skin-and-Blood (Horvath2), Pediatric-Buccal-Epigenetic age (PedBE)], pace of aging (DunedinPACE) and stress response reactivity (Epistress).

Results: Peer victimization was not associated with the epigenetic indices in either cohort. In the QLSCD, higher PedBE epigenetic aging and a slower pace of aging as measured by DunedinPACE predicted higher depressive symptoms scores. In contrast, neither the Horvath1 or Horvath2 epigenetic age estimates nor the Epistress score were associated with depressive symptoms in either cohort, and none of the epigenetic indices predicted suicidal ideation.

Conclusion: The findings are consistent with epigenome-wide and candidate gene studies suggesting that these epigenetic indices did not relate to peer victimization, challenging the hypothesis cumulative epigenetic aging indices could translate vulnerability to depressive symptoms and suicidal ideation following peer victimization. Since some indices of epigenetic aging and pace of aging signaled higher risk for depressive symptoms, future studies should pursue this investigation to further evaluate the robustness and generalization of these preliminary findings.

Keywords : Epigenetic aging, DNA methylation, Early-life stress, Peer victimization, Depressive symptoms, Suicidal ideation, Longitudinal studies, Adolescence.

3.3. Introduction

Peer victimization has been defined as intentional "harm caused by peers acting outside the norms of appropriate conduct" (Finkelhor et al., 2012), and includes bullying which is further characterized by a recurrence of these experiences over time and an imbalance of power between the perpetrator(s) and the victim (Gredler & Olweus, 1993). Peer victimization is a known risk factor for a range of mental health problems across the life course (Arseneault, 2018; Moore et al., 2017; Oncioiu et al., 2021; Rijlaarsdam, Cecil, Buil, Van Lier, & Barker, 2021). To illustrate, experiencing peer victimization in childhood has been longitudinally associated with higher risks of depressive symptoms and severe depression in adolescence (Bowes et al., 2015b; Geoffroy et al., 2018a), which can persist into adulthood (Klomek, Sourander, & Elonheimo, 2015a; Moore et al., 2017; Takizawa et al., 2014). Furthermore, peer victimization has been associated with suicidal ideation and even suicide mortality (Geoffroy, Arseneault, et al., 2022; Geoffroy et al., 2016; Holt et al., 2015; Klomek et al., 2015a; Takizawa et al., 2014). Although the association between peer victimization, depressive symptoms, and suicidal ideation is empirically supported by multiple longitudinal studies, the underlying biological mechanisms are still poorly understood.

Existing mechanistic studies have followed many research avenues, including genetics, neuroscience, psychoneuroendocrinology, and molecular approaches to explain how the adverse experience of peer victimization increases risk for subsequent mental health problems (Vaillancourt et al., 2013). At the forefront of this search to uncover the early roots of mental health disparities are the neurophysiological systems that translate (internal and external) threats into stress biological responses, such as the Hypothalamic Pituitary Adrenal axis (HPA) and its main glucocorticoid hormone, cortisol (Gunnar, 2020; Shonkoff, 2010). For example, prolonged cortisol secretion, triggered by repeated verbal and physical abuses perpetrated by peers, is proposed to

affect the activity and neurocircuitry of brain regions rich in glucocorticoid and mineralocorticoid receptors over time, and to have deleterious effects on a myriad of neurobiological processes, including the immune and inflammatory systems (Heim & Binder, 2012; Shonkoff, 2010).

The molecular mechanisms by which early adverse experiences such as verbal and physical abuse may become embedded could in part be due to epigenetic modifications (Hertzman, 2013; Lang et al., 2020; Lutz, Almeida, M Fiori, & Turecki, 2015; B. S. McEwen, 2017). Epigenetics refers to non-genetic mechanisms that can regulate gene expression in DNA. DNA methylation is one type of epigenetic mechanism characterized by the addition of a methyl group to a cytosine nucleotide, usually one that is paired with guanine (CpG). Although there is evidence that DNA methylation may be associated with early adversity and perhaps more so with depression and suicide ideation, few studies have investigated its association with peer victimization, and those who did have reported inconsistent findings. We further describe these gaps and how the present study may contribute to explore them.

Firstly, epigenetic mechanisms, especially DNA methylation, have been extensively studied in relation to early adversity, such as perinatal stress and childhood maltreatment (Bick et al., 2012; Cecil, Zhang, & Nolte, 2020; Parade et al., 2021; Provenzi, Brambilla, Scotto di Minico, Montirosso, & Borgatti, 2020; Suderman et al., 2014; Szyf, 2013; Turecki & Meaney, 2016). However, much less is known about the association between DNA methylation and peer victimization, which can induce a strong stress response. One study found increased methylation of the serotonin transporter (*5-HTT*) gene in bullied twins (Ouellet-Morin et al., 2013), another study by Efstathopoulos et al. (2018) found higher methylation in the glucocorticoid receptor (*NR3C1*) gene. However, these early studies targeted single genes. In the largest analysis carried

out to date, Marzi et al. (2018) tested associations of peer victimization with DNA methylation in twin pairs (N= 2,232) at CpG sites located across the genome and within candidate genes, including *5-HTT* and *NR3C1* genes. No DNA methylation differences between victimized children or adolescents and their non-victimized counterparts were uncovered (Marzi et al., 2018). Another two-cohort study (total N= 1,352) investigated changes in DNA methylation across the genome at two timepoints; 6 and 10 years in the first cohort, and 7.5 and 17 years in the second cohort (Mulder et al., 2020). A weak signal for difference was uncovered at only one CpG site.

This study proposes a complementary approach to previous candidate gene and genome-wide studies by investigating differences in DNA methylation indices encompassing DNA methylation levels at multiple CpG sites thought to be relevant to either the experience of peer victimization, or depressive symptoms, or suicidal ideation. As others have done before in the context of childhood adverse experiences, we argue that a cumulative index grouping specific CpG sites known to be responsive glucocorticoids, hypothesized to indicate the "wear and tear" of aging, or the accelerated pace of aging may help to uncover stronger and more robust epigenetic effects of peer victimization. Importantly, we could also use these cumulative indices to test if DNA methylation partly mediates the association between peer victimization and depressive symptoms, and suicidal ideation. The use of a cumulative index may overcome some limitations of prior approaches. Namely, epigenome-wide approaches can be limited by the fact that individual CpG sites with small effects may not reach epigenome-wide significance or be hard to replicate. At the opposite end of the spectrum, although candidate gene approaches have greater statistical power to detect associations, they may only provide partial evidence when a collection of genes may be involved.

Cumulative epigenetic indicators of biological aging, often referred to as epigenetic age or clocks, have been created to capture the accumulation of changes in DNA methylation linked to aging (Ryan, 2021). One of the most widely known epigenetic age is Horvath's pan-tissue clock (Horvath1) which is known to strongly correlate with chronological age and was derived from an array of tissues, including blood and saliva (Horvath, 2013). The Horvath1 has been associated with adverse childhood experiences including abuse and exposure to violence in samples composed of children and adolescent populations (Sumner et al., 2019), and childhood trauma in adults (Jansen et al., 2021). Notably, only one study has examined whether peer victimization between 0-14 years predicted differences in Horvath1 at 17 years, but no association was found (Tang et al., 2020). More recent indicators of epigenetic aging, such as the Horvath's skin-and-blood clock (Horvath2) (Horvath et al., 2018) and the Pediatric-Buccal-Epigenetic clock (PedBE) have shown to better predict chronological age using DNA methylation data derived from skin, blood, and buccal epithelial cells (L. M. McEwen et al., 2020). In addition to epigenetic age, which is trained to predict chronological age, epigenetic pace of aging has been derived to predict how fast epigenetic aging is occurring. Specifically, the Dunedin Pace of Aging Calculated from the Epigenome (DunedinPACE) was derived based on blood samples from 26-45 year-old participants (Belsky et al., 2022), and its predecessor, the Dunedin Pace of Aging methylation (DunedinPoAm) was based on smaller age range of 28-38 year-old participants (Belsky et al., 2020). Both indices have been linked to adverse childhood experiences, including poverty (Belsky et al., 2022; McCrory et al., 2022; Raffington, Belsky, Malanchini, Tucker-Drob, & Harden, 2020) and experiences of polyvictimization; e.g., child abuse and neglect, peer victimization (Bourassa et al., 2021). However, no study has yet tested if specific types of adverse childhood experiences, such as peer victimization, predict the pace of aging. Finally, other epigenetic biomarkers build on

surrogate measures of sensitivity to chemical or hormonal exposures, including glucocorticoids. Notably, Provençal et al. (2020) have created a score (the Epistress) that includes 24 CpG sites that are sensitive to glucocorticoids. Since peer victimization has been repeatedly associated to both salivary cortisol stress response and cumulative hair cortisol levels (Isabelle Ouellet-Morin et al., 2011; Ouellet-Morin et al., 2021), the Epistress score represents another cumulative epigenetic index of interest. However, to date, the Epistress score has never been examined in relation to peer victimization. The present study aims to fill this gap in knowledge.

A few studies have nevertheless explored associations between epigenetic age with depressive symptoms and suicidal ideation. Specifically, Horvath1 was associated with depressive symptoms in childhood (Sumner et al., 2019; Tollenaar et al., 2021) and in adulthood in some studies (Han et al., 2018; Whalley et al., 2017), but not all (Beydoun et al., 2019; Klopack, Crimmins, Cole, Seeman, & Carroll, 2022; Oblak, van der Zaag, Higgins-Chen, Levine, & Boks, 2021). To our knowledge, Horvath2 has not been examined with depressive symptoms. Only a few studies have investigated its association with internalizing symptoms (including depression and/or anxiety) with the PedBE. One study has found higher PedBE age among children with internalizing disorder (depression and/or anxiety disorders) (Dammering et al., 2021), although two others reported non-significant findings in similar phenotypes during childhood (Manczak, Scott, & Millwood, 2021; McGill et al., 2022). In regards to suicidal ideation, only one study, conducted in a clinical sample of patients with schizophrenia, did not find an association with Horvath1 (Dada et al., 2020). Finally, neither the DunedinPACE nor the Epistress score have been examined in relation to depressive symptoms or suicidal ideation. However, DunedinPACE's predecessor, the DunedinPoAm, had been previously linked to concurrent depression in adults aged between 50 and 87 years (McCrory et al., 2022). In sum, existing evidence on whether

cumulative epigenetic indices, such as epigenetic indicators of aging, pace of aging, or the Epistress score, points to some inconsistent association with peer victimization, depressive symptoms, or suicidal ideation, but this investigation remains new. To the best of our knowledge none have formally tested whether these indices partly mediate the associations between peer victimization and depressive symptoms, or suicidal ideation. Even though many theoretical frameworks propose such a causal pathway (Heim & Binder, 2012; Vaillancourt et al., 2013).

The main objective of this study was to test longitudinal associations between childhood peer victimization, depressive, and suicidal ideation in adolescence and adulthood, with cumulative epigenetic indices measured in childhood and adulthood, using the Quebec Longitudinal Study of Child Development (QLSCD) cohort and the 1958 British Birth (1958BBC) cohort. The Horvath2 and PedBE were specifically selected because the QLSCD included DNA derived from saliva samples, whereas the 1958BBC had blood-derived DNA. Using two different cohorts with different tissues measured at distinct developmental periods (10 years, vs 45 years) may help to unravel robust signals detected across both tissues and age, or potentially identify distinct mechanisms. This study specifically tests whether: 1) childhood peer victimization was associated with epigenetic aging (Horvath1, Horvath2, & PedBE), accelerated pace of aging (DunedinPACE) and the Epistress score; 2) each epigenetic index was associated with depressive symptoms and suicidal ideation measured in adolescence and mid-adulthood; and 3) any of the epigenetic indices partly mediated the association between peer victimization, depressive symptoms, and suicidal ideation.

3.4. Methods

3.4.1. Participants

This study uses datasets from two cohorts (**Supplemental Figure 1**): The QLSCD and the 1958BBC (also known as The National Child Development Study). The QLSCD is an ongoing prospective birth cohort of 2,120 participants born in the Canadian province of Québec in 1997-1998, managed by *Institut de la Statistique du Québec*. Further details about the cohort can be found online (https://jesuisjeserai-stat-gouv-qc-ca) and in the cohort profile (Orri et al., 2021). The Ethics Committee of the *Institut de la Statistique du Québec,* and the Research Ethics Board of the CHU Sainte-Justine Research Center approved each phase of the study, and informed consent was obtained for all participants. The QLSCD study sample and analyses included 149 individuals with data on DNA methylation, peer victimization at 6-8 years, depressive symptoms, and suicidal ideation at 15-17 years (see **DNA methylation indices** for more information on participant number).

The 1958BBC is an ongoing longitudinal birth cohort including an initial sample of 17,416 participants born in England, Scotland, and Wales during 1 week in March 1958. The final sample of 18,558 participants also included immigrants born in the same week but added in subsequent follow-ups in childhood and adolescence. The cohort profile (Power & Elliott, 2006) and the Centre for Longitudinal Studies at the University College London website contain more information (http://www.cls.ioe.ac.uk). Ethical approval for the 45-year survey was given by the South East Multi-Centre Research Ethics Committee (ref. 01/01/44) and consent was obtained for all participants. The current study included 238 individuals from the 1958BBC with information on DNA methylation at 45 years, peer victimization at 7-11 years, and suicidal ideation at 45 years. Study analyses with depressive symptoms scores at 50 years in the 1958BBC included 226 participants due to missing data on depressive symptoms scores for 12 participants.

There were no significant differences on key sociodemographic variables between participants included in our analyses and the remainder of each respective cohort. However, the QLSCD study participants who provided DNA methylation data at age 10 years reported lower depressive symptoms later in adolescence compared to non-included participants. Similarly, the participants included in our analyses from both cohorts reported less suicidal ideation compared to those who were not included.

3.4.2. DNA methylation indices

QLSCD: 365 saliva samples at 10 years were collected using the Oragene DNA sample collection kit (DNA Genotek). DNA was extracted and used for genotyping purposes, which reduced the remaining DNA available for DNA methylation quantification. 154 DNA samples were selected for quantification using absorbance (Nanodrop) and fluorometry (Pico green), and bisulfite-conversion was performed with the EZ-96 DNA Methylation Kit (Zymo Research, cat. No. D5004). After excluding 2 missing, 1 duplicate, and 1 poor quality DNA samples, 150 DNA samples were run on the Infinium Methylation EPIC BeadChip Array (Illumina); a methylation array that allows for quantitative interrogation of over 850,000 CpG methylation sites across the genome. Beta values, ranging from 0 to 1, were extracted, processed, and normalized using R software (version 3.6.2). Noob normalization was performed on all samples to calculate the epigenetic aging indicators (described below) following quality control steps. Functional normalization with the first 9 principal components of our control matrix was performed without background correction for the Epistress score. Variance introduced into our data by the array (ex. Beadchip position/batch, etc.) following functional normalization (used for Epistress scores only) was removed with ComBAT using the R package sva. All cross-hybridizing and cross-reactive probes were removed. Probes with a detection P-value greater than 0.001 in 25% of samples were

removed (cut-offs according to detection of Y chromosome probes in female samples). Cell type deconvolution (Epithelial cells, Fibroblasts, B cells, Natural Killer cells, CD4 T cells, CD8 T cells, Monocytes, Neutrophils, Eosinophils) was performed with the R package EpiDISH. A principal component analysis was then performed on all cell types and the resulting two principal components were subsequently statistically controlled for in all epigenetic indices through residuals. One participant was excluded from further analyses because they had a very high unadjusted epigenetic aging indicators; Horvath2 and Horvath1 age > 10 standard deviations (SD) above the mean. The final sample thus included 149 participants.

1958BBC: The biomedical follow-up at 45 years included 9,426 participants with blood collected. Genomic DNA samples were collected from blood in 238 participants at age 45. DNA methylation was measured using the Infinium Methylation EPIC BeadChip Array. Quality of raw microarray data was assessed using standard procedures for detecting outliers, dye bias, signal noise and technical artifacts. After preprocessing (subtracting background signal and removing dye bias), the DNA methylation data was normalized using functional normalization (Fortin et al., 2014) to subsequently calculate the Epistress score (described below). Noob normalization was performed prior to calculating the epigenetic aging and pace of aging indicators (described below). Cell type deconvolution (B cells, CD4 T cells, CD8 T cells, Eosinophils, Monocytes, Neutrophils, Natural Killer cells) was performed with the Houseman method (Houseman et al., 2012). A principal component analysis was then conducted on all cell types, and the resulting three principal components were subsequently statistically controlled for in all epigenetic indices through residuals.

Epigenetic aging and DunedinPACE

We used R software (version 4.1.0) to calculate epigenetic aging indicators for both cohorts. Horvath1 utilizes 353 CpGs selected through elastic net regression in samples aged 0-100 (Horvath, 2013), the Horvath2 includes 391 CpGs (60 sites overlapping with Horvath1) selected through elastic net regression with greater tissue diversity in samples aged 0-90 years (Horvath et al., 2018), and the PedBE with 94 CpGs selected through elastic net regression (1 site overlapping with the Horvath1 and Horvath2, and 11 more with the Horvath2), was optimized for pediatric cohorts (0-20 years) (L. M. McEwen et al., 2020). The Horvath2 was a key benchmark for comparison because it performs well in both saliva and blood samples. The PedBE was of interest because we targeted childhood experiences, especially for the QLSCD cohort in which the DNA was collected at 10 years. Epigenetic aging indicators (unadjusted scores) were derived using R codes supplied by the authors for each clock in each cohort separately. The DunedinPACE was computed from DNA methylation data using the publicly available scripts (https://github.com/danbelsky/DunedinPACE).

Epistress

The Epistress score was derived from DNA methylation data as previously described by Provençal et al. (2020). Briefly, a set of 496 CpG were identified as cross-tissue glucocorticoid sensitive sites following exposure of hippocampal stem cells and whole blood with a synthetic glucocorticoid (dexamethasone). A further subset (24 CpGs) were selected using elastic net regression to create the Epistress score with corresponding weights reflecting the magnitude of change in DNA methylation following dexamethasone treatment (Provençal et al., 2020). One CpG of the original 24 CpGs included in the Epistress score did not pass quality tests of control and was thus substituted for the next most sensitive CpG. The weighted Epistress score was derived for each cohort in R.

Epigenetic index residuals

Residuals were calculated for each epigenetic index to account for potential confounders.

QLSCD: The residual scores of each epigenetic index included 1) decimal age in years at the 10-year follow-up, 2) principal components of cell heterogeneity, and 3) the most correlated principal components associated to genetic ancestry with epigenetics indices (i.e., the first three), and 4) Body Mass Index (BMI) at 10 years. PedBE and Horvath2 unadjusted scores for one participant were winsorized (scores beyond 3 SD and replaced by the closest score within the ±3 SD threshold). All residual scores were standardized into z-scores.

1958BBC: The residual scores of each epigenetic index included 1) decimal age in years at the 45-year follow-up, 2) principal components of cell heterogeneity, 3) smoking status at 42 years (0=never, 1=occasional or ex-smoker, 2=current smoker), and 4) BMI at 45 years. PedBE and Epistress unadjusted scores were winsorized for five participants. All residual scores were standardized by calculating z-scores.

3.4.3. Peer victimization

QLSCD*:* Peer victimization was self-reported at 6, 7, and 8 years using a 7-item modified version of the Self-reported Peer Victimization Scale (Ladd & Kochenderfer-Ladd, 2002). Participants reported how often (0=never, 1=once or twice, 2=more often) they experienced physical (i.e., “pushed, hit or kicked”), verbal (i.e., “called names, insulted, said mean things to you,” “teased you in a mean way”), relational peer victimization (i.e., “did not let you play with or be part of his or her group,” “said bad things about you to other children”), and property attacks (i.e., “took away things that belong to you without asking your permission and without giving them back to you”, “purposely broke something that is yours”) since the beginning of the school year.

Cronbach's alpha was 0.73 at 6 years, 0.76 at 7 years, and 0.74 at 8 years. Peer victimization at 6-8 years was calculated as the mean score at each time point and then averaged. Peer victimization between each time point were moderately correlated (*r*s range from .26 to .51, $p<.001$).

1958BBC*:* Peer victimization was reported by mothers when participants were aged 7 and 11 years. At each time point, mothers were asked if their child was "bullied by other children" (0=never, 1=sometimes, or 2=frequently). Peer victimization at 7-11 years was calculated as the mean score. Peer victimization at 7 and 11 years were moderately correlated ($r=.32$ $p<.001$).

Childhood peer victimization scores were standardized into z-scores in each cohort.

3.4.4. Depressive symptoms

QLSCD: Depressive symptoms in the past year were self-reported at 15 and 17 years using 8 items from the Mental Health and Social Inadaptation Assessment (MIA) (Côté et al., 2017; Geoffroy et al., 2018a). The MIA is not a diagnositic tool, but its items reflect symptoms in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition. Participants reported how often (0=never, 1=sometimes, 2=often) they experienced each symptom in the past 12 months**; "**Nothing was fun for me, I wasn't interested in anything", "I felt sad and unhappy", "I lacked energy or felt tired", "I lost interest in things I usually like", "I felt I couldn't do anything well", "I felt I wasn't as good-looking or as smart as other people", "Doing even little things made me feel really tired", "I had trouble thinking clearly". Cronbach's alpha was 0.84 at 15 years and 0.74 at 17 years. Pearson correlations between ages were $r=.495$ ($p<.001$) between 15 and 17 years.

1958BBC: Depressive symptoms in the past 4 weeks were self-reported at 50 years using the emotional well-being scale of the SF-36 (also known as the Mental Health Index- 5 items) (Taft, Karlsson, & Sullivan, 2001; Ware, 2000). Participants rated 5 items on a 6-point scale

ranging from “all” to “none of the time”; “Have you been a very nervous person?”, “Has felt so down in the dumps nothing could cheer you up”, “Have you felt downhearted and low?”, “Have you felt calm and cheerful?”, “Have you been a happy person?”.

In both samples, responses were summed to produce a continuous score of depressive symptoms, which was standardized into Z-scores to ease interpretation. In addition, to explore if these cumulative epigenetic indices better predicted the occurrence of more severe symptoms, participants with elevated depressive symptoms scores in the top 30% were identified. This also facilitated comparison with previous studies that focused on elevated depressive symptoms.

3.4.5. Suicidal ideation

QLSCD: Suicidal ideation frequency was measured by one item; “In the past 12 months, did you ever think about suicide?” and scored 0=never, 1=rarely, 2=fairly often, 3= very often, at 15 or 17 years (13 years data was used for 10 participants with missing information at either age). Participants who indicated having suicidal ideation rarely to very often, at either 15 or 17 years, were coded as yes, while those who answered never at both ages were coded as no.

1958BBC: Suicidal ideation was measured using the depressive ideas subscale of the Clinical Interview Schedule-Revised (Lewis, Pelosi, Araya, & Dunn, 1992), as previously investigated by Stansfeld et al. (2017). The subscale evaluates 5 symptoms in the past 7 days by summing affirmative answers (0=no, 1=yes) to the following questions: “Have you on at least one occasion felt guilty or blamed yourself when it hasn't been your fault?”, “During the past week have you been feeling you are not as good as other people?”, “During the past week have you felt hopeless about your future?”; “In the past week have you felt that life isn't worth living?”, “In the past week have you thought of killing yourself?”. This five-point scale was dichotomized (⩾2 =

suicidal ideation) to indicate a clinically significant symptoms based on the CIS-R scoring protocols (Lewis et al., 1992).

3.4.6. Covariables

QLSCD: Family socioeconomic status at 5 months was an aggregate of annual gross income, parental education level, and occupational prestige, standardized into z-scores (Willms & Shields, 1996). Sex and birthweight (grams) information were obtained from medical records. Height and weight were collected at 10 years, and BMI was derived from these variables.

1958BBC*:* Socioeconomic status was based on the father's occupation at birth (imputed at 7 years if missing) using the Registrar General's Social classification, grouped as I or II (professional/managerial), III-NM (skilled non-manual), III-M (skilled manual) and IV and V (semi-skilled and unskilled manual, including single mother households). Information on sex and birthweight (ounces) was collected at birth from medical records. Seven participants had missing information on birthweight (2.9% of the sample). We replaced these missing values with the mean birthweight of participants with the same gestational age (in days). BMI was obtained at 45 years using weights and heights measured by a nurse.

3.4.7. Statistical Analyses

First, we examined this possibly sequentially by examining associations between peer victimization (QLSCD: 6-8 years; 1958BBC: 7-11 years) and depressive symptoms (QLSCD: 15-17 years; 1958BBC: 50 years), or suicidal ideation (QLSCD: 15-17 years; 1958BBC: 45 years). Second, we tested associations between the epigenetic indices (residuals) and peer victimization, depressive symptoms, or suicidal ideation in a series of linear and logistic regressions according to the continuous and dichotomous variables. In each case, two regression models were conducted: Model 1 was unadjusted, whereas Model 2 adjusted for sex, socioeconomic status, and birthweight.

To avoid unnecessary tests and thus minimize the likelihood of identifying false positives, the mediation analyses were only conducted for epigenetic indices with significant associations with both peer victimization and depressive symptoms or suicidal ideation.

3.5. Results

3.5.1. Descriptive of the epigenetic indices

Table 3.1 describes the unadjusted scores of each epigenetic aging, pace of aging and the Epistress score. In the QLSCD, the mean chronological age was 10.47 years (SD±0.35, range=9.7-11.3 years). The unadjusted Horvath1 and PedBE epigenetic age accurately estimated the chronological age within the appropriate range (9.83 years (SD±1.49), 9.70 years (SD±0.78) and respectively). The Horvath2 slightly underestimated chronological age to an average of 7.04 years (SD±0.82). The mean age in the 1958BBC was 45.13 years (SD±0.37). Horvath1 epigenetic mean age was 41.72(SD±4.86), which was close to the mean chronological age. While the Horvath2 overestimated by approximatively 14 years the mean chronological age (59.16 years, SD±3.07), the PedBE greatly underestimated chronological age by about 35 years (9.91 years (SD±0.94)).

Table 3.2 presents the correlations between the three epigenetic indicators of aging, pace of aging (DunedinPACE) and the Epistress score. In the QLSCD, the Horvath1 was correlated with the other two epigenetic age estimates, Horvath2 and PedBE (r=.310, p<.001; r=.271, p<.001, respectively). The PedBE was also correlated to the Horvath2 (r=.291, p<.001). The DunedinPACE was correlated to Horvath1 and the Epistress score (r=-.175, p=.032; r=-.220, p=.007, respectively). Lastly, the Epistress inversely correlated with all epigenetic indices (r=-.165, p=.045; r=-.178, p=.030; r=-.220, p=.007, respectively), except for Horvath1 to which it was not significantly correlated. In the 1958BBC, Horvath1 correlated with Horvath2 (r=.415, p<.001). The PedBE only correlated with the Horvath2 (r=.247, p<.001). The Epistress score only

correlated with Horvath1 (*r*=.165, *p*=.011). DunedinPACE did not correlate with any of the other epigenetic indices. These patterns of correlation indicate that while some overlaps exist between the cumulative epigenetic indices, due in part to common CpG sites, they also captured distinct variance, hence pointing to their complementary value. Since the PedBE grossly underestimated chronological age, that the expected correlation with Horvath1 was not present, that this epigenetic aging indicator has not been optimized for use in DNA extracted from blood samples and was initially derived for youth aged 0-20 years, we decided to exclude this index from further analyses in the 1958BBC.

3.5.2. Associations between peer victimization and depressive symptoms

Linear and logistic regression analyses indicated that, in the QLSCD cohort, childhood peer victimization (6-8 years) predicted depressive symptoms (15-17 years) whether the depression score was distributed continuously (beta=.256, SE=.075, *p*=<.001) or dichotomously (OR=1.78, 95% confidence interval (CI): 1.46-2.16, *p*=.004). In the 1958BBC, peer victimization (7-11 years) predicted depressive symptoms at 50 years, according to both the continuous (beta=.151, SE=.066, *p*=.022) and dichotomous scores (OR=1.35, 95% CI: 1.17-1.56, *p*=.033).

3.5.3. Associations between the epigenetic indices and peer victimization or depressive symptoms

Childhood peer victimization was not associated with any of the epigenetic indices in both models in the QLSCD or the 1958BBC (**Table 3.3**). However, in both cohorts, significant associations were detected between epigenetic indices and depressive symptoms. In the QLSCD, PedBE derived from DNA collected at age 10 predicted higher depressive symptoms at age 17 (beta=.186, SE=.023, *p*=.023) in the unadjusted model, but this association was weakened when additional covariates sex, birthweight, and socioeconomic status were included in the model

(beta=.139, SE=.076, *p*=.076) (**Table 3.4**). This association was, however, observed for the top 30% depressive symptoms in both adjusted and unadjusted models (OR=1.65, 95% CI: 1.36-2.00, *p*=.010; OR=1.55, 95% CI: 1.27-1.89, *p*=.026, respectively). Epigenetic pace of aging (DunedinPACE) was inversely associated with depressive symptoms, and a lower risk of reporting top 30% levels of depressive symptoms at the end of adolescence in this cohort (beta=-.168, SE=.077, *p*=.030; OR=0.65, 95% CI: 0.53-0.79, *p*=.034, respectively, in adjusted models).

In the 1958BBC, only the DunedinPACE positively predicted higher levels of depressive symptoms and a higher risk of top 30% depressive symptoms in unadjusted models (beta=-.147, SE=.066, *p*=.028; OR=1.34, 95% CI: 1.15-1.56, *p*=.047, respectively). Epigenetic age estimates derived from the Horvath1 or Horvath2, and the Epistress score did not predict depressive symptoms in either the QLSCD or 1958BBC cohort.

3.5.4. Associations between peer victimization, suicidal ideation, and epigenetic indices

In the QLSCD, each 1-SD increase in peer victimization at 6-8 years was associated to a 1.5 increased risk of suicidal ideation at 15-17 years in fully adjusted models which controlled for sex, socioeconomic status, and birthweight (OR=1.57, 95% CI: 1.30-1.90, *p*=.016). In the 1958BBC, a 1-SD increase in peer victimization at 7-11 years was associated with a 1.7 increased risk of suicidal ideation at 45 years in the fully adjusted models (OR=1.66, 95% CI: 1.30-2.11). No association was detected between any of the epigenetic indices and suicidal ideation, in either cohort (**Table 3.5**).

Since no associations were found between the epigenetic indices and childhood peer victimization, as well as depressive symptoms or suicidal ideation, mediation analyses were not conducted.

3.6. Discussion

This two-cohort study (i.e., QLSCD and 1958BBC) explored for the first time the role of three epigenetic indicators of aging (Horvath1, Horvath2 and PedBE), epigenetic pace of aging (DunedinPACE) and a cumulative epigenetic index capturing sensitivity to glucocorticoids (Epistress score) in association with childhood peer victimization, depressive symptoms, and suicidal ideation. The consistency of our results was showcased by three consistent patterns of findings uncovered in these two independent cohorts. First, childhood peer victimization predicted higher levels of depressive symptoms and risk of suicidal ideation in both adolescence (QLSCD) and adulthood (1958BBC). Second, childhood peer victimization was not associated with any of the epigenetic indicators of aging, pace of aging (DunedinPACE), or the Epistress score, at both 10 years (QLSCD) and 45 years (1958BBC). Third, none of the epigenetic aging indicators, the DunedinPACE, or the Epistress score predicted suicidal ideation in adolescence or adulthood. These similar observations are noteworthy because 1) they were tested in adolescence and adulthood, 2) they rely on prospectively collected data offering a stronger indication of the temporal sequence of events, 3) they emerged in samples composed of participants from distinct generations (participants born in 1997/1998 and 1958), who lived in different countries (Canada and the United Kingdom), and for whom different informants had reported peer victimization (self- and mother-reported experiences in the QLSCD and 1958BBC, respectively).

Nonetheless, some inconsistent findings were also detected, which may also point to other key differences between samples. Namely, the two cohorts used different tissues (blood in the 1958BBC; saliva in the QLSCD) collected in childhood vs adulthood (45 years in the 1958BBC; 10 years in the QLSCD) to ascertain DNA methylation and derive the epigenetic indices. Furthermore, the PedBE was associated with depressive symptomology in the QLSCD, but we

elected that the association could not be reliably tested in the 1958BBC due to concerns over the validity of the epigenetic age estimate predicting the chronological age, and because it did not covary with another epigenetic indicator of aging. Furthermore, this index was originally derived in saliva samples and younger samples (less than 20 years of age). Our findings thus contrasted with the PedBE shown to correlate with chronological age in youth using blood samples, as well as in adult saliva samples (L. M. McEwen et al., 2020). Our PedBE estimates suggest that it is not optimized for blood samples later in life. It is also important to note that the Epistress score has been validated in blood samples, but not in saliva samples (Provençal et al., 2020). Thus, further studies would be needed to understand whether this index is suitable for use in saliva samples and beyond the perinatal period. That is, it is important to account for differences between cohorts (age and tissue-type) as putative factors underlying inconsistent results between the cohorts.

3.6.1. Associations between epigenetic indices and peer victimization

We did not detect associations between the Horvath1 (10 years) and our averaged self-reported measures of peer victimization (6-8 years), which is consistent with the finding reported by the only prior study that had tested the association between bullying experienced before the age of 14 and this index measured from DNA collected at 17 years (Tang et al., 2020). Our study extended this search into adulthood (1958BBC), and according to other indicators of epigenetic aging (PedBE in the QLSCD, and Horvath2 in both cohorts). These null findings are in line with some studies focusing more generally on early childhood adversity, although the evidence is also inconsistent overall. For example, while some studies did not observe associations between cumulative adversity and epigenetic age estimates (Hamlat, Prather, Horvath, Belsky, & Epel, 2021; Marini et al., 2020; Wolf et al., 2018), others have reported significant associations with the epigenetic aging indicators (Sumner et al., 2019; Tang et al., 2020). The epigenetic indicator of

pace of aging (DunedinPACE) was not associated with peer victimization in the QLSCD or the 1958. Prior work had linked faster epigenetic pace of aging with polyvictimization (Bourassa et al., 2021), however it is possible that peer victimization alone does not predict faster aging.

Our inclusion of the Epistress score known to be sensitive to stress, also failed to uncover any new evidence for an association with peer victimization. More generally, this study reminds us of the difficulty of replicating earlier findings related to peer victimization on DNA methylation differences in specific CpG sites in the *SERT* and *NR3C1* genes (Efstathopoulos et al., 2018; Ouellet-Morin et al., 2013) or dispersed across the genome (Marzi et al., 2018; Mulder et al., 2020). Such negative findings remain important as they contribute to expand on this scarce literature and reflect on the complexity of identifying the molecular pathways transducing social adversity to poorer later health. Future studies with greater statistical power could also investigate these associations into their biological (genes, other epigenetic biomarkers), psychological (e.g., emotion regulation, coping strategies) and social contexts (e.g., social support, social norms discouraging violence).

3.6.2. Associations between epigenetic indices, depressive symptoms, and suicidal ideation

The Horvath1 was not associated with depressive symptoms in adolescence or adulthood. This finding is somewhat inconsistent with the previous cross-sectional and longitudinal associations reported between this epigenetic aging indicator derived from DNA collected at 6 years and internalizing symptoms at ages 6, 7, and 10 years (Tollenaar et al., 2021). However, there are differences in study design that could explain the apparent inconsistency. First, internalizing problems include depression as well as anxiety symptomatology, thus it is unclear whether the association with Horvath1 would be linked to the comorbid presence of both anxiety and depression symptomatology or their severity. Secondly, symptoms were measured in childhood

while we measured depression in mid to late adolescence when these symptoms are more common (Maughan, Collishaw, & Stringaris, 2013). This difference in the timing of symptom assessment may have contributed to differences across studies. Of note, although our association were not significant, Horvath1 was nevertheless associated with a risk of reporting top 30% depressive symptoms scores at trend level in the QLSCD (p=0.08). Lastly, one study found that the Horvath1 was cross-sectionally associated with depressive symptoms in youth aged between 8-16 years (Sumner et al., 2019), using similar control variables to our study. Our study however was longitudinal rather than cross-sectional since epigenetic aging estimates were calculated from DNA methylation measured several years before symptoms. It is possible that cross-sectional study captured transient, concurrent effects that lessen over time. More studies with similar designs will help compare and further understand differential findings. Alternatively, we did find that the PedBE predicted elevated depressive symptoms in adolescence (QLSCD). Our finding is nevertheless inconsistent with a prior study reporting that PedBE at 6 years was not associated with internalizing problems from 6 to 10 years in a community sample (McGill et al., 2022). The presence of a significant association between depressive symptoms and the PedBE, but not the Horvath1 scores, may capture biological mechanisms involved with aging that may be differentially related with depression, in term of subtypes, severity, or persistence. Future studies could further investigate this possibility. Furthermore, DunedinPACE predicted fewer depressive symptoms in adolescence (QLSCD), after accounting for childhood socioeconomic status. The same epigenetic indicator of pace of aging was associated to socioeconomic disadvantage in youth (Raffington et al., 2020) and adulthood (McCrory et al., 2022). We speculate that a slower pace of aging may reflect a delayed development in childhood (or other accounted individual characteristics) which may in turn heighten the risk to develop depressive symptoms in

adolescence. In adulthood, a faster pace of aging was found with depressive symptoms. However, this association weakened after controlling for sex and socioeconomic status to trend level (p=0.07).

For the first time, this study tested the association between the Epistress score and depressive symptoms. Although the Epistress is a novel score, it was thought to be a suitable potential mediator due to prior knowledge on HPA axis reactivity in association to depressive symptoms, and early life stress. However, in our study, the Epistress scores were not associated with neither depression nor peer victimization. Provençal et al. (2020) had reported that lower Epistress scores in newborn cord blood were associated with higher prenatal maternal depression. Associations between the Epistress and depression in individual participants has not been tested before. Overall, prior literature on HPA axis reactivity and depression remains inconsistent, likely due to variations in study design (Hammen, 2015). Further studies are needed to clarify if the Epistress score and depression (or peer victimization) association is more likely to occur at specific periods of life (e.g., perinatal, vs childhood).

Neither epigenetic indicators of aging or pace of aging, nor Epistress score, predicted suicidal ideation in either cohort. Dada et al. (2020) did not find a cross-sectional association between Horvath1 and suicidal ideation in patients with schizophrenia. It is important to note, however, that our measure of suicidal ideation captured a broad phenotype of suicidal ideation which did not specifically capture suicidal ideation as well as behaviors (e.g., attempts); with passive suicidal ideation (without information on plan or intent) in the QLSCD, and depressive ideas (including hopelessness, worthlessness, and thoughts of death) in the 1958BBC. A recent review found that most studies have reported an association between epigenetic changes and suicide attempts, but not ideation (Dada, Qian, et al., 2021), which may partly explain the lack of association in the

present study. Considering the scarcity of studies that examined this association, and the somewhat small size of the cohorts used in the current analysis, it would be premature to dismiss a possible association between epigenetic aging and suicidal ideation.

3.6.3. Study limitations

While this study has many strengths, including the two-cohort study design, there are important limitations to take into consideration. First, information about DNA methylation was available only in subsamples of these cohorts, which precludes generalization to the larger population, and which may have constrained our power to detect associations small effect sizes. Second, DNA was extracted from peripheral tissues which may not reflect mechanisms in the central nervous system involved in the stress response or the onset of depressive symptoms or suicidal ideation. One future avenue to account for the use of peripheral most accessible tissues (e.g., blood, saliva) may be to compute indicators of aging which include CpG sites that are conserved from DNA derived from brain tissues to blood and saliva samples (Grodstein et al., 2021). Third, we did not have information on pubertal timing at 10 years in the QLSCD, which warrants attention since early pubertal onset is linked to epigenetic aging (Hamlat et al., 2021) and pace of aging (Raffington et al., 2020). Fourth, peer victimization was self-reported using 6 items in the QLSCD, while it was measured using a single mother-reported item in the 1958BBC. The use of different raters has been supported by prior studies showing that although mother-reports and self-reports are moderately correlated, they both associated similarly with health outcomes (Shakoor et al., 2011). Additionally, it is possible that our measures of peer victimization did not capture frequent and repeated peer victimization as we averaged scores over several time points. Future studies could investigate whether more severe and persistent experiences of peer victimization relate to cumulative epigenetic indices. Lastly, while indicators of epigenetic aging, pace of aging, and

Epistress may not relate to peer victimization, it is possible that other epigenetic biomarkers and mechanisms may be involved.

3.7. Conclusion

To conclude, no associations were found between peer victimization, suicidal ideation, and the epigenetic indices. Inconsistent findings have been detected between the epigenetic indices and depression. Perhaps one indicator of epigenetic aging alone does not reflect the full complexity of biological aging on a molecular level. One possibility could be to adopt a composite epigenetic indicator approach, as suggested by Jansen et al. (2021), to account for several aging indicators that could cumulatively explain a greater portion of variance than independent CpGs and aging indicators. As research on the association between early adverse social experiences and epigenetic aging is at its infancy further studies are needed to advance our understanding of the biological mechanisms behind adversity and to directly test whether changes in DNA methylation relate to depression and suicidality.

3.8. References

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3.9. Tables

3.9.1. Table 3.1**:** Descriptive statistics of chronological and epigenetic age estimates, DunedinPACE, and Epistress in both cohorts [a]

QLSCD	Chronological age	Horvath1	Horvath2	PedBE	DunedinPACE	Epistress
Mean (±SD)	10.47 (0.35)	9.83 (1.49)	7.04 (0.82)	9.70 (0.78)	1.17 (0.16)	-1.02 (0.22)
Range (min. to max.)	9.7 to 11.3	6.54 to 14.53	5.06 to 9.71	8.25 to 12.09	0.82 to 1.51	-1.58 to -0.58
1958BBC		Horvath1	Horvath2	PedBE	DunedinPACE	Epistress
Mean (±SD)	45.13 (0.37)	41.72 (4.86)	59.16 (3.07)	9.91 (0.94)	1.00 (0.12)	-1.16 (0.28)
Range (min. to max.)	44.53 to 45.93	28.49 to 55.19	50.94 to 67.25	7.21 to 12.52	0.71 to 1.39	-1.80 to -0.50

[a]Unadjusted winsorized epigenetic clocks, DunedinPACE, and Epistress.
QLSCD: Data were compiled from the final master file (1998–2015), © Gouvernement du Québec, Institut de la Statistique du Québec.
Max N based on data available for epigenetic clocks and Epistress (QLSCD: n=149; 1958BBC: n=238).

3.9.2. Table 3.2: Correlation matrix for the epigenetic age estimates, DunedinPACE, and Epistress in both cohorts

QLSCD		Horvath1	Horvath2	PedBE	DunedinPACE	Epistress
Horvath1	Pearson *r* *p*-value	-				
Horvath2	Pearson *r* *p*-value	**.310** **<.001**	-			
PedBE	Pearson *r* *p*-value	**.271** **<.001**	**.291** **<.001**			
DunedinPACE	Pearson *r* *p*-value	**-.175** **.032**	.054 .511	-.095 .251	-	
Epistress	Pearson *r* *p*-value	.032 .701	**-.165** **.045**	**-.178** **.030**	**-.220** **.007**	-
1958BBC		Horvath1	Horvath2	PedBE	DunedinPACE	Epistress
Horvath1	Pearson *r* *p*-value	-		-		
Horvath2	Pearson *r* *p*-value	**.415** **<.001**	-			
PedBE	Pearson *r* *p*-value	-.022 .736	**.247** **<.001**	-		
DunedinPACE	Pearson *r* *p*-value	.033 .611	.022 .738	-.020 .759	-	-
Epistress	Pearson *r* *p*-value	**.165** **.011**	.012 .852	.114 .081	.080 .221	

Notes: Epigenetic index residuals adjusted for principal components for cell type heterogeneity, smoking status at 42 years (1958BBC only), and body mass index (QLSCD: 10 years; 1958BBC: 45 years), and principal components for ancestry (QLSCD only), and chronological age (QLSCD: decimal age at the 10 years data collection; 1958BBC: decimal age at the 45 years data collection). Max N

based on data available for epigenetic clocks, DunedinPACE, and Epistress. (QLSCD: n=149; 1958BBC: n=238). QLSCD: Data were compiled from the final master file (1998–2015), © Gouvernement du Québec, Institut de la Statistique du Québec.

3.9.3. Table 3.3: Linear regressions between epigenetic residuals and peer victimization

QLSCD	Horvath1		Horvath2		PedBE		DunedinPACE		Epistress	
	Beta(SE)	*p*-value	Beta(SE)	*p*-value	Beta(SE)	*p*-value	Beta(SE)	*p*-value	Beta(SE)	*p*-value
Model 1 Peer victimization 6-8y	.012 (.082)	.887	.000 (.082)	.997	-.014 (.082)	.868	.079 (.082)	.340	.007 (.082)	.931
Model 2 Peer victimization 6-8y	.022 (.084)	.792	.022 (.082)	.787	-.004 (.083)	.960	.079 (.083)	.345	.012 (.084)	.888
1958BBC	Horvath1		Horvath2		PedBE		DunedinPACE		Epistress	
	Beta(SE)	*p*-value	Beta(SE)	*p*-value	Beta(SE)	*p*-value	Beta(SE)	*p*-value	Beta(SE)	*p*-value
Model 1 Peer victimization 7-11 y	.013 (.065)	.841	-.077 (.065)	.236	.024 (.065)	.710	.057 (.065)	.379	.045 (.065)	.485
Model 2 Peer victimization 7-11 y	.034 (.067)	.607	-.090 (.066)	.176	.017 (.066)	.803	.057 (.065)	.385	.059 (.067)	.378

Notes: Years (y). Epigenetic residuals adjusted principal components for cell type heterogeneity, smoking status at 42 years (1958BBC only), and body mass index (QLSCD: 10 years; 1958BBC: 45 years), and principal components for ancestry (QLSCD only), and chronological age (QLSCD: decimal age at the 10 years data collection; 1958BBC: decimal age at the 45 years data collection). Max N based on data available for epigenetic clocks, DunedinPACE, and Epistress. (QLSCD: n=149; 1958BBC: n= 238). Model 1 was unadjusted; Model 2 is adjusted for sex, birthweight, and socioeconomic status (QLSCD: at 5 months; 1958BBC: at birth). QLSCD: Data were compiled from the final master file (1998–2015), © Gouvernement du Québec, Institut de la Statistique du Québec.

3.9.4. Table 3.4: Linear and logistical regressions between epigenetic residuals and depression

	QLSCD				1958BBC			
	Depressive symptoms at 15-17y				Depressive symptoms at 50y			
	Continuous (z-scores)		Top 30% (dichotomized)		Continuous (z-scores)		Top 30%(dichotomized)	
	Beta(SE)	*p*-value	OR(95% CI)	*p*-value	Beta(SE)	*p*-value	OR(95% CI)	*p*-value
Model 1 Horvath1	.115 (.082)	.162	1.37 (1.14-1.65)	.086	.016 (.066)	.806	1.03 (0.89-1.19)	.825
Model 2 Horvath1	.111 (.078)	.154	1.38 (1.14-1.67)	.089	.016 (.066)	.812	1.04 (0.89-1.20)	.804
Model 1 Horvath2	.045 (.082)	.589	1.04 (0.86-1.24)	.843	-.071 (.066)	.287	0.90 (0.78-1.04)	.465
Model 2 Horvath2	-.016 (.079)	.843	0.93 (0.78-1.12)	.716	-.056 (.066)	.402	0.91 (0.79-1.05)	.517
Model 1 PedBE	**.186 (.081)**	**.023**	**1.65 (1.36-2.00)**	**.010**	-	-	-	-
Model 2 PedBE	.139 (.078)	.076	**1.55 (1.27-1.89)**	**.026**	-	-	-	-
Model 1 DunedinPACE	**-.190 (.081)**	**.020**	**0.65 (0.53-0.78)**	**.024**	**.147 (.066)**	**.028**	**1.34 (1.15-1.56)**	**.047**
Model 2 DunedinPACE	**-.168 (.077)**	**.030**	**0.65 (0.53-0.79)**	**.034**	.124 (.068)	.071	1.32 (1.13-1.54)	.068
Model 1								

Epistress	.089 (.082)	.280	1.10 (0.92-1.32)	.594	-.005 (.066)	.941	0.97 (0.84-1.12)	.825
Model 2								
Epistress	.105 (.078)	.180	1.14 (0.94-1.37)	.491	-.009 (.066)	.894	0.97 (0.84-1.12)	.821

Notes: Years (y). Epigenetic residuals adjusted principal components for cell type heterogeneity, smoking status at 42 years (1958BBC only), and body mass index (QLSCD: 10 years; 1958BBC: 45 years), and principal components for ancestry (QLSCD only), and chronological age (QLSCD: decimal age at the 10 years data collection; 1958BBC: decimal age at the 45 years data collection). Max N based on data available for epigenetic clocks, DunedinPACE, and Epistress. (QLSCD: n=149; 1958BBC: n= 238). Model 1 was unadjusted; Model 2 is adjusted for sex, birthweight, and socioeconomic status (QLSCD: at 5 months; 1958BBC: at birth). QLSCD : Data were compiled from the final master file (1998–2015), © Gouvernement du Québec, Institut de la Statistique du Québec.

3.9.5. Table 3.5: Logistical regressions between epigenetic residuals and suicidal ideation

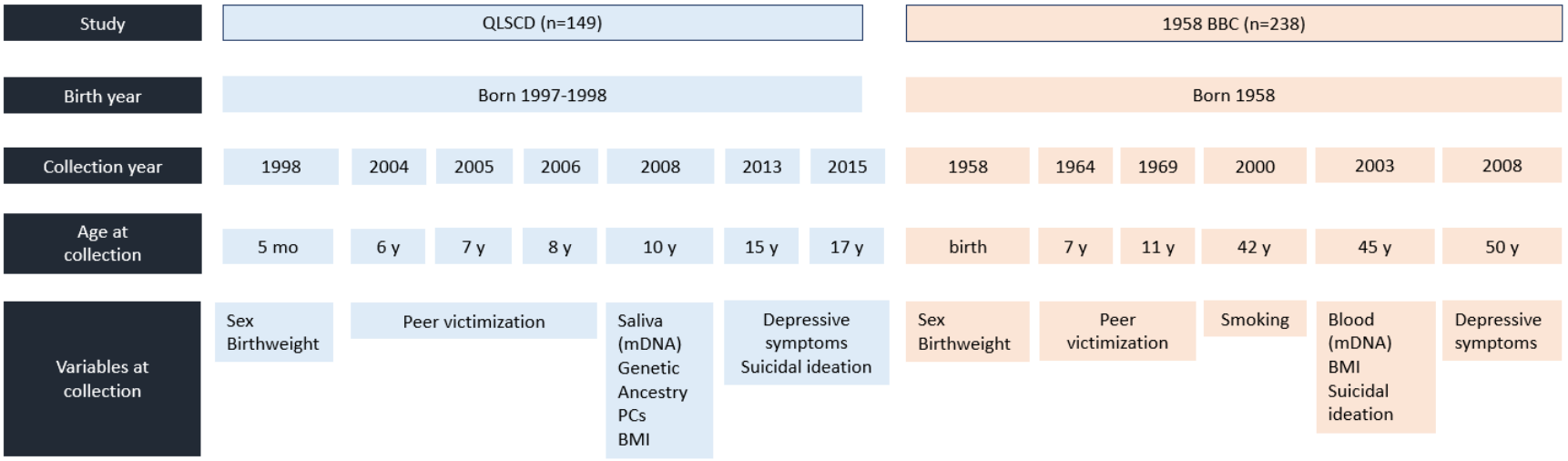
	QLSCD		1958BBC	
	Suicidal ideation at 15-17 years		Suicidal ideation at 45 years	
	OR(95% CI)	*p*-value	OR(95% CI)	*p*-value
Model 1 Horvath1	0.94(0.78-1.13)	.727	0.87 (0.67-1.14)	.611
Model 2 Horvath1	0.92(0.79-1.16)	.836	0.88 (0.69-1.14)	.634
Model 1 Horvath2	1.11(0.93-1.34)	.555	0.72 (0.55-0.95)	.232
Model 2 Horvath2	1.09(0.90-1.31)	.658	0.76 (0.57-1.00)	.317
Model 1 PedBE	1.25(1.03-1.50)	.237	-	-
Model 2 PedBE	1.19(0.99-1.43)	.355	-	-
Model 1 DunedinPACE	0.96(0.80-1.16)	.835	1.48 (1.14-1.93)	.133
Model 2 DunedinPACE	1.01(0.83-1.23)	.954	1.29 (0.97-1.71)	.361
Model 1 Epistress	1.00(0.83-1.21)	.983	1.02 (0.78-1.33)	.943
Model 2				

Epistress	1.04(0.86-1.25)	.851	1.03 (0.79-1.35)	.904

Notes: Years (y). Epigenetic residuals adjusted principal components for cell type heterogeneity, smoking status at 42 years (1958BBC only), and body mass index (QLSCD: 10 years; 1958BBC: 45 years), and principal components for ancestry (QLSCD only), and chronological age (QLSCD: decimal age at the 10 years data collection; 1958BBC: decimal age at the 45 years data collection). Max N based on data available for epigenetic clocks, DunedinPACE, and Epistress. (QLSCD: n=149; 1958BBC: n= 238). Model 1 was unadjusted; Model 2 is adjusted for sex, birthweight, and socioeconomic status (QLSCD: at 5 months; 1958BBC: at birth). QLSCD: Data were compiled from the final master file (1998–2015), © Gouvernement du Québec, Institut de la Statistique du Québec.

3.10. Supplemental Materials

3.10.1. Supplemental Figure 3.1 : Two-cohort study design with variables of interest and main confounders



Note: y=years, mo=months, mDNA=DNA methylation, BMI=Body Mass Index, PCs= Principal Components

DISCUSSION

i. General summary

The overarching aim of this thesis was to better understand associations between peer victimization, including cybervictimization, with depressive symptoms and suicidal ideation, as well as exploring potential underlying biological mechanisms. Firstly, our main findings show that peer victimization assessed in childhood and adolescence through self, teacher and mother reports is associated to depressive symptoms and suicidal ideation in adolescence and adulthood (**Chapter 1, 2, 3**). Results from **Chapter 1** indicate that both cybervictimization and face-to-face victimization were independently associated with suicidal ideation, although differences were noted when examining cross-sectional and longitudinal associations. For cross-sectional associations, cybervictimization was associated to suicidal ideation at 13, 15, and 17 years beyond face-to-face victimization. However, cybervictimization did not predict suicidal ideation 2 years later from 13 to 15 years, and 15 to 17 years, after accounting for baseline suicidal ideation at 13 and 15 years, respectively. This may indicate that cybervictimization is linked to a heightened concurrent risk of reporting suicidal ideation which persist over time. Face-to-face peer victimization predicted suicidal ideation concurrently and longitudinally in fully adjusted models.

Subsequent analyses in Chapters 2 and 3 examining longitudinal associations of peer victimization, depressive symptoms, and suicidal ideation, focused on identifying biomarkers influencing or underlying these associations (**Chapters 2 & 3**). More specifically, a partial measure of a genetic vulnerability for depression (PRS-depression) did explain a very small portion of variance of depressive symptoms in adolescence (**Chapter 2**), however it did not influence the association between peer victimization and depressive symptoms. In other words,

peer victimized adolescents reported increased depressive symptoms, regardless of their genetic vulnerability to depression, as measured by PRS-depression (**Chapter 2**).

Lastly, epigenetic biomarkers of biological aging (Horvath, Skin & Blood, PedBE), pace of aging (DunedinPACE), and stress response reactivity (Epistress) did not predict peer victimization or suicidal ideation in adolescence and adulthood. Thus, these epigenetic markers did not partially drive the association between peer victimization with depressive symptoms and suicidal ideation in adolescence and adulthood in two separate cohorts (**Chapter 3**). However, some epigenetic indices were associated to depressive symptoms in adolescence (PedBE, DunedinPACE) and adulthood (DunedinPACE), thereby adding to the existing knowledge that biological aging and stress response reactivity are linked to depression.

These novel findings add to the existing literature on the longitudinal mental health outcomes of peer victimization. More importantly, these studies investigated unexplored biological markers of peer victimization, depressive symptoms, and suicidal ideation. Furthermore, these thesis findings can inform future research and implications in this field of research.

ii. Peer victimization as a risk factor for depressive symptoms and suicidal ideation: Chapters 1, 2 & 3

The work exhibited in this thesis joins the plethora of studies identifying peer victimization as a risk factor for depressive symptoms and suicidal ideation in adolescence (Geoffroy et al., 2018a; Geoffroy et al., 2016; McDougall & Vaillancourt, 2015) and adulthood (Geoffroy, Arseneault, et al., 2022; McDougall & Vaillancourt, 2015). These findings demonstrate that peer victimization does not need to share the specific attributes of bullying defined by Olweus (1993);

namely the repeated occurrence, the intent to harm, and the power imbalance, to be associated with negative mental health outcomes across the life course. Furthermore, as discussed in Finkelhor et al. (2012) commentary "Let's prevent peer victimization, not just bullying", the technical definition of bullying has been at odds with its usage in research and the school environment. For example, antibullying prevention efforts generally aim to reduce interpersonal violence, not just bullying (Finkelhor et al., 2012; Guzman-Holst, Zaneva, Chessell, Creswell, & Bowes, 2022). Thus, reinforcing that it is important to focus on and prevent peer victimization, rather than bullying. Indeed, our analyses consistently showed that peer victimization was associated to depressive symptoms and suicidal ideation in adolescence using the QLSCD (**Chapter 1, 2 & 3**), and in adulthood using the 1958BBC (**Chapter 3**). More specifically, peer victimization measured in childhood at 6-8 years (QLSCD) and 7-11 years (1958BBC) in **Chapter 3**, and in early adolescence at 12-13 years (QLSCD) in **Chapter 2**, was associated with depressive symptoms and suicidal ideation. These findings replicate prior evidence that peer victimization in childhood and adolescence is longitudinally associated with depressive symptoms (Reijntjes, Kamphuis, Prinzie, & Telch, 2010).

Our findings also expand on prior studies using multiple informants, including mother-, teacher-, and self-reports of peer victimization to assess associations with later mental health. All together, Chapters 1, 2, & 3 confirmed associations between self-reported peer victimization, depressive symptoms, and suicidal ideation in subsamples of the QLSCD. Chapter 2 reported associations between teacher-reported peer victimization, depressive symptoms, and suicidal ideation in a QLSCD subsample. Finally, Chapter 3 showed significant associations between mother-reported peer victimization, depressive symptoms, and suicidal ideation in a 1958BBC subsample. Similarly, Zwierzynska et al. (2013) had found that regardless of the informant;

mother-, teacher-, and self-reported peer victimization at 7-10 years were associated with internalizing problems (including depressive symptoms) at 11-14 years, in a UK cohort of 3,692 participants known as the Avon Longitudinal Study of Parents and Children (ALSPAC). Furthermore, our findings add to the existing literature on peer victimization in the 1958BBC and the QLSCD. The 1958BBC and its five-decade follow-up has yielded an extensive literature on the long-term associations between mother-reported childhood bullying and mental health, health, and socioeconomic outcomes in young and mid-adulthood (Brimblecombe et al., 2018; Evans-Lacko et al., 2017; Geoffroy, Arseneault, et al., 2022; Takizawa, Danese, Maughan, & Arseneault, 2015; Takizawa et al., 2014). This study also adds to the published work using the contemporary QLSCD cohort replicating associations between self-reported peer victimization, depressive symptoms, and suicidal ideation (Geoffroy et al., 2018a; Geoffroy et al., 2016; Ouellet-Morin et al., 2021). Our findings also add to studies using teacher-reports of childhood peer victimization and investigating their link to childhood depressive symptoms (Perron et al., 2012). Importantly, many of these studies published in the QLSCD, 1958BBC, and ALSPAC, produced robust findings by controlling for pre-existing vulnerabilities; such as prior mental health symptoms, family and socioeconomic factors. As previously mentioned, controlling for these variables is essential in order to capture unique effect of peer victimization on later depressive symptoms and suicidal ideation.

iii. Pre-existing vulnerabilities in associations between peer victimization, depressive symptoms, and suicidal ideation: Chapter 1 & 2

The following section will discuss the rationale behind including certain pre-existing vulnerabilities when studying associations between peer victimization, depressive symptoms, and suicidal ideation. In short, we will discuss our work in **Chapters 1 & 2** which applied similar

stringent control of potential confounders when testing these associations, compared to previously mentioned cohort studies (Bowes et al., 2015b; Geoffroy et al., 2018a; Geoffroy et al., 2016). Furthermore, we will discuss the inclusion of genetic vulnerability measured by PRS-depression as a potential confounder in **Chapter 2.** Briefly, tested whether peer victimization predicted depressive symptoms and suicidal ideation after taking into account a partial measure of genetic vulnerability to depression (PRS-depression). Finally, **Chapter 3** explored relevant confounders to associations between peer victimization, depressive symptoms, suicidal ideation, and epigenetic indices.

A number of studies have discussed the bidirectionality between peer victimization and mental health. While peer victimization has been linked to depressive symptoms and suicidal ideation in a plethora of studies, it is not clear whether these associations are causal or are driven by environmental and/or genetic confounding factors. Therefore it is imperative that studies at least control for pre-existing vulnerabilities such as mental health symptoms, sociodemographic and family factors. A major limitation of cross-sectional and longitudinal studies alike is that if pre-existing vulnerabilities are not taken into account, such as prior suicidal ideation or depressive symptoms, then it is likely that associations reflect risk in youth that are already at-risk for peer victimization exposure and later suicidal ideation or depressive symptoms. To that effect, studies on peer victimization, including cybervictimization, and mental health symptoms from **Chapter 1 & 2** (Perret et al., 2020), as well as in our research team (Geoffroy et al., 2018a; Geoffroy et al., 2016; Perret et al., 2021) and others (Gámez-Guadix et al., 2013; Rose & Tynes, 2015) have emphasized the importance of controlling for these factors.

Some studies have used other methods to control for pre-existing vulnerabilities, such as using monozygotic and dizygotic twin samples (sharing 100% and 50% of there genetic make-up,

respectively), in order to capture the unique effect of peer victimization after controlling for genetic confounding. For example, a recent study using a co-twin control design found that on cybervictimization was cross-sectionally associated to depression, suicidal ideation, and a wide range of other mental health problems at 22 years old, after controlling for mental health problems at 16 years, face-to-face victimization at 22 years, genetic confounding and shared family environment (Baldwin, Ayorech, Rijsdijk, Schoeler, & Pingault, 2021). Interestingly, the co-dizygotic twin control diminished the individual associations of cybervictimization to mental health symptoms by an average of 26%, while the monozygotic twin control attenuated the associations to an average of 47% (Baldwin et al., 2021). From this study, although associations remained significant, it is clear that cybervictimization has a small direct effect after accounting for pre-existing environmental and genetic vulnerabilities and concurrent face-to-face victimization. Thus, it further stresses the importance of including these confounders when studying these associations in the context of cybervictimization. Although we were not able to control of genetic vulnerability in **Chapter 1**, we can hypothesize that associations between cybervictimization, face-to-face victimization and suicidal ideation/attempt would have diminished in effect size but would have remained significant.

In the larger context of peer victimization, twin studies have found that genetic factors are associated to peer victimization, and some of them have also been linked to depressive symptoms (Bowes et al., 2015b; Brendgen et al., 2011; Brendgen et al., 2017; Brendgen et al., 2009). With this knowledge at hand, we sought to understand if having a genetic vulnerability to depression, as measured by the PRS-depression, would confound the association between peer victimization, depressive symptoms, and suicidal ideation. **Chapter 2** revealed a *r*GE with self-reported peer victimization and PRS-depression which may support previous non-genetically informed studying

showing that pre-existing vulnerabilities, such prior mental health symptoms, increase an individual's risk of being peer victimization (Reijntjes et al., 2010). However, the absence of *r*GE with teacher-reported peer victimization points to the need to more studies to further understand this discrepancy. In terms of genetic confounding, **Chapter 2** showed that peer victimization remained associated with later depressive symptoms and suicidal ideation, even after adjusting for PRS-depression. Interestingly, PRS-depression also predicted depressive symptoms beyond peer victimization, even if effect sizes were small. This further indicates that genetic vulnerabilities and environmental stressors, such as peer victimization, each play a part in predicting depressive symptoms even after including stringent confounding variables.

iv. Gene-environment interplay: Chapters 2 & 3

Several studies have investigated biomarkers as moderators and mediators of peer victimization and its association to mental health symptoms (Vaillancourt et al., 2013; Vaillancourt, Sanderson, Arnold, McDougall, & Bradshaw, 2017). Indeed, the moderation and mediation hypotheses have been tested with the general assumption that early-life stressors, such as the experience of peer victimization, can be associated to negative outcomes, such as mental health symptoms. The moderation hypothesis involves factors that can condition or influence the consequences of strain. **Chapter 2** tested this hypothesis and found that PRS-depression did not condition the association between peer victimization, depressive symptoms or suicidal ideation, thereby negating this hypothesis. However, prior studies had explored other genetic variables as potential confounders and had found a GxE with peer victimization in predicting depressive symptoms (Benjet et al., 2010; Brendgen et al., 2009). It is important to note that a newer technique to compute PRS-depression using the PRS-CS method would yield different results in our study, as it has been found that this method can better predict a genetic vulnerability to psychiatric

disorders, including major depressive disorder (Ge, Chen, Ni, Feng, & Smoller, 2019; Ni et al., 2021). For example, a similar method used in Chapter 2 explained about 2.2% of the variance on a scale of liability to major depressive disorder, while PRS-CS explained 3.5% of the variance (Ni et al., 2021). Furthermore, emerging studies in the last few years have tested certain factors as potential mediators of the association between a PRS and a mental health outcome. For example, Pat et al. (2022) found that reward sensitivity and cognitive abilities partially explained the association between the PRS for Attention-Deficit Hyperactivity Disorder and psychopathology. This leads us to the mediation hypothesis which involves the testing whether certain factors partly explain the relationship between adversity and negative outcomes. Since evidence in **Chapter 2** as well as in Armitage et al. (2022) and Schoeler et al. (2019) shows an association between self-reported peer victimization and PRS-depression, it is possible that investigating PRS-depression as a mediator is an appropriate venture. Indeed, PRS-depression has been linked to peer victimization, depressive symptoms, as well as suicidal ideation. Future studies would need to investigate this possibility.

The mediation hypothesis was used in **Chapter 3**. Our findings consolidated prior findings on the lack of association between peer victimization and epigenetic markers. Indeed, peer victimization was not associated to epigenetic indices reflecting biological aging, pace of aging, or stress response reactivity in childhood or in adulthood. Thereby, the mediation hypothesis was rejected. While no epigenetic index was associated to suicidal ideation, some indices of aging and pace of aging (DunedinPACE, PedBE) were associated with depressive symptoms in adolescence and adulthood. Interestingly, a slower pace of aging was associated to depressive symptoms in adolescence, while a faster pace of aging was associated to depressive symptoms in adulthood at trend level. These results may indicate that a delayed development as showcased by the slower

pace of aging in childhood may be a relevant marker for a depressive symptomology, but not for suicidal ideation. It is important to note that the DunedinPACE was optimized for blood samples, but not for saliva samples, as provided by adolescents in the QLSCD. Additionally, it was created from participants in young and mid-adulthood, which may raises the possibility that it is not optimized for younger participants or for saliva samples. Nonetheless, these findings add to existing literature on biological aging, pace of aging, and the stress response in the association between adversity and depression as previously mentioned in **Chapter 3** (Anacker, O'Donnell, & Meaney, 2022; Klopack et al., 2022; Mitchell, Schneper, & Notterman, 2016; Sumner et al., 2019). This literature does contain inconsistent findings, along with important methodological differences, such as the wide variety of biomarkers of biological aging and the stress response. The novelty of this study raised additional methodological questions on the appropriate epigenetic indices that would best reflect the experience of peer victimization, as well as depression, and suicidal ideation or suicide attempt. Furthermore, it is important to consider that there is an interplay between genetics and epigenetics that was not taken into account in this thesis' work. To illustrate, a co-twin control study found that Horvath was not associated with depression, indicating that the association was confounded by genetic or familial factors (Liu et al., 2022). It is thus possible that Chapter 3 findings were genetically confounded. Furthermore, some studies have found that DNA methylation at specific genes can mediate the interaction between genotype and adversity (Klengel et al., 2013). Thus, further studies would ideally take into account DNA methylation of genetic markers studied in the association between peer victimization, depressive symptoms and suicidal ideation. As such, DNA methylation at PRS-depression relevant sites may better inform ones genetic vulnerability, and thus it's potential role as a moderator of the associations between peer victimization, depressive symptoms, and suicidal ideation.

v. Limitations: Chapters 1, 2 & 3

Several limitations are to be noted in this thesis. First, self-reported peer victimization, depressive symptoms, and suicidal ideation in community samples were used in all studies. With the exception of teacher- (QLSCD) and mother-reported (1958BBC) peer victimization in Chapters 2 & 3, as well as suicidal ideation in Chapter 3 (1958BBC) which was measured through a semi-structure clinical interview. Due to the use self-report for the exposure (i.e., peer victimization) and outcomes (i.e., depressive symptoms, suicidal ideation), it is possible that our effect sizes were inflated.

Second, although the QLSCD and 1958BBC were initially representative, attrition occurred over time most notably in vulnerable individuals. In order to account for this attrition, weighted analyses were performed in Chapter 1. Chapters 2 & 3 included subsamples of participants with genetic and epigenetic information in the QLSCD and 1958BBC. This limitation was acknowledged, and these chapters did present differences on early life characteristics in the included vs non-included participants in the cohort subsamples. Chapter 2 reported that included individuals were more likely to be female, have sufficient family income, have a mother reporting less depressive symptoms and that were more likely to have a high school diploma, as well as more likely to live with both biological parents or a blended family. Chapter 3 did not find socioeconomic differences between included and excluded participants. However, included participants reported less depressive symptoms and suicidal ideation. Overall, these characteristics point towards an attrition and unintended exclusion of more vulnerable individuals. Chapter 1 did attempt to account for these individuals by adding a weighted analysis, which did not alter our results. While our results cannot be generalized to the representative population, the extent of the bias is likely small.

Third, our sample sizes in Chapter 3 of 149 and 238 in the QLSCD and the 1958BBC, respectively, may have limited our predictive power. Specifically, we could not test for sex interactions. This may be of importance since some studies have reported sex differences in HPA axis markers in the association between peer victimization and depressive symptoms (Ouellet-Morin et al., 2021). Additionally, different types of adversities have been associated with epigenetic aging in girls and boys (Marini et al., 2020). Thus, more studies are needed to replicate our findings and explore potential sex differences. We would however like to point out that sex differences were tested in Chapters 1 & 2 and indicated the absence of a sex interaction.

Fourth, Chapter 2 only explored the GxE with PRS-depression in predicting depressive symptoms and suicidal ideation. However, these two phenotypes have been associated with other PRS which may also be relevant in the context of peer victimization. For example, PRS for neuroticism has been found to predict depression and suicidal ideation (Chioqueta & Stiles, 2005), as well as peer victimization (Schoeler et al., 2019). Thus, testing GxE using a multiple polygenic risk score approach may be a promising avenue of research to better understand genetic vulnerabilities that moderate these associations.

Fifth, the epigenetic associations with peer victimization tested in the 1958BBC in Chapter 3 were very distal, as measures were separated by nearly 40 years. It is possible that associations are diluted by other factors after these many years have passed. However, we did replicate these non-significant findings with more proximal measures of epigenetic indices and peer victimization within a 2-year period in childhood in the QLSCD.

vi. Implications & future research

Various psychological factors had been tested as potential moderators and mediators between peer victimization, depression, and suicidal ideation (Khaki, El-Salahi, & Cooper, 2022; Kretschmer, 2016), however there is an overall lack of studies on biological markers. Indeed, biological markers have been investigated in association to peer victimization, depression, and suicidal ideation. However, perhaps inconsistent findings and a multitude of genetic and epigenetic markers have hindered the search for biological moderating and mediating factors. Specifically, biological aging has been linked to adverse life experiences and mental health (Han et al., 2019). Although telomere length had been investigated in association with peer victimization (Shalev et al., 2013) and depression (Ridout, Ridout, Price, Sen, & Tyrka, 2016), studies are lacking and inconsistent. The work exhibited in this thesis has not identified biological characteristics of individuals experiencing peer victimization who will develop depressive symptoms or suicidal ideation, but ultimately, we may discover biological markers linked to peer victimization, depressive symptoms, as well as suicidal ideation. Evidence in this thesis shows that genetic vulnerability explains little variance of reporting depressive symptoms, regardless of peer victimization status. Thus, this work highlights that prevention and intervention efforts should focus on peer victimization as a modifiable risk factor by reducing its occurrence to prevent the development of depressive symptoms and suicidal ideation. Furthermore, intervention programs may act on known psychosocial moderating and mediating factors of the associations between peer victimization and these mental health outcomes. Indeed, this thesis focused on biological factors which may influence or explain this association, however a multitude of psychosocial factors have been studied as moderators or mediators (e.g., perceived stress, loneliness, social support, sleep problems) (Chang, Wu, Lin, Chang, & Yen, 2019; Hunter, Durkin, Heim, Howe, & Bergin, 2010; van Hoof, Raaijmakers, van Beek, Hale, & Aleva, 2008). The implication of identifying these

factors can be of particular interest for developing prevention and intervention programs. For example, friend support has been found to reduce depressive symptoms in peer victimized youth (Perret et al., 2021). In parallel, a recent systematic review and meta-analysis did report a small reduction in internalizing symptoms after implementing antibullying interventions, particularly those working with peers as mediators or by encouraging bystander behavior (Guzman-Holst et al., 2022). This highlights the need for more research on risk, protective, moderating, and mediating factors of the association between peer victimization, depressive symptoms, and suicidal ideation in order to increase the efficacy of intervention programs.

CONCLUSION

Depressive symptoms and suicidal ideation emerge in early adolescence, and have been associated to peer victimization. However, not all adolescents will develop depressive symptoms or suicidal ideation in adolescence or adulthood. Our work shows evidence that cybervictimized adolescents are more at-risk of reporting suicidal ideation compared to non-victimized adolescents, as are adolescents victimized face-to-face. Furthermore, genetic vulnerability to depression was linked to self-reported peer victimization, depressive symptoms, and suicidal ideation. Some epigenetic indices were associated to depressive symptoms in adolescence and adulthood. However, genetic vulnerability did not influence, nor did epigenetic indices partially explain the association between peer victimization and depressive symptoms. The identification of biological markers of peer victimization, depressive symptoms, and suicidal ideation would help further understand underlying biological mechanisms and identify at-risk individuals. However, due to the novelty of this field of research in the context of peer victimization, there is a dire need for more studies in order to compare this thesis' work and further understand inconsistencies in the literature.

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