Don't leave me out in the cold

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HOW PEER EXPERIENCES PREDICT PHYSICAL HEALTH IN ADOLESCENCE

MARIEKE DE BRUINE

DON'T LEAVE ME OUT IN THE COLD

HOW PEER EXPERIENCES PREDICT PHYSICAL HEALTH IN ADOLESCENCE

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Promotores

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General Introduction

The scope of the dissertation

One of the things that characterize us as humans is an innate need to belong (Baumeister, 1985). To fulfill this need, we form bonds with others around us, which contribute to our happiness and overall well-being. However, when we feel that we do not belong, this can have lasting consequences for our well-being and affect our physical health (Miller et al., 2011). Every single person can probably remember a time during school when they wanted to be included in a group but were left out and the pain this caused them. The odds are high that this was a situation that happened during adolescence (Eslea & Rees, 2001). During adolescence, our need to belong becomes predominantly fulfilled by our peers (Leibovich et al., 2018). Whereas in childhood, the bond with parents is vital, during adolescence we learn to become more independent from our parents and begin to focus more on the bonds with our peers (Brown & Larson, 2009; Hartup

& Stevens, 1997). At the same time, in adolescence, we are more sensitive to the social experiences that we have with our peers (Crone & Dahl, 2012). Therefore, especially in adolescence, peer experiences, such as peer victimization and peer acceptance, are salient experiences that have been empirically shown to predict adolescents' mental health (e.g., depression, anxiety; Bukowski & Adams, 2005; Prinstein & Giletta, 2016).

But what if these experiences do not only affect how adolescents feel mentally, but also their physiology (i.e., "get under their skin")? Theoretical and empirical work suggests that social experiences may influence individuals' physical health (Slavich & Cole, 2013). However, little is known about how peer experiences can affect adolescents' physical health. For example, it remains unclear which different peer experiences might be particularly influential. Moreover, it is unclear which physiological processes, if any, are impacted. Finally, do these peer experiences interact with other experiences that are already known to affect physical health? These questions are highly relevant, especially in adolescence, given that this developmental period is characterized by profound social and biological changes (National Academies of Sciences, Engineering, and Medicine, 2019), which makes it a particularly interesting moment for examining how social experiences can influence physical health. Moreover, understanding how peer experience can affect physical health in adolescence might result in tools to prevent illness. By combining theoretical and empirical work from early life adversity and peer relations research, the current dissertation aimed to answer different questions about how peer experiences affect physical health during adolescence. Specifically, the current dissertation aimed to examine 1) the extent to which different types of peer experiences predict adolescents' health-related outcomes, 2) the extent to which peer experiences predict adolescent levels of systemic inflammation, and 3) the extent to which the independent and interactive effects of peer experiences with early-life adversity predict adolescents' physical health.

Peer experiences in adolescence

Following Rubin and colleagues (2015), peer experiences refer to a broad set of experiences that individuals of all ages have with their nonfamilial age-mates, such as peer victimization or peer popularity. With the transition to adolescence, these peer experiences play a critical role due to individual and social changes that characterize adolescence. First, adolescents spend an increasing amount of time with their peers. The frequency of peer interactions intensifies, and adults less often oversee these interactions (e.g., Berndt, 1982). Second, the influence of peers increases because the opinions and expectations of peers become particularly important (Blakemore, 2018). This influence gets further amplified because the adolescent brain is especially sensitive to social information and both positive and negative peer cues (Blakemore, 2018; Brown & Larson, 2009; Crone & Dahl, 2012). Third, peer experiences become more complex as the peer network expands and becomes more elaborate (Brown & Larson, 2005). Adolescents do not only have to take into account experiences with individual peers, but they also have to find their place in the broader peer group. For example, they might become part of a specific group of peers based on shared interest or status (e.g., the popular clique; Pattiselanno et al., 2015).

Altogether these changes contribute to make peer experiences among the most important experiences to affect adolescents' well-being. Adolescents who have positive peer experiences (e.g., high-quality friendship, peer acceptance) tend to be well-adjusted, mentally healthy (good self-esteem, low depression rates) and have a better overall well-being than their counterparts with less positive experiences (see for review Prinstein & Giletta, 2016). Instead, adolescents who experience negative relationships with their peers (e.g., due to peer victimization, peer rejection) are at increased risk of becoming maladjusted and for developing different forms of psychopathological symptoms (e.g., externalizing and internalizing symptoms; Reijntjes et al., 2010, 2011). Notably, due to adolescents' heightened peer sensitivity, exposure to negative

peer experiences may result in more severe negative consequences, in terms of maladjustment and poor well-being, than in other periods of life (Blakemore, 2018; Rudolph et al., 2016).

Within the current dissertation, I focus on two types of group-level peer experiences: peer victimization and (low) peer status (i.e., peer preference and peer popularity) because of at least two reasons. First, they are key constructs within the field of peer relations that can be important sources of stress (Flack et al., 2011; Rubin et al., 2015; Troop-Gordon, 2017); both constructs can threaten adolescents' sense of belonging and need to fit in the peer group (Flack et al., 2011). Therefore peer victimization and low peer status can be seen as major stressors in adolescence as troubles with interpersonal relationships, especially with peers, constitute the main source of stress experienced by adolescents (Compas & Phares, 1991; Seiffge-Krenke et al., 2009). Second, in this dissertation, I have chosen to focus on (stressful) peer experiences at the group level as the link between social stressors and physical health has often been hypothesized to stem from an evolutionary risk of falling outside of the (peer) group (Slavich & Irwin, 2014). This means that other peer experiences (e.g., dyadic friendships) that operate outside this group level and that also contribute to adolescents' sense of belonging are not considered.

Peer victimization

Peer victimization is one of the most common peer stressors in adolescence. Approximately 10 to 15% of adolescents can be classified as victims (Troop-Gordon, 2017). Many adolescents likely experience some form of peer victimization throughout childhood and adolescence, whether it is gossip, verbal insults, exclusion, or physical aggression (Troop-Gordon, 2017). Peer victimization can involve all these experiences and can be defined as being the target of any form of intentional peer aggression (Kochenderfer & Ladd, 1996). This definition of peer victimization differs slightly from the definition of bullying victimization, in which the victim of aggression is characterized by

having less power than the bully (Salmivalli, 2010). Overall, peer victimization threatens adolescents' sense of belonging and therefore represents an intense stressor for adolescents (Hawker & Boulton, 2001).

Peer status

As already indicated, (low) peer status is another key group-based peer experience that can cause stress for adolescents. In adolescence, the peer network becomes broader and more complex, and concurrently hierarchies and status become more important. Adolescents become increasingly aware of their reputation within their groups of close friends but also within the broader peer network (Brown & Larson, 2009). Adolescents no longer have to think only about their relationships with their close peers but also about questions like: "Do my peers like me? "; "Am I popular?". For some adolescents, gaining more social status (e.g., becoming popular) can become an important goal (Cillessen & Marks, 2011). Unsurprisingly, having low peer status, which signals a weaker position in the peer group, can cause adolescents stress. Not only are many adolescents concerned about their status among peers, but they also are very well aware of the peers who have high status (Cillessen & Mayeux, 2004). Therefore, combining the nominations of all individuals in a peer group on questions like "Who is popular?" and "Who is liked?" gives a reliable indication of peer status (Cillessen & Marks, 2011). This method is especially reliable as all members of the peer group together determine the peer status of each individual (Cillessen & Marks, 2011).

TWO TYPES OF PEER STATUS. The developmental literature distinguishes between two kinds of peer status: peer preference and peer popularity (Cillessen & Marks, 2011). On the one hand, peer preference reflects the extent to which an adolescent is liked by their peers (Cillessen & Marks, 2011). Specifically, it is a combination of whom peers indicate they like most (peer acceptance) and whom they indicate they like least (peer rejection). On the other hand, peer popularity reflects the reputation, visibility, and social power (e.g., power to influence others) in the

peer group (Prinstein et al., 2018). In childhood, children who are well-liked by their peers are often also popular. However, from early adolescence onwards, these two forms of peer status arise as clearly distinct phenomena (Cillessen & Mayeux, 2004). Consequently, in adolescence, the group of popular peers and preferred peers show little overlap (Parkhurst & Hopmeyer, 1998).

Both forms of peer status can also be distinguished by having different psychosocial correlates (LaFontana & Cillessen, 2002; Prinstein et al., 2018). Preferred adolescents are perceived as trustworthy, high on prosocial behavior, experiencing less friendship conflict, and at low risk for developing both externalizing and internalizing problems (Litwack et al., 2012; Parkhurst & Hopmeyer, 1998; Prinstein et al., 2018). Conversely, popular adolescents show a more mixed profile. Although they can also show prosocial tendensies, they are more likely to show aggressive, delinquent behaviors and engagement in (health) risk behaviors, as compared to their peers (e.g., substance use; Choukas-Bradley et al., 2015; Cillessen & Mayeux, 2004). Due to this aggressive behavior, popular peers may not be well-liked because they are (sometimes) mean to their classmates and make use of aggression to maintain their high status (e.g., Cillessen & Mayeux, 2004; Merten, 1997).

The relation between peer experiences and physical health

Recent research suggests that peer experiences in adolescence, and the social stress these can bring, might be of particular interest for understanding physical health outcomes. Based on evolutionary theories as well as empirical research, social experiences (e.g., social relationship conflicts) are thought to impact physical health not only through common physiological stress pathways such as dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis but also through more direct pathways such as immune system functioning; Sbarra &

Coan, 2018; Slavich & Cole, 2013). Evolutionary theories pose that the ability of humans to form social relationships increased individual survival. Experiences that (negatively) impacted those social relationships indicated a risk for survival. Falling outside of the group's safety would increase the risk of getting injured, grow feeble, and thus eventually represented a risk for physical health. Therefore evolutionary theories have hypothesized that our bodies have adapted to respond to social stress in a similar way as to physical stress (e.g., a cut, bacteria) by preparing our body to deal with health risks (e.g., more immune system activity). To date, research across a range of ages has shown that difficulties with social relationships can impact physical health and predict mortality rates (Cacioppo et al., 2015; Holt-Lunstad et al., 2010). For example, relationship conflict has been related to an increased risk of cardiovascular diseases (De Vogli et al., 2007), and social connectedness is related to better well-being decades later in life (Olsson et al., 2013). Interestingly, some research also suggest that adolescence might be one of the most important periods for understanding how social relationships affect future health difficulties (Yang et al., 2016). This research builds on the existing support that adolescence is a period of developmental plasticity during which considerable reprogramming occurs in stress-response systems (Dahl, 2014). Therefore, negative peer experiences such as peer victimization and low peer status, which both signal a weaker social position, might significantly influence adolescents' physical health in adolescence as well as later in life.

A large body of research has shown that adolescents who experience peer victimization perceive their general health as poorer than their counterparts (see meta-analysis: Gini et al., 2014; Gini & Pozzoli, 2013; Moore et al., 2017; van Geel et al., 2016). This meta-analytic work indicates that victims are approximately two times more likely to experience physical health complaints (e.g., headache, abdominal pain) and often need more medical care, as compared to their non-victimized peers (Gini et al., 2014; Gini & Pozzoli, 2013; Moore et al., 2017). These effects of peer experiences have been found concurrently but also longitudinally, with effects on physical health over longer periods of time (Ames et al., 2019;

Gini & Pozzoli, 2013; Lee & Vaillancourt, 2019). For example, Lee and Vaillancourt (2019) found with a cross-lagged panel model that peer victimization is associated concurrently with physical health symptoms in adolescence but also predicted subsequent physical health symptoms a year later.

Although the link between peer victimization and self-reported physical health has been demonstrated in numerous studies, it remains unclear which biological processes, if any, give rise to this link. Some studies have also examined how peer victimization can affect biological outcomes in adolescence, in particular the HPA-axis functioning (Copeland et al., 2014; Kliewer et al., 2019; Takizawa et al., 2015). However, this research has yielded rather inconsistent evidence, with results in opposite directions (e.g., blunted or heightened reactivity; see for a review Kliewer et al., 2019). Notably, only a handful of studies have examined the effects of peer victimization on other biological systems which may have more direct implications for understanding health outcomes, such as the immune system. These studies do indicate that peer experiences could predict inflammation, a key process of immune system functioning. For example, a study by Copeland and colleagues (2014) has indicated that adolescents who were victimized by peers were more likely to demonstrate steeper increases in inflammation over time. Accordingly, Takizawa and colleagues (2015) have indicated that victimized youth were more likely to have higher levels of inflammation in adulthood up to 30 years later. These initial findings are noteworthy, yet more research is still needed to investigate how different peer experiences could become biologically embedded, thus allowing for a better understanding of how peer experiences could affect physical health.

Altogether, research on peer victimization shows how important peer experiences could be for adolescents' health, but it also has three main limitations. First, this body of research focuses on peer victimization and mostly does not consider other peer experiences. However, it is important to also consider the two types of peer status for several reasons. Just as peer victimization, low peer preference and low peer popularity can be important

stressors that signal a weaker peer-group position (Cillessen & Marks, 2011). Such disconnection and lack of integration are sufficient to trigger physiological processes (Slavich & Cole, 2013). Additionally, self-perceived social acceptance in the peer group has already been indicated to affect general health (Adam et al., 2011; Joffer et al., 2019). However, notably, not only low peer status but also high peer status, in particular peer popularity, may be stressful. New insights have indicated that high levels of peer popularity are associated with more stress exposure (Litwack et al., 2012). Thus, next to peer victimization, both high and low levels of peer status might thus affect adolescents' physical health. Therefore, this dissertation examines the two types of peer status next to peer victimization.

Second, most of these studies examined health outcomes based on the adolescents' own perceptions (i.e., self-reported physical health). Although this represents an important way of examining how peer experiences influences adolescents' physical health, it is only one of many. Physical health refers to everything related to the physical fitness and well-being of a person (Malik & Khan, 2014). Just as general health (which includes mental, physical, and social well-being; Huber et al., 2011; WHO, 1948), physical health is a multidimensional construct that includes both subjective (e.g., self-perceived general health) and objective (e.g., symptom checklist, biological measures) aspects of health (Malik & Khan, 2014). Therefore, to understand how peer stressors affect physical health, it is important to look at health outcomes at different levels by focusing on both subjective as well as objective outcomes. A main contribution of the current dissertation will be to examine physical health not only by focusing on perceived health outcomes but also on biological markers of immune system functioning, as discussed in more detail in the next section.

Third, little to no research has considered how these peer experiences might interact with earlier life experiences. This is surprising because the basis of why peer experiences might affect adolescents' physical health stems from early adversity research. Sometimes peer experiences have been considered part of early life adversity (Danese & J Lewis, 2017; Kuhlman et al., 2020). However,

to fully understand the role that peer experiences may play in influencing adolescents' physical health, the effects of peer experiences should be considered independently and in the context of other early life adversities, which are already known to impact adolescents' physical health negatively (Baumeister et al., 2016).

Assessment of physical health

Self-reported physical health

As mentioned before, most existing peer relations research has focused on how peer stressors might affect self-reported indicators of physical health. This can include an individual's overall sense of physical well-being but also self-reported physical health symptoms such as headaches, stomachache, loss of appetite, and sleep problems (Gini & Pozzoli, 2013; van Geel et al., 2016). The broad nature of these measures make them highly suitable to assess general indicators of adolescents' physical health. Moreover, evidence supporting the validity of these measures has been reported in several studies. For example, similar measures have emerged as a good predictors of medication use later in life (Vie et al., 2018) and they have been related to mortality rates and physician visits during adulthood (Burström & Fredlund, 2001; Miilunpalo et al., 1997). A limitation of these measures, however, is that self-reported physical health can be biased (e.g. by differences in health expectations) and therefore it remains unclear what gives rise to the association between peer experiences and adolescents' physical health. Therefore, it is also important to investigate the effects of peer experiences on biological outcomes.

Systemic inflammation

In this dissertation, I will also focus on one salient health-related outcome, namely the innate immune system functioning. One of the main functions of the immune system is to deal with physical injury and diseases adequately. By

withstanding physical threats such as pathogens and diseases, it is crucial in helping humans to remain healthy. An essential part of the immune response to physical injury or pathogens and diseases is the inflammatory response that is aimed at clearing infections, healing injured tissue, and restoring homeostasis. Inflammation can not only be activated by physical injury or pathogens but can also be regulated by a chain of psychophysiological processes starting in the brain in anticipation and response to social threats (Irwin & Cole, 2011; Slavich & Irwin, 2014). Just as physical stressors, social stressors might signal situations in which physical injuries and infections are more likely to occur (Eisenberger et al., 2017; Slavich & Cole, 2013). Therefore, social stressors might activate the immune system similarly to physical stressors. Correspondingly, recent research has indicated that social stressors may trigger inflammatory responses (Slavich & Cole, 2013).

Normally, inflammation is a complex adaptive process that protects the body. An acute inflammatory response is activated when the body encounters tissue stress, injury, or invasion of a pathogen, and this short-term process restores the body to homeostasis. However, it can happen that acute inflammation becomes chronic because active inflammation fails to resolve itself (e.g., expression of anti-inflammatory proteins is delayed or reduced) or because of prolonged activation of the acute inflammatory response (Nathan & Ding, 2010). This chronic response is commonly referred to as low-grade systemic inflammation and poses a risk for physical health (e.g., cardiovascular diseases, diabetes, and depressive symptoms; Valkanova et al., 2013). Systemic inflammation can be measured by different markers in the blood.

MARKERS OF INFLAMMATION. One group of inflammation markers are cytokines. These small proteins are produced by cells that are part of the immune system (Woo, 2002). In the first phase of the inflammatory response, pro-inflammatory cytokines are produced (e.g., tumor necrosis factor-α (TNF-α); interleukin-1 (IL-1); interleukin-6 (IL-6); Slavich & Cole, 2014). These cytokines stimulate the

inflammatory process and can coordinate cell communication. In response to these acute cytokines, in particular IL-6, C-reactive protein (CRP) is produced, which is a common marker of systemic inflammation (Miller et al., 2011). In comparison to the acute phase cytokines, CRP is a marker of more stable and persistent changes in the immune system functioning. Consequently, elevated CRP levels can have more direct and profound consequences for poor physical health. Indeed, research has shown that high CRP levels predict, amongst others, cardiovascular diseases, diabetes, cancer, and even mortality rates (Ridker & Cook, 2004; Valkanova et al., 2013). Notably, levels of systemic inflammation increase across the course of the lifespan (i.e., inflammaging Hanahan & Weinberg, 2011). Therefore, systemic inflammation levels (e.g., of CRP) are normally very low in adolescents, which makes it harder to examine these effects already among youth. Unsurprisingly, most research has assed these markers in adulthood, and far less is known about these effects in younger populations (Baumeister et al., 2016; Kuhlman et al., 2020). In sum, there are different ways to look at inflammation: cytokines are most commonly used for acute responses and, CRP for longer-term effects, which might be harder to predict in adolescence.

Pro-inflammatory cytokines and CRP are common markers of inflammation. A more novel way to measure systemic inflammation is by assessing levels of the soluble urokinase plasminogen activator receptor (suPAR). suPAR is the soluble form of the membrane-bound receptor urokinase plasminogen that is mainly expressed on the cell membrane of immunologically active cells (Rasmussen et al., 2016). suPAR has, amongst others, the function to assist cell migration. SuPAR is released from immune cells after inflammatory activation. Specifically, suPAR is cleaved from the membrane of immunologically active cells and thus represents a person's level of overall immune activity (Thunø et al., 2009). suPAR can identify people with elevated inflammation otherwise missed by examining IL-6 and CRP (Rasmussen et al., 2019). Its validity is shown in that it is positively associated with other inflammatory markers (e.g., IL-6, CRP;

Rasmussen et al., 2019; Zimmermann et al., 2012) and predicts similar health outcomes (Eugen-Olsen et al., 2010; Rasmussen et al., 2016)

As compared to the most traditional assessment of systemic inflammation, suPAR has a number of advantages. First, suPAR levels show more variation among people, and with levels of systemic inflammation in adolescence being very low, this is a major advantage. Second, suPAR could predict disease and mortality above and beyond CRP (Botha et al., 2015; Rasmussen et al., 2016). Finally, supAR has been indicated to be more stable and less sensitive to acute influences than other biomarkers (Lyngbæk et al., 2013). Thus overall, because of its stable and normally distributed nature, suPAR might be particularly suited for investigating the longer-term effects of peer stressors on levels of systemic inflammation during adolescence.

Confounders in relation to physical health

There are many factors that can influence physical health, and these factors might play different roles. Most commonly, they are taken into account as covariates but they can also function as mechanisms or as moderators (Horn et al., 2018; Raposa et al., 2014). To demonstrate that peer experiences can have an effect on physical health, there are many confounding factors to take into accounts, such as socio-demographic variables, health-related factors, and psychosocial factors (Horn et al., 2018). Especially health-related factors, such as BMI and smoking are robustly associated with health outcomes (e.g., inflammation levels and general physical health outcomes (Flegal et al., 2013; J. Lee et al., 2012; Winter et al., 2014) and should be taken into account when examining physical health at the immune system level (Horn et al., 2018). But also individual differences in temperament have been suggested to be as strongly related to physical health as BMI and smoking (Niles & O'Donovan, 2019).

However, recent research suggests that these factors might not only act as confounders. For example, early adversity research has shown that the association between early life experiences (e.g., child abuse) and physical health

outcomes can be explained by BMI and smoking (Brummett et al., 2013; Hagger-Johnson et al., 2012; Matthews et al., 2014; Raposa et al., 2014). Research has also shown that peer victimization can lead to more smoking behavior and higher BMI in adolescence (Achenbach, 1997; Adams & Bukowski, 2008; Tharp-Taylor et al., 2009). However, to my knowledge, BMI and smoking have not yet been considered as mechanisms for how peer experiences can affect physical health in adolescence.

Finally, some confounders might function as moderators. Not every adolescent might experience the same consequences when experiencing peer stress, and individual factors may modify how peer stressors affect adolescents' physical health. Likely candidates for this are individual differences in temperament, such as an anxious disposition (Capitanio, 2011). In sum, these confounders are not only necessary to rule out when examining the effects of peer experiences on physical health; they could also help understand how and for whom peer experiences affect physical health in adolescence.

Adversity frameworks over the life course

There are three main hypotheses that can provide a theoretical framework that could help understanding why and how peer victimization and peer status could affect physical health in adolescence 1) biological embedding, 2) stress amplification, and 3) cumulative stress/chronic stress. It should be noted that these three hypotheses are not mutually exclusive and at times can co-exist, First, I will discuss the biological embedding hypothesis that provides a general hypothesis of how adversities (e.g., peer experiences) can become reflected in biological processes. Second, the stress amplification hypothesis, for which different terms are used (e.g., stress- sensitization, double hit model; double risk model), elaborates how the timing of adversity can contribute to poorer physical

health outcomes. Finally, the cumulative risk hypothesis elaborates how the repetition of adversities and type of adversity can contribute to poorer physical health in adolescence.

Biological embedding hypothesis

The biological embedding hypothesis poses that stressful experiences might become biologically embedded and, through this pathway, affect physical health (Hertzman, 1999; Miller et al., 2011). Biological embedding refers to the process through which (early) environmental experiences affect the sculpting and neurochemistry of the body, altering future biological responses to stressful experiences, consequently affecting physical health (Hertzman, 1999). For example, for those who experience adversity early in life, immune cells may be programmed and calibrated to respond in a more pro-inflammatory way later in life (Chen et al., 2017; Hertzman, 1999). Negative peer experiences have been acknowledged to be one of those early life adversities (Danese & J Lewis, 2017). Thus, the effect of peer experiences could follow such a biological embedding pathway, and through this, affect physical health (Hertzman, 1999; Rudolph et al., in press). Additionally, following this hypothesis, peer victimization and peer status might impact adolescents' immune system resulting in more pronounced responses later in adolescence or later in life. Moreover, adolescence has been suggested to be a period of interest for biological embedding because adolescents undergo biological changes that can make them highly sensitive to changes in biological processes (Del Giudice et al., 2011).

The biological embedding hypothesis has been predominantly researched in the field of early life adversity. This field has made major strides in understanding how salient developmental stressors in early childhood could affect physical health later in life (Baumeister et al., 2016; Kuhlman et al., 2020). Studies examining the effects of early-life adversity have already indicated that adversities such as low childhood SES and maltreatment affect the stress system and immune system and lead to higher levels of inflammation and more negative health outcomes

(Baumeister et al., 2016; Carpenter et al., 2010; Kiecolt-Glaser et al., 2010). A meta-analysis has shown that although the effect sizes are small (confidence interval: 0.05-.45), the social environment can increase the levels of biological markers (e.g., CRP) later in life (Baumeister et al., 2016). Moreover, biological embedding could be not only important for adversity experienced in the first few years of life but also for understanding how other developmentally salient adversities in different developmental periods (such as adolescence) could pose a risk for health.

Stress amplification models

Closely related to the biological embedding hypothesis is the stress amplification hypothesis. According to this hypothesis, current peer experiences that adolescents encounter may interact with stressful experiences they were exposed in the first few years of life. Note that this is not the same as framing peer experiences as early life adversities themselves (as discussed in the biological embedding hypothesis). Thus, peer experiences are hypothesized to affect physical health most for those adolescents who already experienced prior adversity. For example, stressors occurring in the first years of life might program the body of adolescents to be more sensitive to peer adversities later in life (Miller et al., 2011). Adolescence might then be a particular developmental period of interest because, during adolescence, biological sensitivity is theorized to be heightened, as adolescents undergo many biological changes and reprogramming occurs in stress-response systems (Dahl, 2014; Del Giudice et al., 2011).

Until now, the amplification hypothesis has been supported by work in adults that indicates that early life adversity is associated with biological greater responses to stressors in adulthood (Carpenter et al., 2010; Kiecolt-Glaser et al., 2011; Pace et al., 2006). For example, Carpenter and colleagues (2010) showed in a small study that early adversity was associated with a stronger pro-inflammatory response to acute social stress in otherwise healthy adults. That said, some researchers proposed that the opposite might sometimes also be true: moderate doses of early adversity could affect responsivity to later stressors by making

individuals more resilient (see, for instance, Seery et al., 2010). However, existing evidence is still incomplete on whether and how stressors occurring early in life and peer experiences in adolescence may interact to influence physical health (e.g., the immune system functioning).

Cumulative stress models

Whereas the stress amplification model assumes that the timing of stressors matters, the cumulative risk hypothesis poses that it is not the type or timing of the stressful experiences that matters but the number of experiences people are exposed to (Evans et al., 2013). The cumulative risk hypothesis is based on the co-occurrence of stressors and asserts that the larger the number of stressors people experience, the more (physical) health problems occur because of increased wear and tear of the body (Evans et al., 2013). A common approach to test this hypothesis is to count the number of stressful experiences to create a risk score (e.g., 1= is one stressor, 4= four stressors, etc.). In sum, this hypothesis assumes that this risk score predicts health independent from a particular stressor (e.g., peer victimization) being present or absent (Appleyard et al., 2005). The cumulation of these stressful experiences can happen in two ways. First, cumulation in response to multiple environmental adversities (e.g., peer victimization and peer status). Second through the chronic accumulation of the same adversity that repeatedly occurs over a prolonged period of time (e.g., repeated peer victimization). An example of the latter would be that those people who experienced the most stressors in both childhood and adolescence might have the most negative health outcomes independent of which type of stressors and when this stressor happened.

The cumulative stress hypothesis has been supported by several epidemiological and adversity studies (e.g., Appleyard et al., 2005; Evans & Kim, 2007; Rasmussen et al., 2019a; Sameroff, 2000). These studies indicate that the cumulation of stressors predicts worse outcomes later in life (e.g., adult self-reported health; Power & Matthews, 1998; behavior; Appleyard et al., 2005;

Rutter 1979; Sameroff 2000). A few studies have also shown that cumulative risk factors in childhood and adolescence can be an important predictor of physical health-related outcomes such as cardiovascular response and immune system functioning (Evans & Kim, 2007; Rasmussen et al., 2019, 2020). For example, Rasmussen and colleagues (2019a) have shown in a British cohort study that those youth who were exposed to cumulative victimization across both childhood and adolescence had elevated suPAR levels (age 18). However, to my knowledge, the cumulative risk of multiple stressful peer experiences on physical health remains largely unexamined. Adolescents who experience peer victimization, who are not liked by peers and are also unpopular might be the ones who have the worst health outcomes in comparison to adolescents who just experience one or two of these stressors (independent of the type of peer stress).

Together these three hypotheses provide a theoretical framework that guides the work of this dissertation. First, the biological embedding hypothesis provides a general framework about how peer experiences could influence physical health (adolescents' levels of systemic inflammation). Second, the stress amplification hypothesis provides a framework about how peer experiences might interact with earlier stressful experiences. Finally, the cumulative stress hypothesis provides an alternative to test if the type of peer experiences (peer victimization, peer preference, peer popularity) or the cumulative effects of multiple experiences matters for adolescents' physical health.

Aims and outline of the dissertation

The goal of the current dissertation is address the research gaps discussed in this introduction and contribute to the understanding of how peer experiences can affect adolescents' physical health by examining three main questions (see Figure 1.1 for a visual representation). First, the current dissertation aimed

to examine the extent to which different types of peer experiences predict adolescents' health-related outcomes by comparing different peer stressors (e.g., peer victimization, low peer status) and how they interact. This aim is addressed in both **chapter 2** and **chapter 3,** where the independent effects of peer victimization and two types of peer status were examined. Additionally, **chapter 2** examined whether the two types of peer status also interact with one another.

The second aim of the dissertation is to examine to what extent peer experiences can predict adolescents' levels of systemic inflammation. Therefore, **chapter 3** examined the effects of early life adversity and adolescents' peer status on levels of high sensitive CRP, a marker of systemic inflammation. Additionally, **chapter 4** examined the effects of cumulative peer victimization on a different marker of systemic inflammation (suPAR) while also examining a possible

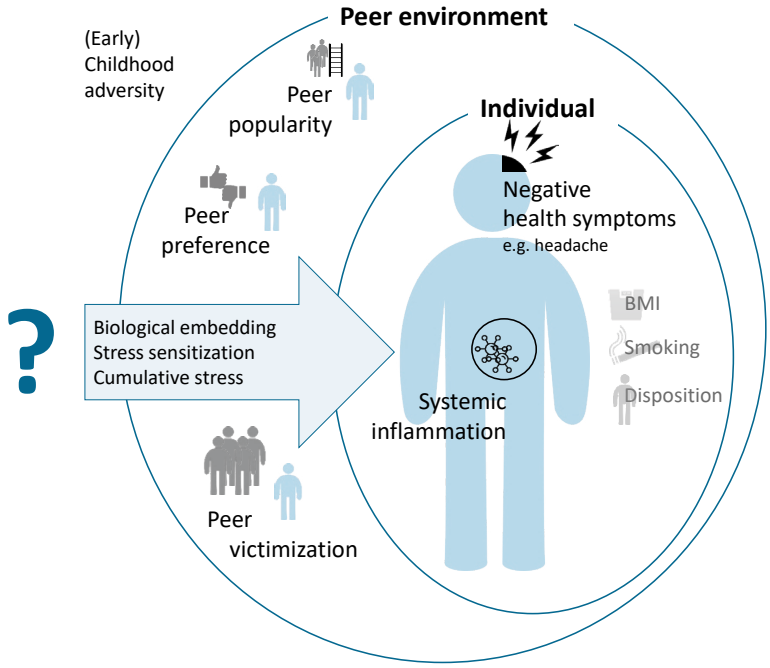

FIGURE 1.1 Visual representation of the main concepts and relations proposed in this dissertation, displaying how peer experiences can affect physical health in adolescence.

indirect pathway from peer victimization to suPAR through BMI and smoking. Additionally, this dissertation examines a pathway from peer experiences to adolescents' systemic inflammation levels through health-related factors (e.g., smoking and BMI).

Finally, the current dissertation aimed to examine the independent and interactive effects of peer experiences with early-life adversity in predicting adolescents' physical health. This aim is addressed in chapters 3 and 4 by testing a stress amplification hypothesis. In **chapter 3**, stress amplification was examined by investigating the interaction between early childhood adversity and two types of peer status (i.e., peer preference and peer popularity). In **chapter 4,** stress amplification was examined by investigating the interaction between two early childhood adversities (i.e. low childhood SES and lack of maternal warmth) and peer victimization.

Study designs and samples

The current dissertation investigates multiple group-based peer experiences and their effect on different levels of adolescents' physical health-related outcomes. To this end, the current dissertation made use of three longitudinal studies, all with multi-wave designs and multi-informant reports (see for an overview Table 1.1). For example, peer stressors were examined by relying on multiple informants, including self-report, peer-report, and parent-report. Furthermore, physical health-related outcomes were measured on both the self-perceived and the biological (immune system functioning) level.

The Peer Power Project

Chapter 2 used data from the "Peer Power Project," which examined the effects of peer experiences on adolescents' physical health outcomes across four waves of data (starting in autumn of 2016) with approximately 6 months between

TABLE 1.1 Overview of the Research Question, Study Design, Sample, Peer Experiences and Physical Health-Related Outcome in each Empirical Chapter.

Ch.	Main Research focus	Study Design	Constructs			Sample
			Peer experiences	Outcome	Confounders, predictors	
2	Unique and interactive effects of peer victimization and peer status **(Aim 1)**	Longitudinal: 4 waves approximately 6 months apart	— Peer victimization — Peer preference — Peer popularity — Cumulative peer stress	Self-reported physical health symptoms	— Gender	Peer Power Project n=233 Ages=11-15
3	Interaction between early life adversity and adolescent peer status on a marker of systemic inflammation (**Aim 1, 2, and 3)**	Longitudinal: 3 waves at approximately 11, 13, and 16 years old	— Peer victimization — Peer preference — Peer popularity	hsCRP	— Gender — Early Life Adversity — SES — Fat percentage — Physical activity — Medication use — Contraceptive use — Temperament	TRAILS n= 587 Ages=5-18
4	Effects of cumulative peer victimization on systemic inflammation through BMI & smoking **(Aim 2)** Moderation of the association between cumulative peer victimization and systemic inflammation by individual and family level factors **(Aim 3)**	Longitudinal: 5 waves at approximately 5, 7, 10, 12, and 18 years old	— Cumulative peer victimization	suPAR	— Gender — Smoking — BMI — SES — Maternal warmth — IQ — Anxious depressed disposition	E-Risk n=1,418 Ages=5-18

Note. hsCRP=high sensitive C-reactive Protein; suPAR= soluble urokinase plasminogen activator receptor; SES = social-economic status; TRAILS= TRacking Adolescents' Individual Lives Survey; E-Risk = Environmental Risk Longitudinal Twin Study.

consecutive waves. Retention rate between each consecutive wave was > 90%. Participants were 233 adolescents (47% girls, M_{age}=12.69 years, *SD*=.49 at Wave 1) from two secondary schools in the Netherlands. Adolescents filled out peer nominations to assess peer status (i.e., peer preference and peer popularity) and self-reported on their peer victimization, physical health symptoms, and perceived general health.

TRacking Adolescents' Individual Lives Survey (TRAILS)

Chapter 3 used data from the TRacking Adolescents' Individual Lives Survey (TRAILS), a multidisciplinary longitudinal study that examined the social, mental and physical development of Dutch adolescents across six waves until the age of 25 years. This chapter used data from the first three waves, when adolescents were approximately 11, 13, and 16 years old (retention rate 96.4% at Wave 2 and 81.6% at Wave 3). Participants were 587 adolescents (54.6% girls, M_{age} = 11.11 years, *SD* =.56). At Wave 1, early life adversity was measured with a standardized semi-structured parental interview. Subsequently, at Wave 2, adolescents filled in peer nominations to assess peer experiences (i.e., peer preference, peer popularity, peer victimization). Finally, at Wave 3, immune system functioning was measured by assaying high sensitive CRP from blood samples.

Environmental Risk (E-Risk) Longitudinal Twin Study cohort

Chapter 4 used data from the Environmental Risk (E-Risk) Longitudinal Twin Study cohort, which is a population-representative sample from England that tracks the development of a 1994-95 birth cohort. Data collection took place when participants were respectively 5, 7, 10, 12, and 18 years old (93% overall retention rate at age 18). Immune system functioning was measured at age 18 assaying suPAR from blood samples. Peer victimization was assessed by multiple informants (mother, teacher and child) at age 7, 10, 12 & 18 by making use of interviews. Moreover, maternal warmth, social-economic status (SES), IQ, and an anxious depressed disposition were assessed at age 5, and BMI and smoking at age 18.

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Disentangling the Effects of Peer Status and Peer Victimization on Physical Health in Adolescence

de Bruine, M., Denissen, J. J., Giletta, M., (2021). *Disentangling the Effects of Peer Status and Peer Victimization on Physical Health in Adolescence*. Manuscript submitted for publication.

Abstract

During adolescence, exposure to stressful peer experiences has been related to poor physical health. Yet, different peer stressors have been mostly researched in isolation and the extent to which these associations reflect within-person processes remains largely unknown. Thus, the current study investigated the unique, interactive and cumulative effects of peer victimization and two types of peer status (i.e., peer preference and peer popularity) on adolescent physical health, while separating between- and within-person effects. 233 Dutch adolescents (M_{age}=12.7 years; 47.2% female) completed self-report measures and measures of sociometric status four times during the first two years of secondary school. Multilevel analysis showed that adolescents who reported higher levels of peer victimization than their peers also reported higher levels of physical

problems. Moreover, when adolescents were exposed to higher levels of peer victimization (as compared to their own average levels) they also reported poorer physical health (as compared to their own average levels). No main or interactive effects with peer status were found and the effect of a cumulative peer stress score emerged to be driven by peer victimization. Overall, findings indicate a specific role of between- and within-person effects of peer victimization on adolescents' physical health.

During adolescence, peers increasingly function to fulfill the need to belong and enable social comparison (Brown & Larson, 2009; Hartup & Stevens, 1997). This goes hand in hand with an increased sensitivity to group affiliation and peer status on the positive side but also with episodes of peer exclusion and victimization on the negative side (Somerville, 2013), making negative peer experiences amongst the most salient stressors in adolescence (Bowker et al., 2000). Accordingly, peer stressors (e.g., low peer status, peer victimization) have been shown to have detrimental consequences for adolescents' mental health (Parker & Asher, 1987; Prinstein & Giletta, 2016) but also for their physical health (e.g., somatic complaints; sleep problems; Lee & Vaillancourt, 2018; Moore et al., 2017; Prinstein & Giletta, 2020). However, not all peer stressors may influence adolescents' physical health in the same way. Until now, research has mainly focused on the relationship between peer victimization and physical health outcomes, so that it is unclear whether results generalize to other peer stressors. This is an important omission because less severe stressors might also affect health, either alone or in interaction with other stressors. Additionally, few studies have considered the possibility that peer stressors may act in a cumulative manner, as would be the case if the experience of multiple peer stressors, rather than of a single stressor, would affect adolescents the most. This study aimed to address these gaps in the literature. First, it examined the unique and interactive roles that different types of peer status (i.e., peer preference and peer popularity)

and peer victimization play in predicting adolescent physical health. Second, it investigated the possible cumulative effects of peer stressors (i.e., types of peer status and peer victimization) on physical health.

Peer victimization is defined as a situation in which youth are the target of peer aggression (Kochenderfer & Ladd, 1996). This stressful experience has been related to poor physical health (Moore et al., 2017). For example, meta-analytic work suggests that victims are approximately two times more likely to experience physical health complaints (e.g., headache, abdominal pain), as compared to non-victims (Gini et al., 2014; Gini & Pozzoli, 2013; Moore et al., 2017). Moreover, research indicates that adolescents exposed to higher levels of peer victimization tend to need more medical care and to show altered immune system functioning, as revealed by associations with increased levels of systemic inflammation (Copeland et al., 2014). However, this research builds predominantly on studies that investigated between-person associations, which do not necessarily reflect processes as they occur within a given individual (Curran & Bauer, 2011). That is, even if as compared to adolescents with low exposure to peer victimization, peer victimized adolescents report poorer physical health, it cannot be assumed that when adolescents are exposed to more peer victimization (as compared to their own average exposure level) they also report higher levels of physical health problems (as compared to their own average level). Mounting evidence highlights the importance of examining associations at the within-person level (e.g., Hygen et al., 2020; Lervåg, 2020); Masselink et al., 2018), as these are fundamental to provide knowledge that can more directly guide intervention and prevention efforts. To our knowledge, only Lee and Vaillancourt (2019) examined both the between- and within-person effects of peer victimization on physical health symptoms. They found evidence that when adolescents reported higher levels of peer victimization (as compared to their own average level), they experienced more somatic complaints (as compared to their own average level) at the subsequent assessment. Our study aimed to further investigate the relationship

between peer victimization and physical health in a more nuanced manner, by distinguishing within- and between-person associations.

In addition to peer victimization, having low peer status may also be an important source of stress in early adolescence (Cillessen & Mayeux, 2004). In this life period, adolescents often compare themselves to others and they become increasingly aware of the peer hierarchy (Bowker et al., 2000). Research even indicates that early adolescents prioritize peer status above other social constructs such as fiendschips and romance (LaFontana & Cillessen, 2010). Accordingly, having low status can be a stressful experience and has been shown to affect adolescents' well-being (e.g. Coie & Dodge, 1982); yet, research considering the effects of peer status on physical health is still sparse and it is mostly limited to broad measures of perceived peer status. For example, studies have shown that self-reported social acceptance (e.g. the degree to which youth feel socially accepted, liked or disliked) is associated with general health (Adam et al., 2011; Joffer et al., 2019) and poorer physical health (Delfabbro et al., 2019). As a result, less is known about the health and well-being correlates of more specific indices of more independently assessed peer status (e.g., not only relying on self-reports).

Developmental psychologists have long emphasized the importance of using sociometric methods to adequately assess social status within the peer context (Cillessen & Bukowski, 2018). These methods entail asking every youth within a specific peer context (e.g., classroom, grade, school) to nominate a limited or unlimited number of peers (e.g., classmates, grademates) in response to one or more criteria (e.g., most popular peers; Cillessen & Marks, 2011; Coie & Dodge, 1982). Thus, sociometric methods make use of nominations from all group members to determine the status of the adolescents within that group, and they are recognized as the gold standard to assess peer status (Cillessen & Marks, 2011).

Using sociometric methods, researchers have also pointed out the need to distinguish between two types of peer status: peer preference and peer popularity. First, high peer status can indicate that an adolescent is well liked and

accepted by their peers (peer preference*;* combination of who peers like most and like least). Second, it can also mean that an adolescent has a reputation as being visible in the peer group and having social power (peer popularity*;* a combination of who peers perceive to be popular and unpopular). Although these two types of peer status can overlap, some adolescents are either well-liked or popular, but not both (Parkhurst & Hopmeyer, 1998). Consistent with this, the two types of peer status are only moderately correlated (see Van den Bergh et al., 2020) and have distinctive behavioral profiles (LaFontana & Cillessen, 2002; Prinstein et al., 2018). For example, adolescents who are high on peer preference tend to engage in more pro-social behavior and are seen as trustworthy, whereas adolescents high on peer popularity have a more mixed profile that also includes aggression, delinquency, and engagement in (health) risk behaviors (e.g., substance use; Choukas-Bradley et al., 2015; Cillessen & Mayeux, 2004). Because of these differences, the two types of peer status may also be differentially associated with physical health outcomes.

Although most studies have focused on the role of peer status broadly defined, preliminary work examined associations between peer preference (or its underlying constructs of high acceptance and low rejection) and physical health outcomes (e.g., Brendgen & Vitaro, 2008; de Bruine et al., 2019; Eisenberger et al., 2017; Plenty & Mood, 2016; Temcheff et al., 2011). These studies revealed that peer preference can have implications for adolescent physical health. For example, children who were well-liked by their peers were found to need less medical care years later (Temcheff et al., 2011). Moreover, during adolescence peer preference predicted lower markers of systemic inflammation (i.e., high-sensitivity C-reactive protein, hsCRP; de Bruine et al., 2019). However, existing work did not yield consistent evidence for a direct link between peer preference and physical health. For example, Hartung and colleagues (2015) only found an indirect association between likability and physical health through perceived social inclusion (Hartung et al., 2015). Moreover, Brendgen and Vitaro (2008) revealed that peer rejection was related to physical health only for emotionally

reactive girls. In sum, results are still mixed, although most existing studies seem to support a negative association between peer preference and physical health. However, all these studies are between-person (and cross-sectional) and did not examine within-person changes over time.

While it can be hypothesized that adolescents who are highly preferred are definitely better off than those who are not, the association between peer perceived popularity and physical health might not be as linear; Non-linearity could emerge if both being unpopular but also being very popular would be stressful (Prinstein et al., 2011; Schwartz & Gorman, 2011). On the one hand, unpopular adolescents might experience negative consequences as they have a weak social position in the peer group. On the other hand, popular adolescents might experience negative consequences because they are highly visible within the peer group. Indeed, popular adolescents have been shown to sometimes experience more friendship conflict, engage in unhealthy risk behaviors and have an increased risk for maladjustment (Litwack et al., 2012; Prinstein et al., 2011; Schwartz & Gorman, 2011). Moreover, both the most popular and least popular adolescents in the peer group have been found to be equally at risk for developing externalizing problems (Stoltz et al., 2016), for engaging in health risk behaviors (Prinstein et al., 2011) as well as for experiencing poorer satisfaction with their social relationships (Ferguson & Ryan, 2019). With regard to physical health outcomes, evidence from two studies (de Bruine et al., 2019; Plenty & Mood, 2016) also suggested the possibility of non-linear (i.e., curvilinear) associations. One study revealed that, under certain circumstances, high levels of peer popularity predicted elevated inflammation markers (i.e., hsCRP; de Bruine et al., 2019), while in the other study, unpopular adolescents reported the lowest levels of general health (Plenty & Mood, 2016). Thus, next to the linear effect of peer popularity on physical health, research should consider the curvilinear effects of peer popularity.

Peer victimization and the two types of peer status may not only be independently associated with adolescents' physical health, but could also act in

combination. First, an under-researched possibility is that the two types of peer status interact with one another. Popular adolescents might only report negative health consequences when they also experience low levels of peer preference. For example, popular adolescents might not experience any negative consequence if they are also well-liked, while popular adolescents who are not liked might be exposed to additional stress to maintain high levels of popularity. Moreover, in line with cumulative stress models (Evans et al., 2013), adolescents who experience multiple peer stressors may be those at the highest risk for poorer physical health; yet, these models have received little attention in peer relations research. Cumulative stress models pose that instead of the severity and type of stressor, the number of stressors experienced is associated with poorer health (Evans et al., 2013);. Early life adversity research has indicated that cumulative adversity is important for predicting physical health outcomes (Jakubowski et al., 2018; Kuhlman et al., 2020). Moreover, it has been found that with each additional adverse childhood experience the risk of diseases increases (Danese et al., 2009). This research suggests that for adolescents, it could be that not a single specific peer stressor affects physical health but a sum of different stressors that each threatens overall peer belonging. However, to our knowledge, the accumulation of peer stressors on physical health remains unexamined.

The present study

The present study aimed to examine the unique, interactive and cumulative effects of multiple peer stressors (i.e., types of peer status and peer victimization) on physical health. By investigating the unique effects of different peer stressors, this study offers the opportunity to compare the association of each type of stressor with adolescents' physical health. Notably, these associations were examined using a longitudinal design that allowed the estimation of both between-person and within-person effects. Our design allowed us to address three clusters of hypotheses. First, we expected that high levels of peer victimization would be associated with poorer physical health at both the

between- and within-person level (Gini et al., 2013; Lee & Vaillantcourt 2019). Second, we expected that low levels of peer preference would be associated with poorer physical health at both the between- and within-person level (see de Bruine et al., 2019; Delfabbro et al., 2019; Temcheff et al., 2011). Moreover, we hypothesized a quadratic association between peer popularity and poor physical health at the between-person level, based on work suggesting that both low and high levels of peer popularity in a group may be stressful and pose risk for adjustment (e.g., Prinstein et al., 2011; Schwartz & Gorman, 2011). We also explored an interaction between the two types of peer status to predict poor physical health. Third and finally, we tested a cumulative risk model (Evans et al., 2013), according to which we expected that adolescents who experienced a sum of multiple peer stressors (e.g., peer victimization and low peer preference) reported the most poor physical health, over and above the effect of these individual stressors.

Methods

Participants and Procedure

Participants were 233 adolescents involved in a larger project (i.e., Peer Power Project) aimed at examining the effects of peer experiences on adolescents' health outcomes in two secondary schools in the Netherlands. This project consisted of four waves of data collection, with approximately six months between consecutive waves. Data collection began in November/December 2016 (Wave1), when adolescents were in the fall of the first year of secondary school and ended in June 2018 (Wave 4), just before the end of the second year of secondary school. At baseline, information letters and consent forms were distributed to the parents of all pupils enrolled in the first year of secondary school (n=459). Parents were also informed about the purpose of the study during information evenings that took place at adolescents' schools. Consent forms could be sent

back by mail or handed in at school. Approximately 57% of the parents returned a consent form, and the majority of those who did (87%) gave consent for their child to participate in the study. Adolescents were informed about the study through in-class presentations and they were asked their assent on the testing days. At baseline, only seven adolescents with parental consent refused to take part in the study; moreover, five adolescents were absent on the days of testing and an additional one had moved to a different school. Thus, a total of 215 adolescents took part in the study at Wave 1 (about 47% of the targeted population). Adolescents who did not participate at Wave 1 had the opportunity to join the study at the subsequent waves. Retention rate between consecutive assessments was high (> 90%), with191 adolescents (82%) participating in all waves of data collection. For these analyses, adolescents were included if they participated in at least one of the four waves of data collection. This resulted in an analytic sample of 233 adolescents who at baseline were approximately 12 years old (M_{age}=12.7 years; *SD*=0.5; 47.2% female participants). Most adolescents identified themselves as being Dutch (91.7%) and 81.5% reported to live with both their biological parents.

At each wave, participants completed a series of self-report questionnaires and took part in a peer nomination procedure (see Measures section). Participants were invited to complete these questionnaires during school time in designated rooms including no more than six pupils at a time. All questionnaires were filled in online, except for the peer nomination procedure that was completed with paper and pencil. This study was approved by the Medical Ethics Committee Brabant (NL56418.028.16).

Measures

POOR PHYSICAL HEALTH. Physical health symptoms experienced during the last months were assessed with six self-report items. The first item assessed general health (i.e., "*In general you could say your health is…*") on a five-point Likert scale that ranged from 1='bad' to 5='excellent'. The other five items assessed somatic

symptoms and sleep quality. Specifically, somatic symptoms included headache, stomachache, loss of appetite and fatigue experienced in the last months. Each of these items (e.g., "*In the past months, how many times did you have headaches?*") was rated on a five-point Likert scale (1='never'; 5='very often'). Sleep quality was assessed with a single question (i.e., "*How would you describe your sleep quality in the past month?*") answered on a four-point Likert scale (1='very bad'; to 4='very good').

Because the somatic symptoms and sleep quality items were assessed on different metrics, the proportion of maximum scaling ("POMS") method (Little, 2013) was used before combining all items in an overall scale. This method transforms each scale to a metric from 0 (=minimum possible) to 1 (=maximum possible), by first making the scale range from 0 to the highest value, and then dividing the scores by the highest value (i.e., POMS = [(observed – minimum)/(maximum – minimum)]). Finally, a physical health score was computed by averaging the transformed responses to the six items (i.e., general health, somatic symptoms and sleep quality), with higher scores indicating worse physical health. Internal consistency was satisfactory, with Cronbach's alphas raging between .69 (Wave 1) and .71 (Wave 4).

PEER VICTIMIZATION. Peer victimization was measured with the Revised Peer Experiences Questionnaire (RPEQ; Prinstein et al., 2001), including items about overt, relational and reputational peer victimization. This self-report measure consists of 13 statements (e.g., "*A peer hit, kicked or pushed me in a mean and harmful way*") that were answered on a five-point Likert scale from 1 (= 'never') to 5 (= 'a few times a week'). A total peer victimization score was computed at each time point by averaging across the 13 items, with higher scores indicating higher levels of peer victimization. Internal consistency was good (Cronbach's α ranged between .84-.90).No log transformation for within-person mean levels of peer victimization was necessary as skewness (1.43) and kurtosis (2) were acceptable (George & Mallery, 2010).

PEER STATUS. Peer status was measured with a peer nomination procedure. Adolescents nominated an unlimited number of same- and cross-gender peers within their grade whom they "like the most" (= acceptance) and "like the least" (= rejection; Coie & Dodge, 1982), and whom they found "most popular" (= popularity) and "least popular" (= unpopularity). To ensure anonymity, adolescents were provided with a roster including the names of all pupils in their grade and were asked to report the numbers associated with the grademates they wished to nominate on a separate questionnaire. For each participant, a peer preference score was computed by subtracting the raw total number of nominations received on the "liked least" criterion from the raw total number of nominations received on the "liked most" criterion (Cillessen & Bukowski, 2018). A peer popularity score was computed by subtracting the raw total number of nominations received on the "least popular" criterion from the raw total number of nominations received on the "most popular" criterion (Cillessen & Bukowski, 2018). We used the raw number of total nominations because in this study grade size was highly similar for the two schools and standardization within schools would have eliminated information of how personal mean scores would change over time, as each wave would be standardized separately (Nezlek, 2012; Velásquez et al., 2013). To still account for any difference in the size of the grade between the two school, grade size was added into the analytic models as covariate. Extreme outliers (i.e., > 3 *SD* below or above the mean; n=2 for peer preference and n=5 for peer popularity) were winsorized to the highest value in the distribution.

Plan of Analyses

All analyses and hypotheses were preregistered and run accordingly (see osf.io/ctbmh). To examine both between- and within-person associations, all study variables were initially transformed in the following way. First, to be able to identify between-person effects, person-specific means of (Level 2) peer victimization, peer preference and peer popularity were computed across all four

assessments. Second, to be able to identify within-person effects, within-person deviations (Level 1) in peer victimization, peer preference and peer popularity were calculated as a given assessment's value minus an adolescent's person mean across all assessments divided by the adolescent's unique standard deviation (i.e., within-person standardized).

For all research questions, a multilevel modeling approach was used. To examine the *unique* associations between peer stressors (i.e., peer victimization, peer preference and peer popularity) and physical health (i.e., unique-effect models), two multivariate multilevel regression models were specified with time at Level 1 and person at Level 2. In the first model, we predicted physical health changes by between-person (i.e., mean peer victimization), and within-person (e.g., within-person deviations over time of peer victimization) levels of peer victimization, peer preference and peer popularity (Model 1). In the second model, we examined a quadratic trend on top of a linear trend of between-person levels of peer popularity (Model 2). Subsequently, to explore whether peer preference interacted with peer popularity (i.e., interaction-effect model; Model 3), we added the interaction term between the two types of peer status at both the between- and within-person level (in this model, the quadratic effect of peer popularity was not included)

Finally, to test a cumulative risk model we used peer victimization, peer acceptance, rejection and unpopularity as risk variables to create a cumulative risk metric score. We a priori decided not to include peer popularity in the cumulative score, as it remained unclear to what extent high levels of peer popularity represent a risk factor/stressor (this was explored in Model 2). In line with research on cumulative risk (Evans et al., 2013), each risk variable was dichotomized to reflect either absence (= '0') or presence (= '1') of the peer stressor. With regard to peer victimization, in line with previous research (Oldenburg et al., 2015; Solberg & Olweus, 2003), adolescents were classified as victims (= "1") when they scored 3 or higher on at least one experience of peer victimization (i.e., one of the 13 items). Adolescents who scored 1 (= "never")

or 2 ("one/two times") were thus classified as not victimized. With this approach, adolescents who were exposed to one or more peer victimization form at least three times a month were classified as victims (Solberg & Olweus, 2003). For peer acceptance adolescents were classified as experiencing risk (i.e., "1") if their scores fell at or below the 25th percentile (reflecting 0/1 nominations). For peer rejection and peer unpopularity, adolescents were classified as experiencing risk (i.e., "1") if their scores were above the 75th percentile (reflecting two or more nominations; Gerard & Buehler, 2004; Hebron et al., 2017).

All models were adjusted for gender and grade size. Missing data across all variables ranged between 0 and 10.7% and were completely at random (Little's MCAR test: $\chi^2(1114) = 305.7$, $p = 1.00$). Thus, maximum likelihood estimators were used to handle missing data.

Results

Descriptive analyses

Table 2.1 presents bivariate correlations among all study variables across all four waves for descriptive purposes. Peer victimization was associated with poorer physical health across all waves (correlations ranging from .17 to .39). In contrast, both types of peer status were not associated with physical ill health, with the exception of a positive concurrent correlation between peer popularity and physical ill health at Wave 3. Finally, positive correlations between the cumulative peer stress index and physical ill health emerged; specifically, Wave 2 and 3 cumulative peer stress correlated with all physical ill health at all waves, and Wave 4 cumulative peer stress correlated with Wave 1 and 4 physical ill health.

Effects of peer experiences on physical health

An intraclass correlation (ICC) of .65 was revealed, indicating that 65% of the variance in physical ill health was at the between-person level. An overview of

TABLE 2.1 Bivariate Correlations Among Study Variables.

			Physical health				Peer Victimization				Peer Preference				Peer Popularity				Cumulative Peer Stress			
Variable	*M*	*SD*	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Physical health																						
Wave 1	0.31	0.16																				
Wave 2	0.33	0.16	.64**																			
Wave 3	0.31	0.16	.61**	.66**																		
Wave 4	0.33	0.17	.60**	.63**	.78**																	
Peer Victimization																						
Wave 1	1.27	0.42	.37**	.30**	.18*	.17*																
Wave 2	1.32	0.38	.39**	.36**	.28**	.24**	.61**															
Wave 3	1.27	0.34	.31**	.22**	.26**	.21**	.41**	.54**														
Wave 4	1.31	0.38	.30**	.22**	.28**	.33**	.38**	.50**	.52**													
Peer Preference																						
Wave 1	2.22	2.92	-.01	.03	.02	.02	-.20**	-.17*	-.12	-.05												
Wave 2	2.10	3.04	-.03	.00	-.01	.04	-.19**	-.17*	-.14*	-.13	.71**											
Wave 3	2.42	2.95	-.05	-.01	-.01	.00	-.20**	-.20**	-.23**	-.17*	.61**	.67**										
Wave 4	2.38	3.00	-.04	-.01	.01	-.03	-.23**	-.13	-.18*	-.18**	.57**	.64**	.66**									
Peer Popularity																						
Wave 1	0.24	3.48	-.03	.00	.07	.01	-.10	-.00	-.01	-.06	.34**	.32**	.34**	.25**								
Wave 2	0.04	4.03	-.03	-.00	.09	.04	-.09	.04	.04	.04	.29**	.35**	.33**	.24**	.85**							
Wave 3	0.17	4.08	-.00	.01	.15*	.05	-.04	.05	.06	.09	.31**	.32**	.32**	.25**	.79**	.86**						
Wave 4	0.02	4.74	-.01	.00	.13	.02	-.10	.04	.03	.04	.31**	.34**	.35**	.26**	.79**	.87**	.90**					
Cumulative Peer Stress																						
Wave 1	0.88	1.00	.13	.09	.03	.08	.43**	.30**	.26**	.19**	-.58**	-.60**	-.50**	-.39**	-.40**	-.37**	-.35**	-.36**				
Wave 2	0.97	1.01	.18**	.19**	.15*	.13*	.33**	.47**	.31**	.27**	-.48**	-.55**	-.54**	-.33**	-.35**	-.36**	-.27**	-.32**	.56**			
Wave 3	0.95	0.98	.22**	.14*	.14*	.16*	.40**	.37**	.43**	.39**	-.37**	-.37**	-.52**	-.55**	-.23**	-.24**	-.22**	-.24**	.48**	.47**		
Wave 4	0.97	0.93	.15*	.12	.11	.14*	.29**	.25**	.35**	.38**	-.48**	-.41**	-.49**	-.52**	-.35**	-.36**	-.28**	-.41**	.48**	.47**	.53**	
Gender	0.53	0.50	-.16*	-.19**	-.25**	-.27**	.11	-.04	.01	-.03	-.29**	-.21**	-.23**	-.21**	.10	.07	.04	.07	.11	.05	.14*	.12
Age	12.69	0.49	.00	-.07	-.01	-.05	.04	.12	-.02	.06	-.11	-.12	-.04	-.04	.07	.12	.12	.16*	.05	-.05	.09	.07

Note. Gender was dummy-coded (0 = female, 1 =male). Values in square brackets indicate the 95% confidence interval for each correlation.*p < .05. **p <.01.

the unique, interactive and cumulative models can be found in Table 2.2. In all models, boys reported less physical ill health than girls (β=-21, *SE*=.05, *p*<.01).

UNIQUE EFFECTS MODEL. Both the person-specific mean and the within-person deviations of peer victimization were related to physical ill health[1]. Thus, a between-person effect was found, indicating that adolescents reporting higher levels of peer victimization had poorer physical health in comparison to adolescents who scored low on peer victimization. Additionally, a within-person effect was revealed, indicating that adolescents who reported more peer victimization experiences (relative to their own mean), also reported poorer physical health (relative to their own mean level).

For peer status, no significant effects were found, both for the person-specific means as well as for the within-person deviations of peer preference and peer popularity. This indicates that between-levels differences and within-person changes of both types of peer status were not associated with physical ill health. Additionally no quadratic trend was found for the association between peer popularity and physical ill health.

INTERACTIVE EFFECTS MODEL. To investigate if adolescents who experienced high levels of peer popularity but low levels of peer preference reported poorer physical health, an interactive effect of peer popularity and peer preference was tested. No interaction effects were found, neither at the between- nor at the within-person level (see Table 2.2).

CUMULATIVE EFFECT MODEL. To investigate if the sum of low peer status and high peer victimization affected physical ill health, a cumulative effect model was

1 We also explored whether peer victimization predicted poorer physical health at the subsequent wave, by estimating a cross-lagged model with physical health at time t regressed on peer victimization at time t-1. These explorative analysis did not emerge to fit the data better (p =.11).

TABLE 2.2 Results of Multilevel Models Predicting Physical Health From Peer Victimization, Peer Preference and Peer Popularity.

Predictor	Outcome: Physical ill health								
	Unique effects model			Interactive Model			Cumulative Model		
	β	*SE*	95% CI	β	*SE*	95% CI	β	*SE*	95% CI
Intercept	.37	.17	[.03;.70]	.36	.17	[.02;.70]	.41	.17	[.07;.76]
Gender	-.43**	.10	[-63;-22]	-.43**	.10	[-63;-22]	-.47**	.11	[-.68;-.26]
Time	.02	.02	[-.02;.07]	.02	.02	[-.02;.07]	.02	.02	[-.02;.07]
Grade size	-.09	.10	[-.28;.10]	-.08	.10	[-.28;.10]	-.11	.11	[-.32;.10]
Person-specific mean Peer Victimization	.36**	.05	[.26;.46]	.36**	.05	[.25;.46]			
Person-specific mean Peer Preference	.00	.02	[-.04;.05]	.00	.02	[-.04;.05]			
Person-specific mean Peer Popularity	.00	.01	[-.02;.03]	.00	.02	[-.03;.03]			
Person-specific mean Peer Popularity*	.00	.00	[.00;.00]						
Person-specific mean Peer Preference X Person-specific mean Peer Popularity				.00	.00	[-.01;.01]			
Within-person deviations from Peer Victimization	.09**	.02	[.06;.13]	.09**	.02	[.06;.13]			
Within-person deviations from Peer Preference	-.02	.02	[-.06;.02]	-.02	.02	[-.06;.02]			
Within-person deviations from Peer Popularity	.03	.02	[-.01;.06]	.03	.02	[-.02;.07]			
Within-person deviations from Peer Preference X Within-person deviations from Peer Popularity				.01	.02	[-.04;.05]			
Person-specific mean Cumulative Peer Stress							.20 **	.05	[.08;.30]
Within-person deviations from Cumulative Peer Stress							.01	.02	[-.03;.04]

Note. * The quadratic trend of peer popularity was tested in a separate model (Model 2). ** p < .01.

tested. Person-specific mean levels of cumulative risk scores, but not within-person deviations, were significantly associated with physical ill health. Thus, adolescents who experienced overall more peer stress (sum of low peer status and high peer victimization) than other adolescents reported poorer physical health. However, when adolescents reported more peer stress (relative to their own peer stress levels) they did not report poorer physical health (relative to their own levels of physical health).

Because the between-person cumulative effect found in this model could be driven by the effects of peer victimization, we conducted a follow up analyses that separated peer victimization from the rest of the cumulative peer stress score (in line with Young et al., 2020). For this model, the cumulative score was recalculated including all peer stressors except high peer victimization. This model included a person-specific mean score and within-person deviations for both the cumulative risk score as well as for peer victimization. Results of this model showed no significant associations involving cumulative peer stress (person-specific mean levels: β=.00, *SE*=.05, *p*=.94; within-person deviations: β=-.03, *SE*=.02, *p*=.08), but only peer victimization (person-specific mean levels: β=.36, *SE*=.05, *p*<.01 within-person deviations: β=.09, *SE*=.02, *p*<.01). These results indicate that the initial between-person effect of cumulative peer stress was likely driven by the fact that those adolescents who experienced more overall peer stress also experienced more peer victimization than other adolescents.

Discussion

This study investigated how different types of peer stressors are associated with adolescent poor physical health at the between- and within-person level. Specifically, we examined the unique, interactive and cumulative associations of peer victimization and peer status on physical health. Results showed that adolescents who experienced higher peer victimization than others reported

poorer physical health. Additionally, results showed that when adolescents experienced more victimization in comparison to their own average levels, they also reported poorer physical health (as compared to their own average levels). These effect were specific for peer victimization as no associations were found between the two types of peer status (i.e., peer preference, peer popularity) and poorer physical health. Moreover, poorer physical health could also not be explained by an interaction between peer preference and peer popularity, and the cumulative effect of peer stress emerged to be driven primarily by peer victimization. Overall these results indicate that the type of peer stress does matter, suggesting that only peer victimization is associated with adolescent physical health, both at the between- as well as within-person level.

The main finding of this study was the negative effect of peer victimization on physical health. At the between-person level, this effect corroborates previous findings showing that victimized youth have poorer physical health, as compared to their non-victimized peers (see meta-analyses of Gini et al., 2014; Gini & Pozzoli, 2013). Consistent with prior work, the magnitude of this effect was moderate. Importantly, the association between peer victimization and physical health also emerged at the within-person level: When adolescents experienced more victimization than usual, they also reported poorer physical health than usual. This within-person effect is in line with a study by Lee and Vaillancourt (2019), that, to our knowledge, is the only one to also discern between- and within-person effects. The within-person effect of peer victimization is of particular importance for at least two reasons. First, they provide a better representation of the real-life processes, as we expect them to occur within individuals. Second, within-person effects have less bias of time-invariant unobserved confounders (e.g., other personality traits; Lervåg, 2020). Therefore, these within-person effects are more suitable to base intervention strategies upon as these within-person effects provide more direct evidence that peer victimization and physical health influence one another. Furthermore, the effects found in this study represent effects specifically for peer victimization and not

other peer stressors. Peer victimization has mostly been studied in isolation and therefore, past effects could have included effects of other peer stressors. For example, because peer victimization is often correlated with low peer status, the effects could have included low peer status (Kochel et al., 2012).

This study also examined the possible impact of two types of peer status, yet neither peer preference nor peer popularity was associated with adolescent physical health. These results are in contrast with previous studies suggesting that peer status can influence physical health outcomes (Brendgen & Vitaro, 2008; de Bruine et al., 2019; Eisenberger et al., 2017; Temcheff et al., 2011). For example, low peer status has been found to be associated with elevated levels of systemic inflammation (de Bruine et al., 2019). Moreover, neither low nor high popularity was associated with poorer physical health. And, adolescents who were low on peer preference and high on peer popularity did not have better physical health. Overall, these findings indicate that when taking into account peer victimization, peer status does not play any role in explaining adolescents' physical health.

The lack of association found for peer status could be due to a number of reasons. First, as low peer status and peer victimization represent different types of peer stress, the different association with physical health might stem from differences in the severity of low peer status and peer victimization. On the one hand, peer victimization might represent a very powerful stressor that can generate immediate distress for the victims and therefor might affect their physical health in the short run. Conversely, peer status might be a less severe stressor that does not directly have effects on physical health. Low peer status does not represent a single experience or situation of stress but a position in the peer group that is formed across an accumulation of situations and experiences. Therefore it could be that peer status might have a longer incubation period and the effects of low status can only be seen over a longer period of time (de Bruine et al., 2019; Kuhlman et al., 2020). On the other hand, the lack of effect might stem from the fact that peer status and peer victimization were measured using

different methodologies. While a self-report measure of peer victimization was used, peer status was assessed with a sociometric procedure. Overall it would be important for future research to measure peer status and peer victimization with both self-report and peer reports and to investigate longer term designs to adequately examine the role of peer stressors on adolescent health.

Finally this study examined whether a count of the amount of peer stressors would affect adolescents' physical health, regardless of the type of stressor. Consistent with cumulative risk models (Evans, et al., 2013), this count variable covaried with physical health at the between-person level: Adolescents exposed to a higher number of peer stressors reported poorer physical health than their peers experiencing fewer peer stressors. However, follow-up analyses indicated that this association was primarily be driven by peer victimization experiences. This study therefore does not support the notion that peer stressors may be interchangeable; instead, it highlights a specific role of peer victimization as a type of peer stressor that may be particularly salient to understand adolescent poor physical health. For clinical practice and intervention efforts, when choices have to be made (e.g., due to limited resources) these study results indicate that it is important to address peer victimization. Needless to say, this does not diminish the potential importance of interchangeable stressor counts (cumulative risk) for other outcome domains in which such counts have shown to be important when (e.g. for biological measures; Danese et al., 2009; Evans et al., 2013) or for combinations of stressors across domains (e.g. family, neighborhood).

This study has a number of strengths, including the focus on multiple peer stressors, the examination of both between- and within-person effects and the preregistration of the study hypotheses and analytic plan. However, the results of this paper have to be viewed in light of some limitations. First, findings did not allow us to draw any conclusion on the direction of effects between peer victimization and physical health problems. Recent research has shown that the associations between peer victimization and physical health is likely bidirectional in nature, with poor physical health also increasing the risk

for subsequent peer victimization (Lee & Vaillancourt, 2019). Because the focus of this paper was on comparing multiple predictors and interactions general multilevel models were used, in which bidirectionality can not be tested. Future research could use random-intercept cross-lagged panel models to test bidirectionality in the current dataset. Additionally, despite the high retention rate over time, participation rate at baseline was below 50%, which may have affected the reliability of the sociometric measures. To attenuate this problem, we used unlimited nominations within each grade. Yet, although sociometric measures of popularity tend to be reliable even with low participation rates, this may not be the case for peer preference (Marks et al., 2013). Although this remains a limitation, concerns were alleviated by the pattern of correlations emerged among peer constructs, especially the associations between peer popularity and peer preference, which was highly consistent with prior research (see van den Berg et al., 2020). Finally, we relied on a self-report measure of physical health. Future work should attempt to replicate these findings using other measures of physical health, such as medical care use/diagnoses or biological markers (e.g., inflammation markers).

Another future line of study would be to examine the interplay between peer victimization and peer status for adolescents' physical health. The cumulative method allowed us combine peer stressors but gave equal weight to each peer stressor. This it could still be that peer victimization differentially affects physical health for adolescents with different levels of peer status. This is supported by an increasing number of studies indicating an interplay between peer victimization and peer status of adolescents' outcomes (Malamut et al., 2020; Swirsky & Xie, 2020).

In sum, the current study indicated that when examining the role of multiple peer stressors on adolescent physical ill health in a stringent and nuanced manner, peer victimization plays a predominate role. Therefore, for addressing physical ill health in adolescence it might especially important in the peer domain to focus on peer victimization.

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3

A Healthy Peer Status: Peer Preference, not Popularity, Predicts Lower Systemic Inflammation in Adolescence

de Bruine, M., Giletta, M., Denissen, J. J., Sijtsema, J. J., & Oldehinkel, A. J. (2019). A healthy peer status: Peer preference, not popularity, predicts lower systemic inflammation in adolescence. *Psychoneuroendocrinology*, *109*, 104402.

Abstract

In adolescence, sensitivity to peers is heightened, which makes peer experiences highly salient. Recent work suggests that these experiences may influence individuals' immune system functioning. Although there is a need to investigate which types of developmental salient social experiences affect inflammation, no studies have examined the role of peer status in inflammatory activity so far. This study is the first to examine the unique role of different types of peer status (i.e., peer preference and peer popularity) on systemic inflammation in adolescence, and the extent to which this association is moderated by early childhood adversity. Participants were 587 Dutch adolescents from the TRacking Adolescents´ Individual Lives Survey (TRAILS). Data were collected when participants were 11 (*SD* =.56), 13 (*SD* =.53) and 16 (*SD* =.71) years old, respectively. At

age 11, early childhood adversity (e.g., hospitalization, death within the family) between 0-5 years was assessed via parent interviews. At age 13, peer preference and peer popularity were assessed with peer nominations of classmates. At age 16, high sensitive C-reactive protein (hsCRP), a marker of low-grade systemic inflammation, was assessed with a venipuncture blood draw. Results showed that adolescents who were rated low on peer preference at age 13 exhibited higher levels of hsCRP at age 16. Importantly, these effects remained after controlling for several covariates, including age, sex, peer victimization, smoking behavior, SES, fat percentage, physical activity and temperament. Additionally, we found a positive effect of peer popularity on hsCRP that depended on early childhood adversity exposure. This suggests that for those adolescents who experienced little early childhood adversity, high levels of peer popularity were associated with high levels of hsCRP. Overall, these findings suggest that it is important to take into account the independent roles of peer preference and peer popularity, as specific types of peer status, to better understand adolescent systemic inflammation.

Adolescents spend much of their day interacting with peers and for most of them, being accepted and liked by peers is of chief concern (Somerville, 2013). In adolescence, peer sensitivity is heightened in comparison to other periods in life. Thus, not surprisingly, adolescents' social position in their peer group has a major impact on their psychological well-being and development (Parker & Asher, 1987; Prinstein & Giletta, 2016). Despite extensive attention to the consequences of peer status, researchers have rarely considered the extent to which these peer experiences may have consequences that extend beyond adolescent psychosocial well-being. Theoretical and empirical work suggests that social experiences may affect individuals' immune system activity (Slavich & Cole, 2013). However, the field has yet to identify specific developmentally salient stressors that can affect

immune system functioning. The current study therefore set out to examine peer status antecedents of adolescent inflammation.

Inflammation, a key process of the immune system, is considered a pathway to many of the most common mental and physical health problems. Markers of systemic inflammation (e.g., C-reactive protein [CRP], a protein of the acute inflammation phase) are independent predictors of cardiovascular diseases, diabetes, and depressive symptoms (Valkanova, Ebmeier, & Allan, 2013). Recent research suggests that inflammatory activity is not only influenced by physical threats but can also be regulated by social factors. Because of the social nature of human beings, the immune system may have evolved to respond to experiences of social disconnection, given that in these situations physical injuries and infections are more likely to occur (Eisenberger, Moieni, Inagaki, Muscatell, & Irwin, 2017; Slavich & Cole, 2013). Consistent with this possibility, environments that threaten the individual's social connections can increase inflammatory activity by up-regulating the expression of pro-inflammatory genes and down-regulating the expression of anti-viral genes, a process that has been referred to as Conserved Transcriptional Response to Adversity (CTRA; Slavich & Cole, 2013). Prolonged activation of pro-inflammatory pathways may eventually lead to elevated levels of systemic inflammation and therefore pose a risk for individuals' health. Indeed, broad measures of social experiences, including social rejection, social conflict, and social disconnection, have been associated with higher inflammation levels in adults as well as adolescents (e.g., Murphy, Slavich, Rohleder, & Miller, 2013; Allen, Loeb, Tan, Narr, & Uchino, 2017). Conversely, experiences of social acceptance have been associated with lower levels of inflammation (Bajaj et al., 2016). Despite this evidence, however, no prior study has investigated whether different types of peer status may affect inflammation.

Peer Status and Inflammation

Two distinct forms of peer status have been identified in the developmental psychology literature, namely peer preference and peer popularity (Cillessen

& Marks, 2011). Whereas peer preference is a combination of who peers like most minus who they like least (it is thus akin to likeability), peer popularity reflects the reputation of having social power (e.g., power to exert influence), access to resources, and visibility within the peer group (Prinstein et al., 2018). Research has indicated that adolescents distinguish between these two forms of peer status, and that both forms of status have different psychosocial correlates (LaFontana & Cillessen, 2002; Prinstein et al., 2018). For instance, peer preference has been associated with more prosocial behavior, less friendship conflict, higher ratings of perceived trustworthiness, and lower risk for developing both externalizing and internalizing problems (Litwack, Wargo Aikins, & Cillessen, 2012; Parkhurst & Hopmeyer, 1998; Prinstein et al., 2018). In contrast, peer popularity has been associated with higher levels of aggression, delinquency, and engagement in (health) risk behaviors (e.g., substance use; Cillessen & Mayeux, 2004; Choukas- Bradley, Giletta, Neblett, & Prinstein, 2015). Furthermore, popular and well-liked adolescents show little overlap (Parkhurst & Hopmeyer, 1998). For example, popular peers may not be well-liked because in some instances they tend to be mean to their classmates and make use of aggression to maintain their high status (e.g., Cillessen & Mayeux, 2004; Merten, 1997). Peer preference and peer popularity thus represent different indicators of peer status.

The lack of research examining the unique role of these two types of peer status on adolescent inflammation represents a missed opportunity for at least three reasons. First, relationships with peers become more salient in adolescence and it is particularly important for adolescents to have positive connections with their peer group (Hartup & Stevens, 1997). Second, because of adolescents' heightened peer sensitivity, threats to social connections during adolescence may induce stronger emotional, neural and physiological responses than during other periods in life (Crone & Dahl, 2012; Somerville, 2013). Third, given the differences between the two types of peer status, it is important to examine their independent effects on systemic inflammation. Previous research has shown that broader experiences of acceptance and rejection that underlie peer preference

may be relevant to inflammatory processes (Bajaj et al., 2016; Eisenberger et al., 2017; Slavich & Cole, 2013). However, it remains largely unknown whether peer popularity also predicts systemic inflammation, as no research has examined the constructs of peer popularity directly. Specifically, because peer popularity has also been associated with higher levels of stress exposure (Litwack, Wargo Aikins, & Cillessen, 2012), it remains unclear if low or high levels of peer popularity would be related to higher levels of inflammation (Murphy, Chen, & Parker, 2013). This study aimed to fill this gap by investigating the independent associations of these two types of peer status with inflammation.

While investigating associations between peer status on inflammation, it is crucial to also take into account other more severe peer experiences that have been previously linked to inflammation. In this regard, prior studies have mostly focused on peer victimization. These studies revealed that peer victimization in childhood and adolescence is associated with higher levels of CRP in adulthood up to 30 years later and can predict steeper increases in CRP over time (Copeland et al., 2014; Takizawa, Danese, Maughan, & Arseneault, 2015). Although the two types of peer status and peer victimization show some overlap, previous research has indicated that they are only moderately correlated (Bukowski & Sippola, 2001). For example, low levels of peer preference can mean that adolescents are disliked or neglected but does not necessarily indicate that peers behave negatively towards them or have victimized them (Coie, Dodge, & Coppotelli, 1982). Low levels of peer status most often indicate a weaker social position in the peer group that could pose a separate risk, in addition to victimization, for heightened inflammation. Indeed, psychoneuroimmunological research has suggested that disconnection and lack of integration may be sufficient to trigger inflammatory activity (Slavich & Cole, 2013). This study therefore examined whether peer preference and peer popularity predict inflammatory responses, even in the absence of less extreme and direct forms of peer threats.

The Role of Early Childhood Adversity

The effects of peer status on adolescent inflammation might be particularly strong for adolescents who have already experienced prior adversity. According to the stress-amplification and neuroimmune network model, adversities occurring in the first years of life may have long-lasting effects on immune system functioning by increasing individuals' reactivity to adversities occurring in subsequent periods (Miller, Chen, & Parker, 2011; Nusslock & Miller, 2016; Rudolph & Flynn, 2007). Specifically, these adversities can increase the proinflammatory tendencies in monocytes and macrophages. The body sensitizes to the stressful environment early in life, and consequently may show more profound inflammatory responses when experiencing stressors later in life (Miller et al., 2011), such as during adolescence, when sensitivity to peer influences is theorized to be already heightened (Del Giudice, Ellis, & Shirtcliff, 2011). The stress-amplification model has been supported by findings that early life adversity may enhance inflammatory responses to stressors in adulthood (Carpenter et al., 2010; Kiecolt-Glaser, Gouin, & Hantsoo, 2011; Pace et al., 2006). However, it has also been proposed that early adversity could affect responsivity to later stressors in the opposite way, by making individuals more resilient (see for instance, Seery, Leo, Holman, & Silver, 2010). Overall, it is therefore unclear whether and how stressors occurring early in life and in adolescence interact to influence the immune system functioning.

The Present Study

In the present study, we aimed to extend existing research on social experiences and immune system functioning by examining for the first time the role of two different types of peer status (i.e., peer preference and peer popularity) among adolescents. Specifically, we had two aims: a) to investigate the independent ability of adolescent peer preference and peer popularity to predict systemic inflammation and b) to examine the moderating role of early childhood adversity on the link between the two types of peer status and systemic inflammation. To

address these goals, we used data from TRAILS (TRacking Adolescents' Individual Lives Survey), a multi-informant longitudinal study that includes interview, self- and peer-reports, and blood samples to assay high-sensitivity CRP (hsCRP) from a large sample of adolescents. We hypothesized that peer preference at age 13 would be negatively related to hsCRP levels at age 16. However, because prior research has been inconsistent, no strong hypotheses on the direction of the association for peer popularity were formulated. Finally, we hypothesized that the associations between peer status and systemic inflammation would be exacerbated by the experience of early childhood adversity. Specifically, we expected that low peer preference would more strongly predict higher hsCRP levels in adolescent with a history of early childhood adversity than in those without. Comparable to the main effect, no hypotheses were formulated for peer popularity. When examining these associations, we accounted for a number of possible confounding factors, including peer victimization, socio-demographic variables, health-related factors, and temperament. Gender differences were also explored, as initial evidence suggests that the association between social stress and systemic inflammation might be stronger in women than in men (Baldwin et al., 2018).

Material and methods

Participants and Procedure

The sample consisted of 587 adolescents (54.6% females) from TRAILS, a multidisciplinary longitudinal study aimed at examining the social, mental and physical development of Dutch adolescents (De Winter et al., 2005). At baseline, adolescents were enrolled in the last two years of primary school (M_{age} = 11.11 years, *SD* =.56). The majority of the adolescents identified themselves as Dutch (92.6%), and had married parents (77.0%, divorced 13.8%, never married 8.2%, other 1.0%).

Participants were recruited on the basis of age (10-12 years old) from 122 primary schools from 5 selected municipalities in the north of the Netherlands. Next to assent from the child, the primary caregiver (e.g., parent or guardian) was asked to give consent for participation in the study. Of all targeted adolescents, 76.0% participated (for a more detailed description of the total TRAILS sample selection, sample characteristics, and methods, see De Winter et al., 2005). This resulted in a baseline sample of 2,230 adolescents, who were followed until the age of 25 years for a total of 6 waves of data collection. The current study was based on data from the first three waves, when adolescents were approximately 11, 13 and 16 years old. At Wave 1, the response rate was 76.0%, and there were good retention rates at follow-up (96.4% at Wave 2; 81.6% at Wave 3).

At Wave 1, trained interviewers visited the parents or guardians at their home to administer a semi-structured interview. At Wave 2, a peer nomination procedure was administrated in all classrooms with at least three TRAILS participants, which was completed by participants as well as their classmates. Because of this, approximately 46.9% of the Wave 2 TRAILS participants (*N*=1,007) were included in the peer nomination procedure (see Figure 3.1.).

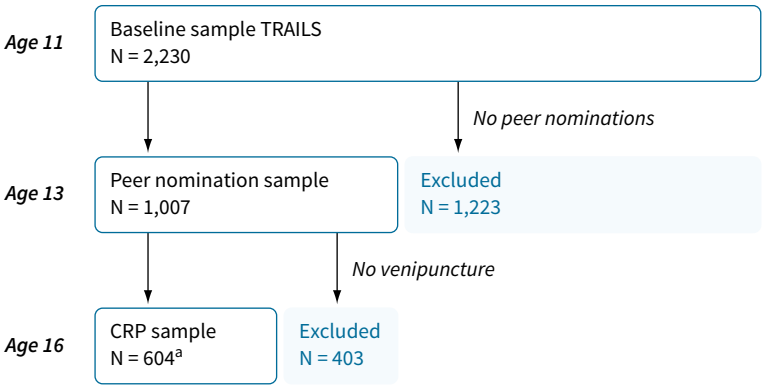

FIGURE 3.1 Flowchart displaying the sample selection procedure. hsCRP= high-sensitivity C-reactive protein.

Note. a An additional 17 participants with venipuncture were excluded because of abnormal hsCRP values (> 10; see description measures).

Information about the consent procedure to recruit participants' classmates is presented in the Supplemental Information and a full description of the peer nomination procedure for the TRAILS study can be found in Dijkstra, Lindenberg, and Veenstra (2008). At Wave 3, consent was obtained from participants and their parents for the collection of blood samples. From the adolescents who participated in the peer nomination procedure, 60.0% (*N*=604) gave consent for the collection of blood samples (see Figure 3.1). For this study, adolescents were selected who took part in both the peer nomination procedure and the collection of blood samples. Of those adolescents, 17 were excluded because of abnormal hsCRP values (see Measures section). We therefore ended up with a sample of 587 adolescents. These adolescents had significantly higher levels of SES and early childhood adversity than the excluded adolescents (*N*=1,643) from the baseline sample (see Table S3.1). No significant differences were observed on any of the other main study variables. The Central Committee on Research Involving Human Participants (the Dutch acronym being CCMO) approved the TRAILS study protocol at all three waves.

Measures

EARLY CHILDHOOD ADVERSITY (AGE 0-5). At Wave 1, information on major stressors occurring within the first five years of life was obtained with a standardized semi-structured parental interview administered by trained interviewers during the home visit. Based on previous studies (e.g., Bosch et al., 2012; Hughes et al., 2017; Slopen et al., 2015), six different adversities were selected to create a measure of early childhood adversity: child hospitalization, out-of-home placement, parental divorce, death of a family member, parental addiction, and other parental mental health problems. These adversities were chosen because they are the most commonly used in research examining early life adversity (for example, see Hughes et al., 2017). For most experiences, parents indicated whether the events occurred when the child was between 0 and 5 years old. For parental addiction and other mental health problems, parents indicated when in their lives they

suffered from these problems. Each experience that occurred when the child was between 0 and 5 was counted, and a sum score was computed across all six adverse experiences, with higher values indicating more types of early childhood adversity (possible range 0-6; *M*=1.03; *SD*=1.20). Finally, the sum scores of childhood adversity were log transformed to normalize the data before analysis. Additional information about the semi-structured interview and validity of the measure can be found in the Supplemental Information.

PEER PREFERENCE. At Wave 2, adolescents were asked to nominate an unlimited number of same- and cross-gender peers within their classroom whom they "like the most" and "like the least" (Coie & Dodge, 1983). To ensure anonymity, adolescents were provided with a roster including all classmates and were asked to report the numbers associated with the classmates they wished to nominate on a separate questionnaire. The nominations received by each participant on each criterion were summed and participants who received no nominations were included in the analyses with a total number of zero nominations. To account for differences in class size, received nominations were subsequently standardized to z-scores within classrooms and a peer preference score was computed by subtracting the standardized "liked least" nominations from the standardized "liked most" nominations. Finally, differences between the two standardized scores were standardized again within classrooms (*M*=.02; *SD*=1.02; Coie & Dodge, 1983). This measure has been widely used and has proven reliable and valid (Cillessen, 2009).

PEER POPULARITY. At Wave 2, peer popularity was assessed with the peer nomination item: "with whom do others want to associate?" (for a description of the peer nomination procedure see "Peer preference"). Peer popularity scores were then summed and standardized to z-scores within classrooms. This item explicitly disentangles personal preferences for being associated with a person from reputation-based preferences by asking respondents to nominate people

with whom others want to be connected. This measure of popularity has been previously used in other studies (see for example, Bowker, Bukowski, Hymel, & Sippola, 2010) and showed convergent and discriminant validity with other types of peer status (see Dijkstra et al., 2008).

HIGH-SENSITIVITY C-REACTIVE PROTEIN (HSCRP). At Wave 3, blood samples were collected by a trained medical worker using venipuncture. Blood samples were drawn into serum separator tubes (5 ml with gel) and were collected at different locations, including schools, community centers or other research sites nearby participants' houses. Samples were transported to the laboratory within 4 hours at room temperature. In the lab, the blood samples were centrifuged (10 min., 2500g, 4C) and serum was stored at -80 degrees. Although blood centrifugation occurred later than what is typically recommended (120 minutes), pilot data and previous research have shown that using a 4-hour timeframe instead of the usual 2-hour one does not alter the results (Abraham et al. 2019; Tanner, Kent, Smith, Fletcher, & Lewer, 2008). Samples were analyzed within one week. hsCRP was determined using an immunonephelometric method, BN2, CardioPhase® hsCRP, Siemens, with a lower detection limit of 0.175 mg/L. Intra-assay coefficients of variation ranged from 2.1% to 4.4%, and inter-assay coefficients of variation ranged from 1.1% to 4.0%. Participants with hsCRP values higher than 10 mg/L were excluded from analyses (N=17), as these values indicate acute infectious or inflammatory diseases that are unlikely to be related to the predictor variables examined in this study (M=0.94; SD=1.44) (Pearson et al., 2003). hsCRP values were log transformed to normalize the data before analysis.

COVARIATES.

Peer victimization was assessed at Wave 2 with the peer nomination item "Whom do you bully?" (for a description of the peer nomination procedure see "Peer preference"). The proportion of nominations received by each adolescent as a victim of bullying was calculated. Due to the lack of variability and the extreme

skewness of peer victimization, this variable was dummy coded to differentiate between victims and non-victims. Adolescents were classified as victims when they belonged to the top 10th percentile (Finkelhor, Ormrod, & Turner, 2009).

Socio-demographic covariates included age, gender, SES, and ethnicity; all assessed at Wave 1.

Health-related covariates included current smoking behavior, fat percentage, contraceptive use, physical activity and medication use; all assessed at Wave 3.

Temperamental covariates included trait negative affect, extraversion, effortful control and affiliation, and were assessed at both Wave 1 and Wave 3. A detailed overview describing the measures used to assess all covariates can be found in the Supplemental Information.

Plan of Analyses

First, bivariate correlations were conducted to examine associations among all study variables. To test the first two hypotheses, a series of hierarchical linear regression analyses were conducted with systemic inflammation (hsCRP) as an outcome. First (Step 1), we tested the effects of peer preference, peer popularity and early childhood adversity in an unadjusted model to account for possible suppression effects. In the subsequent steps, we added three types of covariates to test for robustness of the associations, starting with peer victimization and socio-demographic covariates (Step 2), followed by health-related covariates (Step 3) and temperamental covariates (Step 4). In Step 5, two separate models were run that included the interaction between early childhood adversity and either peer preference or peer popularity to test whether early childhood adversity moderated the association between peer status and systemic inflammation. Finally, additional linear regression analyses were conducted to explore gender differences by including 1) the interactions between gender and peer status and 2) a three-way interaction between gender, early childhood adversity and peer status. Gender differences were examined by adding interaction terms separately

for peer preference and peer popularity. Significance levels were set at $p = <.0125$ to correct for multiple testing (four hypotheses; peer preference, peer popularity, and the two interactions with both types of peer status).

Missing data were observed only on the covariates (range 0-23.2%). Little's (1988) Missing Completely ad Random (MCAR) test was performed to assess the pattern of missing data. The Little MCAR test was significant, χ^2 (261) = 425.86, p <.01. However, the normed chi-square (χ^2/df = 1.61) justified the inclusion of adolescents with missing data in the analyses (Bollen, 1989). Thus, missing data were estimated using the expectation maximization (EM) algorithm.

Results

Descriptive Analyses

Table S3.2 presents bivariate correlations among all study variables for descriptive purposes. A small negative correlation was observed between peer preference and hsCRP and a small positive correlation between peer popularity and hsCRP. Specifically, lower levels of peer preference but greater levels of peer popularity at age 13 were associated with higher levels of hsCRP at age 16. No significant correlation was found between early childhood adversity and hsCRP. Furthermore, hsCRP was positively correlated with negative affect and health-related covariates (i.e., smoking, fat percentage, anticonception use), and negatively with SES. Gender differences were observed in hsCRP and early childhood adversity, with females having higher hsCRP values, $t(585)=3.34$, $p<.01$ (M = -.26 and -.39, SD =.48 and .44 for females and males respectively), and males more early childhood adversity, $t(585)=-4.83$, $p<.01$ (M = .82 and .1.29, SD = .93 and 1.42, for females and males respectively).

TABLE 3.1 Results from Hierarchical Regression Analyses Predicting hsCRP.

	Step 1			Step 2			Step 3			Step 4		
Steps and Predictors	b	95% CI	β	b	95% CI	β	b	95% CI	β	b	95% CI	β
		R2=.02 F= 5.33**			R2=.08 ΔR2=.05***			R2=.24 ΔR2=.16***			R2=.24 ΔR2=.00	
Step 1												
Early childhood adversity	-.01	[-.20,.12]	-.03	.00	[-.17,.15]	.00	.05	[-.10,.19]	.02	.04	[-.11,.18]	.02
Peer preference	-.06	[-.10,-.02]	-.13*	-.07	[-.10, -.02]	-.14*	-.06	[-.09, -.02]	-.12*	-.06	[-.09, -.02]	-.12*
Peer popularity	.04	[.01, .08]	.10+	.04	[.01,.08]	.10*	.03	[.00,.06]	.07	.03	[.00,.06]	.07
Step 2												
Age				.12	[.06,.18]	.16	.05	[.00,.11]	.07	.06	[.00,.11]	.07
Gender				-.14	[-.21, -.06]	-.15**	.17	[.08,.26]	.20**	.19	[.09,.29]	.20**
Ethnicity				-.03	[-.15,.14]	-.02	.00	[-.12,.15]	.01	.00	[-.12,.15]	.01
SES				-.05	[-.09,.00]	-.08+	.00	[-.04,.04]	.00	.00	[-.05,.05]	.00
Peer victimization				-.07	[-.19,.08]	-.04	-.10	[-.22,.02]	-.06	-.10	[-.22,.04]	-.06
Step 3												
Current smoking							.05	[-.02,.13]	.06	.06	[-.02,.15]	.06
Fat percentage							.03	[.02,.03]	.35**	.03	[.02,.04]	.31**
Contraceptive use							.42	[.30,.52]	.31**	.41	[.31,.53]	.34**
Physical activity							.04	[-.03,.11]	.04	.04	[-.04,.11]	.04
Medication use							.36	[-.04,.76]	.06	.34	[-.07,.74]	.06
Step 4												
Negative affect										.03	[-.02,.08]	.06
Extraversion										.00	[-.04,.06]	.02
Effortful control										.03	[-.03,.07]	.04
Affiliation										-.01	[-.05,.04]	-.02

Note. * p <.0125, ** p <.001. hsCRP = high sensitivity C-Reactive Protein. Step 5 was excluded from the table to limit complexity, as it provided little additional information.

Prediction of Adolescent Systemic Inflammation at Age 16

A small main effect of peer preference on hsCRP (see Table 3.1, Step 1) indicated that greater peer preference at age 13 predicted lower hsCRP levels at age 16. The significant association between peer preference and hsCRP held after adjusting for peer victimization, socio-demographic, health-related, and temperamental covariates (see Table 3.1, Steps 2-4). Conversely, however, a small positive effect of peer popularity on hsCRP (see Table 3.1, Step 1-2) suggested that greater levels of peer popularity at age 13 predicted *higher* hsCRP levels at age 16. However, the association between peer popularity and hsCRP was no longer significant when controlling for health-related and temperament covariates (see Table 3.1, Steps 3-4). No main effect of early childhood adversity on hsCRP was observed (see Table 3.1, Step 1).

In Step 5, no significant interaction effect between early childhood adversity and peer preference was found, b =.01; β =.02, 95% CI = [-.05,.07], p =.58. This effect was almost identical in an unadjusted model without covariates, b =.01; β =.03, 95% CI = [-.05,.08], p =.87. However, a significant interaction effect between early adversity and peer popularity emerged, b =-.05; β =-.10, 95% CI = [-.08,-.01], p <.01, R^2=.25, ΔR^2=.01. This effect was marginally significant in a model without covariates, b =-.04; β =-.09, 95% CI = [-.08,-.01], p =.02. Specifically, peer popularity was positively associated with hsCRP for adolescents with low, but not average or high, levels of early childhood adversity (see Figure 3.2).

Gender Differences

Both the interaction terms of peer status with gender were not statistically significant; peer preference, b=.02, β =.04, 95% CI = [-.05,.08], p=.63; peer popularity, b=-.07, β =-.20, 95% CI = [-.17,.03], p=.17. This indicates that the effects of the two types of peer status on hsCRP did not differ between male and female adolescents. Both the three-way interactions between gender, peer preference and early childhood adversity and between gender, peer popularity and early childhood adversity were also not significant, b=-.01, β = -.03, 95% CI = [-.08,.05],

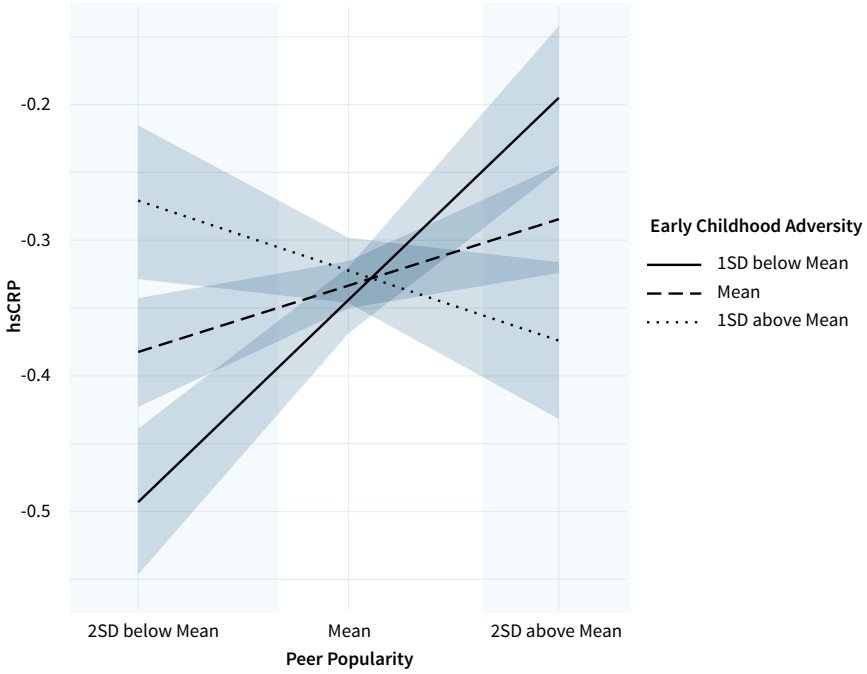

FIGURE 3.2 Plot displaying the moderation of the association between Peer Popularity on levels of systemic inflammation by Early Childhood Adversity.

Note. hsCRP= log transformed high-sensitivity C-reactive protein; dark shaded areas show 95% Confidence Intervals; light shaded areas show area of significance (lower bound Z= -0.59; upper bound Z= 1.37). Only the simple slope of low levels of Early Childhood Adversity was significant (-1 SD, b=.07, *p<.01; M,* b=.02, *p=.17;* +1 SD, b=-.03, *p=.34*

p=.64; b=.02, β = .05, 95% CI = [-.04,.09], *p*=.51, respectively. This suggested that the moderating role of early childhood adversity on the association between the two types of peer status and hsCRP was similar for males and females.

Discussion

Peer status (i.e., peer preference and peer popularity) is of high importance for adolescent development (Somerville, 2013), and has been associated with mental health outcomes (Parker & Asher, 1987; Prinstein & Giletta, 2016). Yet researchers

have not explored whether different types of peer status predict adolescent levels of systemic inflammation over time. For peer preference, our results showed that adolescents with low levels of peer preference at age 13 exhibit higher levels of systemic inflammation (i.e., hsCRP) at age 16. These results were similar for females and males and remained significant after controlling for different types of confounding factors, including peer victimization, socio-demographics, health-related covariates and individual differences in temperament. Moreover, the association between peer preference and systemic inflammation was not moderated by early childhood adversity suggesting that peer preference predicts systemic inflammation equally for adolescents who experienced different levels of adversity in early childhood. For peer popularity, however, our results showed that the association with inflammation depended on early childhood adversity. Specifically, among adolescents who had the least early childhood adversity, high levels of peer popularity were associated with the highest levels of hsCRP. Altogether, these results showed a small effect of peer status on adolescent systemic inflammation, which has important implications for future research.

The finding that low peer preference was associated with higher levels of systemic inflammation three years later suggests that, for adolescents, being accepted (and not rejected) by peers is not only important for their mental health but may also plays a role in their physical well-being. Although this effect was robust when adjusting for covariates and was comparable to prior studies (see for example, Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2016; Copeland et al., 2014), it is important to acknowledge that it was small in size. Moreover, this effect was not moderated by early childhood adversity, which was in contrast with experimental studies showing that early life adversity can up-regulate acute inflammatory responses to social stressors later in life (Carpenter et al., 2010; Pace et al., 2006). Still, the association of peer preference with systemic inflammation extends prior work examining developmental outcomes associated with peer status (e.g., Parker & Asher, 1987; Prinstein & Giletta, 2016) and suggests that the consequences of low preference may be deeper than previously thought.

In addition to more extreme and direct forms of peer stress (e.g., peer victimization; see; Giletta et al., 2018; Takizawa et al., 2015), peer preference as a specific type of social connection was a noteworthy social factor for regulating immune system functioning in adolescence. This suggested that even low impact stressors, like low peer preference, can upregulate pro-inflammatory activity. This effect might stem from the evolutionary importance of being part of a group. Acceptance by group members increases chances of survival, while being rejected by the group makes individuals more vulnerable. Ultimately, the lack of social inclusion may trigger our bodies to prepare for harsher circumstances (Eisenberger et al., 2017). Thus, elevated levels of systemic inflammation because of poor peer connections could be seen as an evolutionary adaptive preserved response.

In contrast to peer preference, greater levels of peer popularity were associated with higher levels of systemic inflammation for those adolescents who had experienced little-to-no early childhood adversity. This suggests that high peer popularity may be stressful for some adolescents. For example, peer popularity has been associated with negative experiences, such as friendship conflict and aggression (Litwack, Wargo Aikins, & Cillessen, 2012; Cillessen & Mayeux, 2004), which may induce stress. Stress could also manifest because popular adolescents have more to lose, given their reputation and visibility within the peer group (Murphy et al. 2013). However, our results indicated that this stress only plays a role for adolescents who did not experience early childhood adversity. Contrary to our expectations, this moderation was not in line with a stress-amplification hypothesis but instead with an inoculation hypothesis. This hypothesis suggests that moderate levels of early childhood adversity may promote resilience and therefore can protect against negative outcomes later in life (Parker, Buckmaster, Sundlass, Schatzberg, & Lyons, 2006). Overall, this could explain why experiences of early childhood adversity might protect against the negative effects of peer popularity on systemic inflammation.

Because we did not hypothesize this pattern, however, replication research is needed to substantiate this explanation.

The contrasting findings of peer preference and peer popularity highlight the importance of disentangling the two types of peer status (Prinstein et al., 2018). On the one hand, these findings suggest that being rejected, or not accepted, by the peer group may have stronger effects as compared to not being perceived as popular by the peer group. This could be due to the fact that while most adolescents are liked by their peers, only a few of them are really popular. Thus, lack of popularity is not necessarily a stressor and therefore may not represent a threat to social connections, as low peer preference does. There is also a difference in what greater levels of ratings within these two types of peer status entail. Whereas high ratings of peer preference are associated with positive outcomes, high ratings in peer popularity have a more mixed profile (Cillessen & Mayeux, 2004; Litwack, Wargo Aikins, & Cillessen, 2012; Murphy et al., 2013). These differences suggest the importance of looking at the independent effects of the two types of peer status in future research. Additionally, future research might also explore how these two types of peer status interact. A prior study revealed that youth who perceive themselves as having a greater social status also have more elevated inflammatory markers when they experience episodes of rejection (Murphy et al., 2013). Thus, low levels of peer preference may be particularly strong in upregulating inflammation for adolescents with high levels of popularity.

An additional noteworthy aspect of our findings was that peer ratings of social rejection (e.g., having fewer positive social ties) can influence adolescent systemic inflammation. Previous work has shown that self-reported and peer-reported experiences of social connection are at most only modestly correlated (Ledingham, Younger, Schwartzman, & Bergeron, 1982; Tucker et al., 2011), and it has been suggested that self-reported experiences (e.g., feelings of loneliness) might influence immune system activity more than less subjective experiences (e.g., number of friends; Slavich & Cole, 2013). Our results indicated that the

less subjective (i.e., peer-reported) indicator of peer status—in particular peer preference—may increase inflammatory activity as well. This was consistent with a meta-analysis by Holt-Lunstad, Smith, Baker, Harris, and Stephenson (2015) that found no difference between the effects of subjective and objective experiences of social isolation on physical health.

In contrast to prior research, no association between early childhood adversity and systemic inflammation was found, even though substantial work has indicated that early life adversity predicts systemic inflammation in adolescence and later in life (e.g., Baumeister et al., 2016). Also within the TRAILS sample, trauma before the age of 16 was found to be related to inflammation (Jonker, Rosmalen, & Schoevers, 2017). It might be that the developmental period used to identify early childhood adversity in this study (0-5), which was purposely selected to disentangle the effects of earlier childhood experiences from those occurring later on during adolescence, is less relevant for predicting inflammation. While we included adversities between zero to up to five years of age, some other studies measured for a longer period, sometimes from zero to 12, 16 or even 18 years (Baumeister et al., 2016). A second reason for this null result might be due to differences in the experiences included in measures of early life adversity across studies (which can often go along with differences in age range). Unfortunately, in this study, no measure of verbal, physical and sexual abuse was available between ages zero to five. Additionally, the measure of early childhood adversity only had small variability as the present study consisted of a relatively healthy sample. Finally, it should be noted that retrospective recall is a limitation of this measure and that the questions, although based on validated measures widely used in prior studies (see for example, Caspi et al., 1996), had to be adjusted to be able to measure the age(s) at the time of adversity. Further research is necessary to examine how different types of stressors in different sensitive developmental periods interact to predict inflammatory activity.

In addition to the limitations related to the early childhood adversity measure, the insights from this study should be interpreted in light of other

shortcomings. First, limitations related to the nature of the sample should be considered. This includes the limited ethnic diversity of the sample and the small number of victims in the sample. Specifically, the sample consisted mostly of adolescents self-identifying as ethnically Dutch, which makes it difficult to generalise the results to a more ethnically diverse population of youth. Additionally, although the sample size was adequate to test our hypotheses, only a small subset of adolescents (N=58) were identified as victims. This limits the generalizability of the results. Second, although this research was longitudinal, it measured systemic inflammation only once, at the age of 16 years. Future research should additionally investigate changes in systemic inflammation over time. This would also enable researchers to examine possible transactional effects and asses longer-term developmental consequences. Additionally, it is important for future research to examine other markers of inflammation, such as pro-inflammatory cytokines (e.g., interleukin-6 [IL-6], tumor necrosis factor alpha [TNF-α] or interleukin -1β [IL-1 β]). Future work should also assess other possible moderators, because not every adolescent reacts to the same extent to peer experiences (e.g., such differences could be related to levels of depression). Overall, given the small effect of peer preference on systemic inflammation, it is uncertain how relevant these effects are from a clinical perspective.

Conclusion

In sum, this study provided initial evidence of the importance of disentangling the roles of peer preference and peer popularity as specific types of social connections in order to further understand adolescent systemic inflammation. Consistent with and in addition to previous findings that extreme peer stressors can affect inflammation, we showed that peer preference is correlated with affect immune system functioning three years later in adolescence. This finding indicates a possible mechanism of how everyday peer experiences in adolescence can increase the risk of developing health problems later in life.

Supplemental material

Additional descriptions of procedures and measures

CONSENT CLASSMATES. For the classmates, consent was obtained by providing separate information letters to the classmates and their parents in which they were invited to participate in the study for one time only. The classrooms that participated were relatively evenly divided across low, middle and high education levels (i.e., N = 60, 53, and 59 classrooms, respectively). On average, a classroom contained 18.39 participating students (SD=5.99; range 7 to 30).

EARLY CHILDHOOD ADVERSITY (SEMI STRUCTURED INTERVIEW). The interview was conducted with one of the parents or caretakers, usually (> 90%) the mother, and it concerned, in addition to major life events and parental psychopathology, topics such as the family situation (e.g., composition, SES, impairments), religion, developmental history (e.g. details about pregnancy/birth, start walking/talking, daycare), physical health and development, social behavior, and care utilization. Parental psychiatric disorders and addiction were assessed with the help of vignettes (e.g. standardized description of psychotic complaints).

The prevalence rates for each of the psychiatric disorders included were largely comparable to CIDI–DSM-IV lifetime rates obtained by direct interviewing in the Netherlands Mental Health Survey and Incidence Study (Ormel et al., 2005). Likewise, the early adversity measure used in this study significantly correlated with perceived stressfulness of the period between zero and five years old, reported by parents and adolescents (Bosch et al., 2012). Additionally, the same early adversity measure has shown to have some predicative validity, as for example in prior work it was found to predict higher levels of depressive symptoms (Nederhof et al., 2010). Furthermore, a subsample of adolescents that was identified by TRAILS to have increased risk of mental health problems, scored significantly higher on the early adversity measure (Mean risk group = 1.22, Mean current study sample = 1.03 t= 1.97, p <.05).

TABLE S3.1 Main Characteristics of the Selected Study Sample and Comparison to the TRAILS unselected Baseline Sample.

	Excluded sample (N=420–1643)†	Study sample (N=587)	t-test/chi2 test statistics
Wave 1 variables			
Age	11.12 (.55)	11.12 (.56)	.11
Gender (% females)	49.4%	54.6%	4.67*
Ethnicity (% Dutch)	89.4%	92.9 %	6.06*
SES	-.14(.79)	.20 (.78)	-9.35*
Fat percentage	28.38 (5.80)	28.28 (3.06)	.33
Smokers	28.5%	26.6%	.67
Early childhood adversity	0.89 (1.10)	1.02 (1.20)	-2.59*
Wave 2 variables			
Peer victimization	.03 (.07)	.02 (.05)	1.72
Peer preference	-.03(1.02)	.06 (1)	-1.33
Peer popularity	.00(.99)	.02 (1.03)	-.44
Wave 3 variables			
hsCRP	1.03 (1.64)	.94 (1.44)	.94

Note. * p <.05. hsCRP = High sensitivity C-Reactive Protein. SES was computed by taking the mean of five standardized scores (educational level father, educational level mother, current profession father, current profession mother and family income).

† Sample sizes differ for specific variables in the unselected sample as participants might not be included in all measures. Age, gender, ethnicity, SES and early life adversity N = 1643; smokers N= 1081, peer preference N=420; hsCRP N=644.

SOCIO-DEMOGRAPHIC COVARIATES (WAVE 1). Adolescents reported their gender, ethnicity and age. At baseline, parents reported information about their educational level (father and mother), current profession (father and mother), and family income. A SES score was computed by taking the mean of these five standardized scores (M=.20; SD=.78).

HEALTH RELATED COVARIATES (WAVE 3). Adolescents reported about their currents smoking behavior (at wave 3), physical activity, contraceptive and medication

use. Current smoking was assessed by the item: "Have you ever smoked cigarettes or roll-ups, even if it was only one cigarette or a few puffs?". Adolescents who indicated that they smoked "every day" or "sometimes" (i.e., "I sometimes smoke but not every day") were considered current smokers (26.6 %). Adolescents were asked to report on their physical activity, including number of hours they were involved in sporting activities, walking and cycling. Those information were used to create an overall measure of physical activity by creating a sum score of all the Metabolic Equivalent (MET) scores of all physical activities from the adolescents (Ainsworth et al., 2000). A METC score reflects the number of kcal/kg/hour, higher MET scores reflecting more physical activity (range within sample: 1.34-4.44). To asses current medication use a short checklist was used. First, medications were divided into 55 categories; subsequently, adolescents were categorized as using medication if they reported using corticosteroids (e.g. Anti-allergic corticosteroids; fluticasone; inflammatory glucocorticoids; general glucocorticoids; n=4).Moreover, a separate variable was created differentiating between adolescents who reported contraceptive use (13.45%) and those who did not. This specific group of medication was selected because they affect inflammation. Body fat percentage was measured with a hand-to-foot bioelectrical impedance analysis (type BIA 101; Akern, Pontassieve, Italy). From this analysis a percentage body fat (%BF) was calculated by using the Deurenberg equation (Deurenberg, Weststrate, & Seidell, 1991).

TEMPERAMENTAL COVARIATES (WAVE 1, 3). Variables included negative affect, extraversion, effortful control and affiliation. These covariates were assed with the Early Adolescent Temperament Questionnaire - Revised (EATQ-R; Ellis, 2002; Putnam et al., 2001) parent report at Wave 1 and Wave 3 and the adolescent report at Wave 1. First, scores of the parent at Wave 1 and Wave 3 were averaged (r= .55) and subsequently this combined scores were averaged with the self-report scores (r = .30-.39).

TABLE S3.2 Correlations among all Study Variables.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1. hsCRP (Wave 3)	1																		
2. Early childhood adversity (Wave 1)	-.02	1																	
3. Peer preference (Wave 2)	-.13**	-.06	1																
4. Peer popularity (Wave 2)	.08*	-.05	.12**	1															
5. Peer victimization (Wave 2)	.05	-.02	-.48**	.03	1														
6. Age	.16**	-.01	-.04	.05	.12**	1													
7. Gender (0=female, 1=male)	-.14**	.20**	-.04	.02	.12**	.04	1												
8. Ethnicity	.03	-.07	.00	.11**	.01	.02	-.09*	1											
9. SES (Wave 1)	-.10*	-.10*	.10*	.02	-.15**	-.04	.00	-.14**	1										
10. Current smoking (Wave 3)	.13**	-.03	-.01	.17**	.06	.06	-.04	.03	-.10*	1									
11. Fat percentage (Wave 3)	.34**	-.13**	-.04	.05	.06	.08	-.60**	.10*	-.14**	.11**	1								
12. Contraceptives (Wave 3)	.36**	-.09*	-.01	.04	-.01	.16**	-.37**	-.01	-.13**	.15**	.29**	1							
13. Sleep (Wave 3)	-.02	-.05	-.15*	-.10	.07	-.03	-.24**	-.10	.00	-.03	.20**	.11	1						
14. Physical activity (Wave 3)	.01	.08	.01	.01	-.01	-.04	.14**	-.03	.07	-.05	-.12**	-.05	-.01	1					
15. Medication use (Wave 3)	-.03	.07	.04	-.03	-.03	-.00	.05	-.01	.03	-.03	-.06	-.02	-	.00	1				
16. Negative affect (Wave 1&3)	.11**	.07	-.11**	-.03	-.01	-.07	-.14**	.03	-.11**	.08	.16**	.09*	.03	-.04	-.03	1			
17. Extraversion (Wave 1&3)	.00	.08*	.11**	.25**	-.02	-.00	.20**	-.04	.04	.03	-.12**	-.01	-.13*	.19**	.02	-.29**	1		
18. Efficacy (Wave 1&3)	-.02	-.07	.16**	-.05	-.08*	.07	-.20**	.00	.21**	-.15**	.09*	-.00	.05	.08*	-.00	-.41**	.10*	1	
19. Affiliation (Wave 1&3)	.07	.01	.03	.05	-.05	.04	-.29**	.03	.05	.11**	.24**	.09*	.03	.03	-.12**	.06	.14**	.25**	1

Note. *p <.05, ** p <.01

Results from empirical studies yielded mixed evidence with regard to the association of personality factors (e.g., neuroticism, extraversion and agreeableness) and inflammation. For instance, a meta-analysis by Luchetti and colleagues (2015) has shown that conscientiousness is related to higher levels of inflammation but that no associations were found for neuroticism, extraversion and agreeableness. In contrast, a recent study by Allen and Laborte (2017) found associations between inflammation, extraversion and agreeableness. Thus, given the mixed evidence, and to ensure that we account for individual differences that may relate to both peer status and inflammation, this study used a conservative approach and controlled for all temperamental factors assed (negative affect, extraversion, effortful control and affiliation).

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4

Unraveling the association between peer victimization and systemic inflammation

de Bruine, M., Moffit, T. E., Giletta, M., Denissen, J. J., & Caspi, A. (2021). *Unraveling the association between peer victimization and systemic inflammation*. Manuscript submitted for publication.

Abstract

Peer victimization in childhood and adolescence is a salient stressor. Mounting evidence suggests that youth who are exposed to peer victimization are at increased risk for heightened inflammatory activity. However, little is known about how and for which children peer victimization may more strongly predict inflammation. This study aimed to address these questions by examining: a) the hypothesis that the effects of peer victimization on inflammation occur in part via health-related factors (i.e., BMI and smoking) and b) whether children's socio-economic status (SES), maternal warmth, IQ and anxious depressed disposition moderated the association between peer victimization and inflammation. Participants (N= 1,415, 47% male) were part of the Environmental Risk (E-Risk) Longitudinal Twin Study which followed a

population representative sample from age 5 till age 18. Peer victimization was assessed at multiple occasions in both childhood and adolescence by interviews with multiple informants, and a recently proposed biomarker of systemic inflammation, soluble urokinase plasminogen activator receptor (suPAR), was measured at age 18.

We found an indirect effect of peer victimization on suPAR: Youth who experienced higher peer victimization throughout childhood had higher BMI and were more likely to be daily smokers during adolescence, which in turn were associated with higher suPAR levels in adolescence. Associations between youth peer victimization and suPAR did not vary according to any of the moderators tested.

Results underscore that special attention should be directed to health behaviors of victimized youth which could prevent them from developing systemic ammation.

Peer victimization is a major stressor for many youth and is increasingly recognized as a public health concern worldwide (Modecki et al., 2014). While ample research acknowledges the effects of peer victimization on mental health problems, increasingly researchers are focusing on physical health outcomes (Arseneault, 2018). For example, peer victimization in childhood and adolescence has been associated with elevated immune system activity (Copeland et al., 2014; Giletta et al., 2018; Takizawa et al., 2015), which in the long run may pose direct risk for cardiovascular disease, cancer, diabetes and mortality in general (Scrivo et al., 2011). However, key questions regarding the link between peer victimization and immune system functioning remain. First, the factors through which peer victimization may affect immune system functioning are largely unknown. Second, although it is likely that individual differences exist in the extent to which peer victimization influences the immune system, it remains unclear which children may be more sensitive to the effects of peer victimization

on their immune system. The current study aimed to address these two questions.

Peer Victimization and Inflammatory Activity

Recently, it has been suggested that the pervasive consequences of peer victimization may be in part explained by the effects that peer victimization may have on immune system functioning. A handful of studies have demonstrated that youth who experience peer victimization are more likely to have increased levels of inflammatory markers, which represent activation of the innate immune response (Copeland et al., 2014; Giletta et al., 2018; Takizawa et al., 2015). For example, Copeland and colleagues (Copeland et al., 2014) have shown that people who experienced peer victimization in childhood and adolescence often had heightened levels of systemic inflammation later in life.

At least two pathways can explain this association. First, psychosocial stressors can trigger pro-inflammatory activity even in the absence of pathogens (Eisenberger et al., 2017; Slavich & Cole, 2013). This may occur as in early life immune cells can become calibrated to respond in a more pro-inflammatory way (i.e., pro-inflammatory phenotype), which could persist until later in life (Edith Chen et al., 2017). Second, social stress can lead to higher levels of inflammation via health-related factors (Raposa et al., 2014). For example, recent research suggests that BMI and smoking might function as pathways through which peer victimization affects inflammation (Raposa et al., 2014). Research has already indicated that not only youth who experience peer victimization are more likely to have a higher BMI than their non-victimized peers, but that experiencing peer victimization may predict increases in BMI over time (Achenbach, 1997; Adams & Bukowski, 2008). Additionally, research has revealed that, as compared to their peers, adolescents who experience peer victimization have an increased risk of smoking more cigarettes (Tharp-Taylor et al., 2009).

In line with this evidence, studies have shown that people who experience early-life adversity (e.g. child abuse, low socio-economic status - SES) had

higher levels of systemic inflammation (i.e., C-reactive protein; CRP) and that this association can be explained by smoking and BMI in adulthood (Brummett et al., 2013; Matthews et al., 2014; Raposa et al., 2014). However, to date few studies examined the link between peer victimization and inflammatory markers (Copeland et al., 2014; Giletta et al., 2018; Takizawa et al., 2015) and none of them tested whether this association might be mediated by health-related factors, such as BMI and smoking. Understanding whether these processes may already occur during adolescence is very important, given work suggesting that high inflammation beginning in childhood can have even more deleterious health consequences (Finch & Crimmins, 2004).

Moderators of the Association between Peer Victimization and Inflammation

Not all young people who experience peer victimization might end up having heightened levels of inflammation. Four possible moderators from four major domains were considered in this study: social economic status (SES; economic domain), maternal warmth (social domain), IQ (cognitive domain) and an anxious depressed disposition (emotional domain).

With regard to the economic domain, young people from low SES families could experience more negative health outcomes from peer victimization exposure than those from high SES families. According to biological embedding models (Miller et al., 2011), experiencing low SES and peer victimization could have interactive effects on inflammation (Hostinar et al., 2015). For example, for children living in low SES families, high levels of family chaos were more strongly associated with CRP than for children living in high SES families (Schreier et al., 2014) (see also; Brummett et al., 2013; John-henderson et al., 2016).

Within the social domain, experiencing maternal warmth could moderate the effect of peer victimization on inflammation. The stress in the family and peer domain might negatively reinforce each other, or high maternal warmth could function as a buffer against the effects of peer victimization (E. Chen et al., 2011).

Consistent with this, high maternal warmth has been shown to protect against the negative effects of peer victimization on emotional and behavioral problems (Bowes et al., 2010).

Within the cognitive domain, having a high IQ might function as a moderator for at least two reasons. Children with a high IQ might use their cognitive resources to identify more efficient strategies to overcome the negative effects of peer victimization (Salekin et al., 2010). Consistent with this, IQ has already been established as an important protective factor for multiple domains of functioning, including emotional and behavioral problems (Ttofi et al., 2016). Furthermore, a recent study by Midouhas and colleagues (Midouhas et al., 2018) found that, among males with a high IQ, psychosocial stress were less strongly associated with inflammation than among males with low IQ.

Finally, youth who show anxious depressed symptoms (Weeks et al., 2017) tend to appraise their environment as particularly stressful and threatening. Due to these biases, anxious depressed children could experience more stress as compared to their non-anxious depressed peers. (Giletta et al., 2018; Slavich & Cole, 2013) Consistent with this, studies have found that children with an anxious depressed disposition experience more negative mental health consequences when faced with peer victimization (Sugimura et al., 2014; Sugimura & Rudolph, 2012).

The Present Study

The present study aimed to extend existing research on the association between peer victimization and systemic inflammation by first examining whether peer victimization in childhood (5-12 years) and adolescence (12-18 years) related to higher levels of inflammation at age 18 and subsequently whether this association was mediated by higher BMI and smoking. Second, we examined whether higher levels of SES, maternal warmth, higher IQ, and lower levels of anxious depressed disposition would attenuate the association between peer victimization and inflammation. We used a newly discovered biomarker of systemic inflammation, soluble urokinase plasminogen activator receptor (suPAR). suPAR is positively

associated with other inflammatory markers (e.g. Interleukin-6 (IL-6), CRP (Rasmussen et al., 2019; Zimmermann et al., 2011)) and predicts similar health outcomes (Eugen-Olsen et al., 2010; Rasmussen et al., 2016). Additionally, research indicates that using suPAR as a marker of inflammation may have some notable benefits, such as making it particularly suited to investigate the effects of peer victimization on levels of systemic inflammation (Botha et al., 2015; Lyngbæk et al., 2013; Rasmussen et al., 2019).

Methods

Sample

Participants were members of the Environmental Risk (E-Risk) Longitudinal Twin Study, which tracks the development of a 1994-95 birth cohort of 2,232 British children (see supplemental material for additional information) (Moffitt, 2002). The E-Risk sample included 1,116 families with same-sex twins (56% monozygotic; 44% dizygotic; 93% of those eligible for participation) who took part in home-visit assessments. Home visits took place when participants were respectively 5, 7, 10, 12 and 18 years old (93% overall retention rate at age 18). Parents gave informed consent and twins gave assent between 5-12 years and then informed consent at age 18. The Joint South London and Maudsley and the Institute of Psychiatry Research Ethics Committee approved the study.

Of the participants at age 18, blood was collected from 82% (n=1,700), and plasma was available for 1,448 of the participants. Of all the participants with available plasma data, only 2% had missing data on the main variables of interest (i.e., peer victimization, suPAR, smoking and BMI)[1]. Given the low percentage

1 For two of the moderating variables, missing data were above 2%. This was the case for IQ (n=1413) and maternal warmth (n=1266). Thus, analyses with SES and maternal warmth as predictor variables, included somewhat fewer participants

of missing data, only participants with complete data on the main variables (n=1,415) were included in the analytic sample. There were no differences between participants with and without complete data for this article with regard to sociodemographic factors or any of the study variables, with the exception of gender. That is, females were overrepresented in the analytic sample for this article (see Table 4.1).

Measures

SUPAR. At age 18, participants' venous blood was collected by a trained research worker and drawn in EDTA tubes. Tubes were spun at 2,500 x g for 10 min, and plasma drawn off. Samples were stored at -80°C. Plasma was available for 1,448 participants. Plasma suPAR was analyzed with the suPARnostic AUTO Flex ELISA (ViroGates A/S, Birkerød, Denmark) following the manufacturer's protocol. The coefficient of variation (CV) was 6% with a lower limit of detection 0.1ng/ml. In line with prior studies, participants with values greater than four standard deviations above the means on suPAR (n=3) were excluded (Rasmussen et al., 2019). The cohort distribution of suPAR was normal and is shown in Figure S4.1.

PEER VICTIMIZATION. During childhood, bullying victimization experiences (age 5-12) were assessed using both mothers' and children's reports. Mothers were interviewed when children were 7, 10, and 12 years old; children were privately interviewed at age 12. Subsequently, mother and child reports were combined to derive a global measure of childhood bullying victimization (see supplemental material for detailed information).

Adolescent peer victimization (age 12-18) was measured at age 18 with the Juvenile Victimization Questionnaire 2nd revision (JVQ-R2) interview (Finkelhor et al., 2011). Peer victimization experiences were rated by an expert in victimology and 3 other trained members of the E-Risk team, and subsequently ratings were collapsed into three classes: 0 = no exposure (score of 0), 1 =

TABLE 4.1 Comparing E-Risk Participants Included and Excluded in this Study on the Study Variables.

	Study Participants (*N*=1,415)	Excluded Participants (*N*= 817)	*t*-test / χ^2test statistics	*p*
	M(*SD*) / *N*(%)	*M*(*SD*) / *N*(%)		
suPAR	3.23 (0.93)	-	-	
Peer Victimization	1.26 (1.06)	1.30 (1.19)	-.84	.39
SES	2.00 (0.81)	2.02 (0.82)	-.61	.54
IQ	95.74 (14.30)	95.88 (13.63)	-.22	.82
Maternal warmth	3.25 (1.00)	3.29 (.99)	-.85	.39
Anxious depressed disposition	3.20 (2.46)	3.26 (2.67)	-.48	.63
Smoking	.23 (.42)	.22 (.41)	.34	.74
BMI	22.95 (4.60)	23.39 (5.41)	1.77	.08
Overweight	3.98 (.91)	4.05 (.92)	-1.52	.13
Gender (male)	668 (47.20%)	424 (51.89%)	-.21*	.03

Note. Excluded participants are those who did not have data for childhood and adolescent victimization, soluble urokinase plasminogen activator receptor (suPAR), BMI and smoking.
*p <.05.

some exposure (score of 1, 2 or 3), and 2 = severe exposure (score of 4 or 5; see supplemental material for detailed information).

Finally, childhood bullying victimization and adolescent peer victimization were combined by adding up both scores to represent a cumulative peer victimization score across childhood and adolescence. This resulted in a measure with a range from 0 = no peer victimization experiences, to 4 = severe peer victimization experiences in both childhood and adolescence.

CHILDHOOD SES. At age 5, family SES was derived by combining standardized scores of parents' income, education, and social class. These indicators were highly correlated (r=0.57-0.67) and loaded significantly onto one latent factor (Trzesniewski et al., 2006). The latent factor was then divided in tertiles for analysis (i.e., low, middle and high SES).

MATERNAL WARMTH. We assessed maternal warmth using procedures adapted from the Five Minute Speech Sample method, which has good internal and construct validity (Pasalich et al., 2011). Mothers were asked to speak for 5 minutes about each of their children at age 5 and again at age 10. Subsequently, two trained raters, who were blind to all other E-Risk Study data, reviewed the tapes of the mothers' speech sample to code maternal warmth (see supplemental material for detailed information). Scores for maternal warmth at age 5 (M = 3.36, SD =.98) were significantly associated with scores at age 10 (M = 3.73, SD =.89; r =.38, p <.01) and were therefore averaged in an overall measure.

IQ. We assessed IQ at age 5 by using a short form of the Wechsler Preschool and Primary Scale of Intelligence–Revised (Wechsler, 1990) comprising Vocabulary and Block Design subtests, which follows the procedures described by Sattler (Sattler, 1992). The children's IQs (M = 95.79 SD =14.46) ranged from 52 to 145 and were normally distributed.

ANXIOUS DEPRESSED DISPOSITION. At age 5, the anxious/depressed subscale of the Child Behavior Checklist for mothers (Achenbach, 1991a) and the Teacher's Report Form (Achenbach, 1991b) were used to assess anxious depressed disposition. Mothers were administered the instrument as a face-to-face interview and teachers responded by mail. Both informants rated whether each item containing a child characteristic was 'not true' (0), 'somewhat or sometimes true' (1), or 'very true or often true' (2) in the 6 months before the interview when applied to their child. Examples of items included are 'Self-conscious or easily embarrassed' and 'worries'. The Cronbach's alphas of mothers' and teachers' reports were .84 and .85 respectively. We combined mothers' and teachers' reports to obtain a comprehensive measure of the anxious depressed disposition (r=.18; M =3.20 , SD=2.46), in line with previous work (Achenbach et al., 2005; Wertz et al., 2015).

BMI. Body mass index (kg/m^2; M = 22.95, SD =4.60) was measured at age 18 by recording weight (kg) and height (m^2).

(OVER) WEIGHT. Based on a visual assessment, at age 12 research workers rated children's weight on a 7-point scale ranging from 1= being underweight to 7= being overweight (M = 3.98 SD =.91).

CURRENT DAILY SMOKING. At age 18, participants were asked about their smoking habits. A dummy-coded variable was created distinguishing between participants who reported daily smoking of at least one cigarette per day (daily smokers) and other participants.

Statistical Analysis

Ordinary Least Squares (OLS) regressions and structural equation modeling (SEM) were used to test the main study hypotheses (see Results section). We report standardized regression coefficients with robust standard errors to control for the non-independence of observations of twins within families. Significance

level was set at p <.025 for the mediation analyses (2 mediators) and p <.0125 for the moderation analyses (4 moderators), to correct for multiple testing. All analyses were carried out in R Version 3.5.2 (for SEM models: package lavaan, Version 0.6-5; for OLS regressions: package estimator Version 0.20.0) and adjusted for gender. Model fit of SEM models was evaluated using standard indices (RMSEA <.10, CFI >.85, TLI >.85, and SRMR <.08) (Hopwood & Donnellan, 2010).

Results

Correlations between all study variables are shown in Table 4.2. Significantly higher levels of suPAR were observed for females (M= 3.42) as compared to males (M=3.00) and for daily smokers (M =3.35) than nonsmokers (M=3.12). Moreover, higher levels of suPAR were associated with more severe experiences of peer victimization, higher BMI, and lower levels of SES and maternal warmth.

The association between peer victimization and SuPAR

In the first OLS regression, after adjusting for gender, we observed an association between peer victimization and suPAR, β=.08, *SE*=.02, 95% CI [.02,.11], p <.01, indicating that more severe cumulative experiences of peer victimization were related to higher suPAR levels. The second model revealed that only childhood bullying victimization, but not adolescent peer victimization, was related to higher levels of suPAR, although effect sizes were both small and comparable (childhood: β=.06, *SE*=.03, 95% CI[.01,.12], p <.05; adolescent: β=.03, *SE*=.03, 95% CI[-.02,.09], *p=.21*).

We then tested if the association between peer victimization and inflammation was mediated by smoking and BMI via SEM. Because adolescent peer victimization (12-18) was assessed at the same time point during which BMI, current daily smoking, and suPAR were also assessed (age 18), in the mediation model we tested only the effect of childhood bullying victimization (age 5-12) on

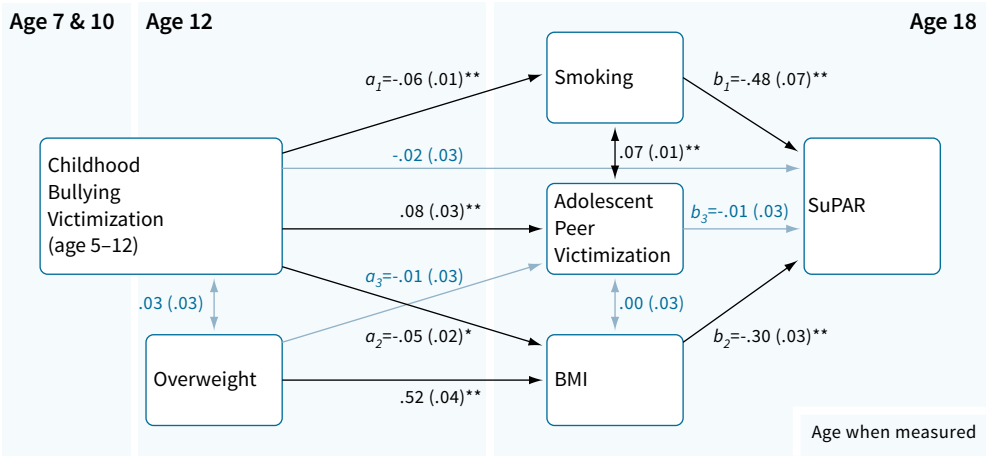
TABLE 4.2 Bivariate Correlations and Associated 95% Confidence Intervals Among Study Variables.

Variable	1	2	3	4	5	6	7	8	9
1. suPAR									
2. Peer victimization	.08** [.02,.13]								
3. SES	-.15** [-.20, -.10]	-.15** [-.19, -.11]							
4. IQ	-.05 [-.10,.00]	-.11** [-.15, -.07]	.37** [.33,.40]						
5. Maternal Warmth	-.07** [-.13, -.02]	-.09** [-.14, -.05]	.23** [.19,.27]	.18** [.14,.22]					
6. Anxious depressed Disposition	.03 [-.02,.08]	.04* [.00,.09]	-.06** [-.10, -.02]	-.03 [-.07,.01]	-.11** [-.16, -.07]				
7. BMI	.31** [.26,.35]	.07** [.03,.12]	-.10** [-.14, -.06]	-.08** [-.12, -.04]	-.05* [-.09, -.00]	-.01 [-.05,.04]			
8. Smoking	.21** [.16,.26]	.22** [.18,.26]	-.24** [-.28, -.20]	-.13** [-.17, -.08]	-.15** [-.19, -.10]	.02 [-.02,.06]	.03 [-.01,.07]		
9. Overweight	.15** [.10, .20]	.02 [-.04, .07]	-.08** [-.13, -.03]	-.08** [-.13, -.02]	-.05 [-.10, .01]	.01 [-.04, .07]	.37** [.32, .42]	.08** [.02, .13]	
10. Gender	.23** [.18,.27]	-.06** [-.11, -.02]	.00 [-.04,.04]	.00 [-.04,.04]	.07** [.03,.11]	.01 [-.04,.05]	.02 [-.02,.06]	.01 [-.04,.05]	-.01 [-.06, .04]

Note. suPAR = soluble urokinase plasminogen activator receptor. Gender was dummy-coded (1=male, 2 =female).
Values in square brackets indicate the 95% confidence interval for each correlation.
T*p <.05; **p <.01

suPAR (age 18) via BMI and smoking (age 18). The paths estimated in this model are depicted in Figure 4.1. This model adjusted for being overweight at age 12, which also allowed us to investigate a reverse mediation model by assessing the indirect pathway from (over)weight at age 12 to suPAR at age 18 through adolescent peer victimization (age 12-18). Indirect effects were calculated by multiplying the path coefficient from peer victimization to each mediation variable (i.e., BMI or smoking) times the path from the respective mediation variable to suPAR (MacKinnon et al., 2002).

The mediation model had a good fit, CFI=.99, TLI=.97, RMSEA=.03, SRMR =.02, and revealed significant indirect effects of childhood bullying victimization on suPAR via both BMI and current daily smoking (see Figure 4.1). The direct effect of childhood bullying victimization on suPAR was no longer significant when BMI and smoking were added to the model, suggesting full mediation. Notably, high levels of suPAR could not be explained by higher weight at age 12 leading to higher suPAR levels through more adolescent peer victimization (see Figure 4.1).



a_1b_1 = .03 (.01)**; a_2b_2 = .02 (.01)*; a_3b_3 = .00 (.00).
Model fit indices: CFI = .99; TLI = .97; RMSEA = .03; SRMR = .02.

FIGURE 4.1 Structural Equation Model Fit indices and regression coefficients of the model testing the effects of of childhood bullying victimization (age 5-12) on suPAR levels at age 18 through BMI and smoking (at age 18). *Note.* * p < .025; ** p < .01.

No moderations of the association between peer victimization and suPAR

Finally, the four possible moderators (i.e., SES, maternal warmth, IQ, anxious depressed disposition) were tested using 4 separate hierarchical OLS regressions. In Step 1 of each regression model, the main effect of that particular moderator was examined. In Step 2, the interaction terms between (standardized) peer victimization and each of the (standardized) moderators (e.g., SES x peer victimization) were added to the regression along with the main effects.

No significant interaction effects between peer victimization and any of the four moderators were found (see effects Table 4.3), indicating that the association between peer victimization and suPAR was similar for youth with different levels of SES, maternal warmth, IQ and anxious depressed disposition (see Figure S4.2 for plots of the interactions). Results from these models remained unchanged after adjusting for BMI and smoking status.

Discussion

This study examined two questions about the association between peer victimization in childhood and adolescence and systemic inflammation in youth. Specifically, we investigated the extent to which the association between peer victimization and suPAR was 1) mediated by smoking and BMI, and 2) moderated by SES, maternal warmth, IQ and an anxious depressed disposition. Results indicated that youth who experienced higher levels of peer victimization had higher suPAR levels, and this effect was fully explained by the fact that victimized youth had a higher BMI and were more likely to be daily smokers. No moderation effects were found with SES, maternal warmth, IQ and an anxious depressed disposition.

The association found between peer victimization and suPAR corroborates the link between peer victimization and systemic inflammation found in previous

TABLE 4.3 Main and Interaction Effects of Peer Victimization, and Moderators on suPAR Levels.

	SES		Maternal warmth		IQ		Anxious depressed disposition	
Step and predictor	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Step 1	R^2=.08, p=.00		R^2=.07, p=.00		R^2=.06, p=.00		R^2=.06, p=.00	
Main effect	-.14	-.20,-.09**	-.08	-.19,-.02**	-.05	-.11,.01	.02	-.03,.07
Peer Victimization	.06	.01,.11	.08	.03,.13	.07	.02,.12	.08	.03,.12
Gender	.43	.32,.54	.46	.34.,.58	.43	.32,.54	.43	.32,.54
Step 2								
Interaction effect	.02	-.03,.06	.03	-.01,.08	-.02	-.07,.03	-.03	-.08,.01

Note. Main effect= effect of the moderator (i.e. SES/maternal warmth/IQ/anxious depressed disposition). Interaction effect= moderator*peer victimization (e.g., SES*peer victimization).
** p<.01

studies with other biomarkers (e.g. CRP, IL-6;(Copeland et al., 2014; Giletta et al., 2018; Takizawa et al., 2015). The current results, together with the relatively normal distribution of suPAR in the current sample (see (Rasmussen et al., 2019)), indicate that suPAR may be a particularly valuable biomarker to be used in developmental research aiming at examining inflammatory processes in youth.

The mediation results extend recent studies showing that health related factors may explain the relationship between social stressors and systemic inflammation (Brummett et al., 2013; Hagger-Johnson et al., 2012; Matthews et al., 2014; Raposa et al., 2014). While this indirect pathway has been previously shown for other social stressors (e.g. low SES, early life adversity; (Brummett et al., 2013; Hagger-Johnson et al., 2012; Matthews et al., 2014; Raposa et al., 2014)), our results indicate that an indirect pathway through smoking and BMI also plays a role in channeling the effects of peer victimization on inflammation. Thus, interventions targeting BMI and smoking behavior could be effective at limiting the effects of peer victimization on inflammation and on associated physical and mental health outcomes. Consistent with this idea, a randomized controlled study showed that stopping smoking reduced suPAR levels among adults. Our results highlight the potential of targeting health behaviors to diminish the impact of peer victimization.

In contrast to previous research, we found that the association between peer victimization and systemic inflammation was fully explained by health related factors (Copeland et al., 2014; Takizawa et al., 2015). There are at least two different explanations for this finding. First, the direct effects of early adversity, including peer victimization, on inflammation might not be visible by age 18 but only become visible later in life (Kuhlman et al., 2020; Raposa et al., 2014). This is in line with recent meta-analytic work showing that the effects of early life adversity (before 18 years old) on inflammation are not observable in childhood and adolescence yet (Kuhlman et al., 2020) but they are during adulthood (Baumeister et al., 2016). This hypothesis requires further exploration as the effects found in previous meta-analyses were similar in size indicating

comparable effects in youth and adulthood. Therefore, future research is warranted to investigate possible direct effects of peer victimization on suPAR later in life (e.g., adulthood). Second, the accumulation of many forms of adverse experiences might influence suPAR more than a single stressor such as peer victimization. Within the E-Risk sample, a broader measure of adverse childhood experiences was found to predict high suPAR levels, even while controlling for BMI and smoking (Rasmussen et al., 2019). It is possible that peer victimization as a separate, single type of stressor is not sufficiently powerful to influence suPAR levels directly.

Contrary to our hypotheses, there were no differences in how peer victimization was related to inflammation between people with different levels of SES, maternal warmth, IQ or an anxious depressed disposition. However, as not all young people who experience peer victimization have heightened levels of inflammation, it is still possible that individual differences in the association between peer victimization and inflammation exist. One possible explanation for why moderation was not found in the current study is that the four moderators examined here were rather broad. For example, instead on focusing on the broader anxious depressed disposition, future work may consider focusing on specific cognitive biases, such as catastrophizing or elevated treat perception (Weeks et al., 2017).

Although, this study has a number of strengths, including the multi-wave design, multi-informant measures, a large sample size and a population representative sample, some limitations should be taken into account. First, suPAR was measured at only one time point, and repeated measurements of suPAR would be necessary to predict changes over time. Second, health-related factors and suPAR were all measured at age 18 while ideally predictors, mediators and outcomes should be all assessed at different time points to infer mediation effects. Future research is warranted that measures peer victimization, health-related factors and suPAR at all time points. Third, the measure of adolescent peer victimization used in this study was a retrospective interview in which

participants reported on peer victimization that occurred during the prior 6 years; thus, this could be affected by recall bias.

Overall, the present study strengthens the current hypothesis that health-related factors, such as smoking and BMI, can act as a mediator between childhood/adolescent stressors and systemic inflammation. These findings underscore the need to address health-related behaviors such as smoking as a possible way to diminish the effects that social stressors may have on systemic inflammation.

Supplemental Material

Supplementary Methods

E-RISK SAMPLE SOCIOECONOMIC CONDITIONS. The families of the E-Risk sample adequately represented the socioeconomic conditions in Great Britain, as reflected in the families' distribution on a neighborhood-level socioeconomic index (ACORN [A Classification of Residential Neighborhoods], developed by CACI Inc. for commercial use): 25.6% of E-Risk families lived in "wealthy achiever" neighborhoods compared to 25.3% nationwide; 5.3% vs. 11.6% lived in "urban prosperity" neighborhoods; 29.6% vs. 26.9% in "comfortably off" neighborhoods; 13.4% vs. 13.9% in "moderate means" neighborhoods; and 26.1% vs. 20.7% in "hard-pressed" neighborhoods. E-Risk thus underrepresents "urban prosperity" neighborhoods because such households are often childless.

CHILDHOOD BULLYING VICTIMIZATION. Mother and child were asked whether either twin (mother)/they (child) had been bullied by another child during primary or secondary school. During the interview, the following standard definition of bullying was read out: "Someone is being bullied when another child (a) says mean and hurtful things, makes fun, or calls a person mean and hurtful names; (b) completely ignores or excludes someone from their group of friends or leaves

them out on purpose; (c) hits, kicks, or shoves a person, or locks them in a room; (d) tells lies or spreads rumors about them; and (e) other hurtful things like these. We call it bullying when these things happen often, and when it is difficult to make it stop. We do not call it bullying when it is done in a friendly or playful way." When a mother or a child reported victimization, the interviewer asked them to describe what happened. Bullying victimization was then coded by an independent rater on a 3-point scale (0=no exposure, 1=probable/less severe exposure, 2=definite/severe exposure).

Notes taken by the interviewers were later reviewed by an independent rater to verify that the events reported could be classified as instances of bullying operationally defined as evidence of (a) repeated harmful actions, (b) between children, and (c) where there is a power differential between the bully and the victim (Shakoor et al., 2012).

When combining mother and child reports first the report at age 12 were joint before combining with the reports at age 7 and 12. At age 12 this created an index with the following levels: a) reported as not victimized by both mother and child; b) reported by either mother or child as being occasionally victimized but not frequently victimized; and c) reported as being occasionally victimized by both informants or as frequently victimized by at least one informant.

This created an index with the following levels: a) children who were never bullied in primary or secondary school or occasionally bullied during one of these time periods were assigned a code of 0 (55.5%); b) children who were occasionally bullied during both primary and secondary school, or frequently bullied during one of these time periods were assigned a code of 1 (35.6%); and c) children who were frequently bullied at both primary and secondary school were as assigned a code of 2 (8.9%). Although inter-rater reliability between mother and child was only modest (kappa=0.20–0.29) reports of both informants did correlate similarly with emotional and behavioral problems (Shakoor et al., 2011). This suggests that each informant provided unique but equally valid information about bullying

victimization. For further details and the standard definition of bullying that was used see the supplemental materials.

ADOLESCENT PEER VICTIMIZATION. The Juvenile Victimization Questionnaire 2nd revision (JVQ-R2) interview was used to measure adolescent peer victimization. This interview included 10 items about peer victimization for the period "since you were 12". Participants indicated for each item whether peer victimization had occurred in the time period by responding "yes" or "no". If participants indicated multiple experiences, they were asked to identify and report about their worst experience. For the worst experience, the interviewer wrote down detailed notes based on the participant's description. Coding on the worst experience was done according to the rules of The Childhood Experience of Care and Abuse (CECA) interview. The CECA is a comprehensive semi-structured interview whose standardized coding system attempts to improve the objectivity of ratings by basing them on the coder's perspective (rather than relying on the participant's judgment) and focusing on concrete descriptions (rather than perceptions or emotional responses to the questions), together with considering the context in which the adverse experience occurred. In our adapted coding scheme, the anchor points of the scale are focused on the frequency of occurrence of peer victimization. Each twin's dossier was evaluated separately and we did not use information provided in the co-twin's dossier about their own or shared peer victimization experiences to rate direct or witnessed peer victimization for the target twin.

For each indicated peer victimization experience, participants were asked 4 follow up questions: 1) How old they were when it (first) happened; 2) whether they were physically injured in the event; 3) whether they were upset or distressed by the event; and 4) how long the peer victimization went on for (by marking the number of years on a Life History Calendar, (Caspi et al., 1996)).

Adolescent peer victimization was then rated by an expert in victimology and 3 other trained members of the E-Risk team. Ratings were made using

a 6-point scale ranging from 0 = not exposed to 5 = severe exposure, based on the coding system used for the Childhood Experience of Care and Abuse interview (CECA, (Bifulco et al., 1994, 1997); see supplemental material for more information about the coding system). High levels of inter-rater reliability were achieved for the severity ratings of peer victimization (ICC=.91, p <.001). Following this, the ratings for peer victimization were then collapsed into three classes: 0 = no exposure (score of 0), 1 = some exposure (score of 1, 2 or 3), and 2 = severe exposure (score of 4 or 5), due to small numbers for some of the rating points. Combining ratings of 4 and 5 is also consistent with previous studies using the CECA, which have collapsed comparable scale values to indicate presence of "severe" abuse (e.g., (Bifulco et al., 1994, 1997; Fisher et al., 2011)).

Supplementary Figures

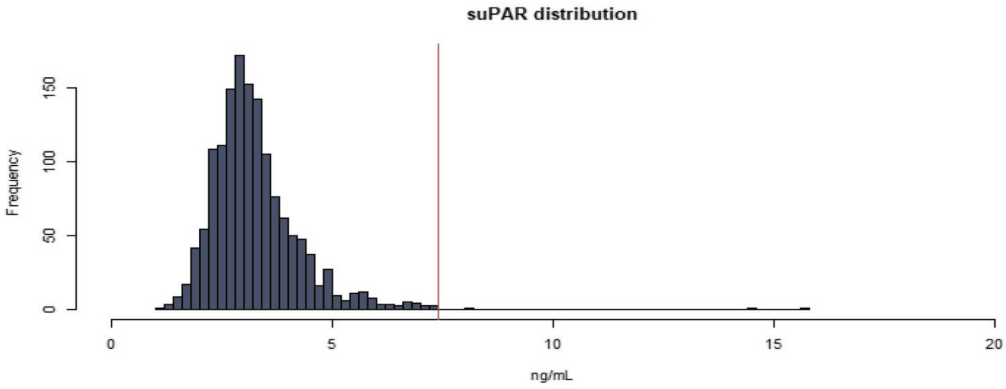


FIGURE S4.1 Distribution of soluble urokinase plasminogen activator receptor (suPAR) in the Environmental Risk (E-Risk) Longitudinal Twin Study from blood samples collected at age 18 years. Participants with suPAR (n=3) levels greater than four standard deviations above the means were excluded; these values are indicated above, by the red line. Adapted from "Association of adverse experiences and exposure to violence in childhood and adolescence with inflammatory burden in young people [Supplementary Online Content]" by Rasmussen, LJH, Moffitt TE, Arseneault L, et al. 2019, JAMA Pediatrics, p.9 (doi:10.1001/jamapediatrics.2019.3875).

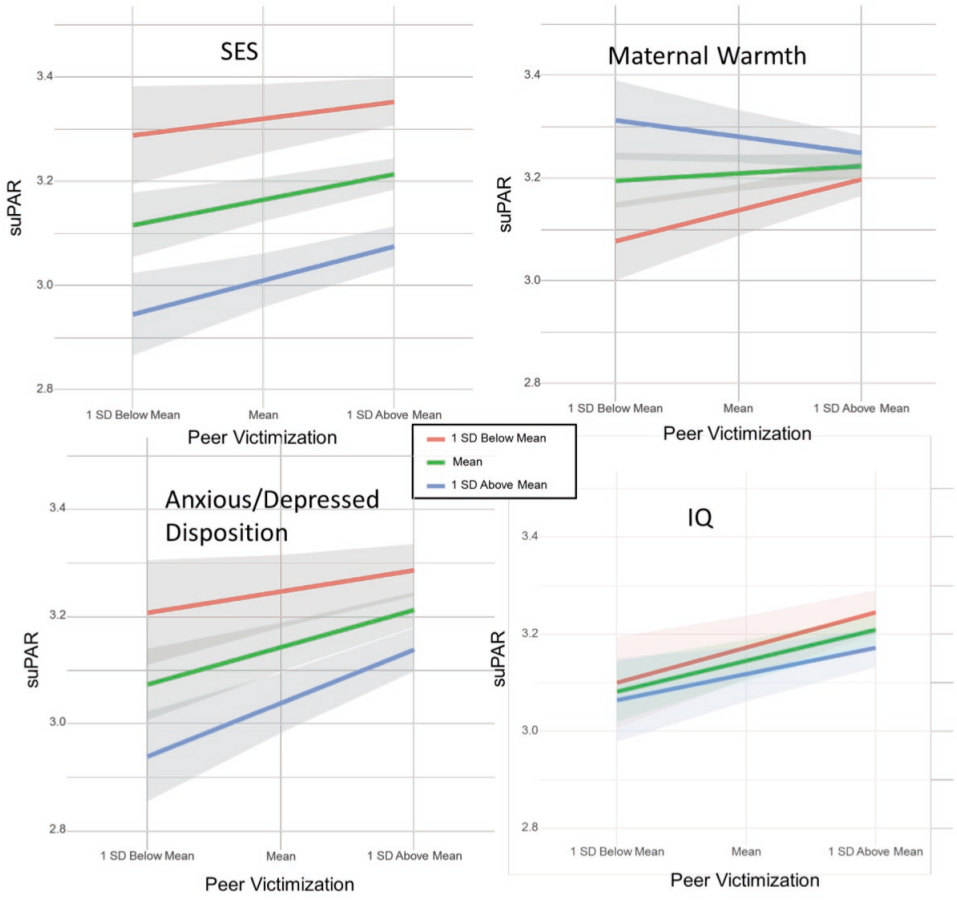


FIGURE S4.2 Plots of the interactions between peer victimization * moderator (e.g., peer victimization * SES) with 95%CI depicted in shaded areas around the slopes.

Note. None of the interactions was significant. SES: β=.02, se=.02, 95% CI [-.03,.06], *p*=.44 Maternal warmth: β =.03, se=.02, 95% CI [-.01,.08], *p*=.17; AD Disposition: β =-.03, SE=.02, 95% CI = [-.08,.01], *p* =.09; IQ: β =-.02, se=.03, 95% CI [-.07,.03], *p*=.51.

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5

General Discussion

Peer experiences play a significant role in the lives of adolescents (Brown & Larson, 2009). This dissertation focused on peer victimization and two types of peer status (i.e., peer preference and peer popularity), as these peer experiences have been shown to affect adolescent well-being (Bukowski & Adams, 2005; Prinstein & Giletta, 2016). Thus far, this research has mainly concentrated on predicting (distal) psychological outcomes, like adolescents' mental health. However, preliminary work indicates that negative peer experiences may threaten humans' need to belong, thereby affecting adolescents' physical health (Schacter, 2021; Slavich & Cole, 2013). Despite existing evidence linking peer experiences to health-related outcomes in adolescence, it is unclear what biological processes, if any, give rise to this association. Furthermore, it is unclear which specific peer experiences play a role for health-related outcomes and which experiences might thus be most important to focus on for intervention to keep adolescents healthy.

For example, examining how both peer victimization and peer status could influence immune system functioning already in adolescence might elucidate links between the social environment and physical health in adolescence.

To further understand the role of peer experiences in predicting adolescents' physical health, the current dissertation aimed to address the following three questions. First, this dissertation investigated the extent to which different types of peer experiences predicted adolescents' health-related outcomes. Second, this dissertation investigated the extent to which peer experiences predicted adolescent levels of systemic inflammation. Finally, this dissertation investigated how peer experiences interacted with other early life stressful experiences in predicting adolescents' physical health. In this general discussion, the findings from all empirical chapters are summarized (see Table 5.1) and integrated to address these three aims further. Additionally, the main implications of this work are discussed, and important directions for future research in this area are provided.

Summary and integration of findings

Aim 1: To what extent do different types of peer experiences predict adolescents' health-related outcomes?

As touched upon in the introduction, prior research suggests that it could be essential to distinguish between peer experiences, as they can differentially influence adolescents' well-being (Cillessen & Marks, 2011). To adequately examine the extent to which peer victimization, peer preference, and peer popularity can predict adolescents' physical health, this dissertation used multiple approaches. First, these experiences were investigated using different measures (i.e., peer nomination in Chapters 2 and 3, self-report in Chapters 2, 3 and 4, mother-teacher reports Chapter 4). Second, peer experiences were

TABLE 5.1 Overview of the Dissertations Main Findings per Empirical Chapter.

Chapter	Main findings
2	— Peer victimization was associated with poor physical health both at the between and within-person level
	— Peer preference was not associated with poor physical health both at the between and within-person level
	— Peer popularity was not associated with poor physical health both at the between and within-person level
	— Cumulative peer stress was associated with poor physical health at the between but not at within-person level. However, this association was mainly driven by peer victimization.
3	— Peer preference (age 13) predicted hsCRP levels 3 years later (age 16). This effect remained after controlling for several covariates, including age, sex, smoking behavior, SES, fat percentage, physical activity and temperament.
	— Peer popularity (age 13) interacted with early childhood adversity (age 0-5) in predicting hsCRP (age 16).
	— Peer victimization (age 13) was not associated with hsCRP 3 years later (age 16).
4	— Cumulative peer victimization during childhood and adolescence predicted suPAR through BMI and smoking.
	— No direct effect of cumulative peer victimization on suPAR was found when controlling for BMI and smoking.
	— The effects of peer victimization on suPAR did not vary as a function of SES, maternal warmth, IQ and anxious depressed disposition.

pitted against each other when predicting adolescent physical health symptoms and inflammation markers (Chapter 2 and 3). Most often, in prior research, effects of peer victimization and peer status have been investigated in separate studies, making it impossible to compare the relative effect of each type of peer experience. By including peer victimization and peer status in the same study, this dissertation offered the opportunity to compare their effects. This comparison is needed to identify if adolescents' physical health is affected by a specific type of peer experience and, in turn, to highlight targets for intervention

(McMahon et al., 2003). Third, this dissertation investigated the alternative possibility that not any given type of peer experience but the sum of different negative peer experiences affect adolescents' physical health (Chapter 2). In the following, I will discuss the findings for peer victimization, peer preference, and peer popularity first separately and subsequently in an integrated fashion to compare the effects across peer experiences.

Peer victimization

Peer victimization has been shown to have concurrent and long-term associations with adolescent self-reported physical health (Gini & Pozzoli, 2013; Hager & Leadbeater, 2016; van Geel et al., 2016). For example, research shows that symptoms such as headaches and stomachache are twice as likely in peer-victimized adolescents (Moore et al., 2017). Increasingly, peer victimization has also been found to affect biological processes in adolescence (see, for example, Arana et al., 2018; Schacter, 2021). However, evidence supporting the link between peer victimization and biological outcomes (e.g., cortisol awakening response, inflammation, gene expression, skin-conductance) is less consistent and remains unclear.

Across the three empirical chapters, peer victimization predicted, although not consistently, adolescents' physical health. In Chapter 2, which examined the effects on self-reported physical health, adolescents who experienced more peer victimization reported poorer physical health. The results at the within-person level further supported this effect: When adolescents increased in their own levels of peer victimization, they also increased in their own levels of physical health symptoms. Overall, this finding is consistent with a previous longitudinal study that has examined both between- and within-person effects of peer victimization on adolescent self-reported physical health (Lee & Vaillancourt, 2018).

With regard to the effects on inflammation, this dissertation showed mixed results. In Chapter 4, peer-victimized adolescents were found to have

higher levels of systemic inflammation (suPAR). In contrast, in Chapter 3, peer–victimized adolescents did not have higher inflammation levels (hsCRP). However, the number of adolescents identified as peer-victimized in the TRAILS sample (Chapter 3) was limited to 58 adolescents, so it might have been underpowered to detect effects that have been found in previous studies (Arana et al., 2018; Copeland et al., 2014; Takizawa et al., 2015). Nonetheless, considering that studies on peer victimization and inflammation are still sparse, especially in adolescence, both the null finding of the TRAILS and the significant finding of the E-Risk sample should be considered as valid data points.

Overall, both the TRAILS and the E-Risk study provided at least one key insight. The relationship between peer victimization and inflammation might not be straightforward. On the one hand, the TRAILS study's null finding could indicate the possibility that no robust association exists, or at least not visible for all peer-victimized adolescents. On the other hand, the E-Risk study provides evidence that the relationship between peer victimization and inflammation might not be direct but indirect. The effect of peer victimization on inflammation (suPAR) in the E-Risk study was the result of increases in BMI and smoking behavior of peer-victimized adolescents. Together, these studies suggest that further exploration of both moderating and mediating factors for the relationship between peer victimization and inflammation is warranted.

Two types of peer status: peer preference and peer popularity

Peer status has been shown to be also a salient peer experience, perhaps especially in early adolescence when youth try to find their position in the broader peer group (Cillessen & Bukowski, 2018; Rubin et al., 2015). Previous research has shown that it is essential to distinguish between two types of peer status: peer preference and peer popularity. Indeed, these two types of status may be differently associated with behavioral profiles and psychopathology (Cillessen & Marks, 2011). The findings from the current dissertation indicate that both

types of status can also have divergent associations with adolescents' physical health. Although the two types of peer status in the Peer Power Project (PPP) Sample (Chapter 2) were both not associated with adolescents' self-reported physical health symptoms, peer preference and peer popularity were differently associated with inflammation in the TRAILS sample (Chapter 4).

For peer preference, the TRAILS study indicated that adolescents who experienced higher peer preference had lower systemic inflammation levels, consistent with our expectations. This finding may suggest that adolescents with high peer preference are less at risk for immune-related health outcomes (e.g., cardiovascular diseases; Scrivo et al., 2011). This is broadly in line with the adult literature on social support, indicating that inclusive and socially supportive experiences can buffer inflammation levels (Yang et al., 2014). This literature finds that mostly low SES and low subjective social status (SSS) are associated with high systemic inflammation levels (Freeman et al., 2016; Milaniak & Jaffee, 2019; Quon & McGrath, 2014). The results in this dissertation are in line with this, although on the other side of the spectrum: high (peer) status can be protective against systemic inflammation levels.

For peer popularity, preliminary findings from the TRAILS study indicated that peer popularity might be a risk factor for elevated inflammation, at least under certain circumstances. Specifically, for those adolescents who had experienced fewer adversities in early childhood, being popular was associated with higher systemic inflammation levels. This result is consistent with the hypothesis that high peer popularity can be stressful (Schwartz & Gorman, 2011). Moreover, the opposite association between the two types of status and inflammation seems also to parallel evidence from animal research. In male baboons, for example, high social status has been shown to affect immune system functioning by increasing the expression of genes involved in inflammatory responses (Lea et al., 2018; Simons & Tung, 2019); on the contrary, an inverse association has been reported in female macaques. Intriguingly, these opposite associations between status and immune system responses have been explained

in light of the fact that while female macaques reach and maintain high levels of status via kinship, male baboons do so via dominant behaviors characterized by aggression, conflict, and physical competitions. Activation of inflammatory responses may be particularly beneficial for high-status male baboons because they are likely to often engage in fights and consequently experience physical injuries. Although such parallels between human and animal research remain speculative, it is notable that in primates that establish and maintain high-status via fights, dominance, and aggression, as it is more commonly done by popular youth in adolescence (van den Berg et al., 2019), inflammatory activity has been shown to increase, rather than decrease, as a function of status.

In sum, in this dissertation, peer status was associated with hsCRP but not with self reported physical health. These findings are in contrast with findings in the field of SSS. A meta-analysis of SSS and adolescent health by Quon and McGrath (2014) showed that SSS was related to self-reported health but not significantly to biomarkers. In this dissertation, no results for peer status on self-reported health were found, but peer status was related to inflammation in the TRAILS study. These differences probably stem from the fact that status in the field of SSS is operationalized differently (e.g., status ladder) and does not distinguish between the two forms of status (i.e., popularity vs. likability).

Integration

Overall, the results across the three peer experiences underline that peer victimization, peer preference, and peer popularity can have unique effects on health. In the PPP study, only peer victimization, and not peer status, was associated with adolescent physical health. In contrast, in the TRAILS study, peer status, but not peer victimization, influenced immune system functioning. Finally, in the E-Risk study, peer victimization was related to immune system functioning. Furthermore, no support was found for a cumulative stress hypothesis. This is in line with the other results in this dissertation that indicated that the type of peer experience does matter when predicting adolescents'

physical health. Thus, altogether these results do not clearly reveal one single peer experience on which future research should focus when examining adolescent physical health. However, the finding that the effect of cumulative peer stress in the PPP sample was driven by peer victimization suggests that peer victimization is a particularly important experience for perceived poorer health in adolescence.

Of course, the findings of the three peer experiences should be interpreted and compared with caution in light of some measurement shortcomings. In the PPP young adolescent sample, peer victimization was measured with a self-report, while peer preference and peer popularity were measured with a peer nomination procedure. Thus, associations between peer victimization and self-perceived physical health could be at least in part due to shared method variance. In the TRAILS sample, peer victimization, peer preference, and peer popularity were all measured through peer nominations. That said, as stated, the statistical power to detect an effect of peer victimization was very limited in TRAILS; therefore, this could also explain why no association for peer victimization was found.

Despite these shortcomings, two main conclusions can be drawn regarding the three peer experiences. First, this research emphasizes the need to differentiate between types of peer experiences and to examine them all in one study (i.e., peer victimization and peer preference and peer status) as they can have unique effects on adolescents' physical health outcomes. Second, the relationship between peer experiences and physical health might not be clear cut, and health-related factors such as smoking and BMI could explain a pathway from peer experiences to adolescents' health.

Aim 2: The extent to which peer experiences predict inflammation

In this dissertation, inflammation was investigated as a health-related outcome, given the possibility that it serves as a pathway through which peer experiences

impact adolescents' physical health. Building on biological embedding models of social stress, peer experiences might alter immune system responses and lead to higher levels of systemic inflammation (Hertzman, 1999; Hostinar et al., 2015; Vaillancourt et al., 2013). Elevated levels of systemic inflammation, in turn, have been shown to have direct links with physical health. For example, markers of systemic inflammations are also often used in diagnosing diseases such as cardiovascular diseases, cancer, and even mortality risks (Scrivo et al., 2011). Therefore, systemic inflammation may represent a possible pathway through which peer experiences influence health outcomes in adolescence and later in life (Slavich & Cole, 2013).

In line with this hypothesis, findings from both the TRAILS and E-Risk indicate that peer experiences in adolescence were associated with systemic inflammation levels. Consistent with prior research (Baumeister et al., 2016; Kuhlman et al., 2020), these associations were modest in size yet quite remarkable. This is because associations found in these two studies represent links with two different biomarkers of systemic inflammation (hsCRP and suPAR) and two possible distinct pathways (direct and indirect). In the TRAILS study, we found a direct association with hsCRP. Specifically, even after controlling for many covariates, including socio-demographic factors, health-related factors (e.g., BMI), and individual disposition, peer preference at age 13 was associated with hsCRP levels three years later (Chapter 3). In line with the biological embedding hypothesis (Hertzman, 2012; Vaillancourt et al., 2013), this finding may suggest that peer experiences could influence the programming of the immune system and therefore affect the biological response in adolescence with potential consequences also for later in life (Baumeister et al., 2016; Kuhlman et al., 2020).

In contrast, within the E-Risk study, no direct effect of peer experiences on inflammation was found after controlling for smoking and BMI. In fact, the association of peer victimization with suPAR was found to be entirely mediated by BMI and smoking. Those adolescents who were victimized were more likely

to have a higher BMI and to smoke, which were in their turn associated with higher suPAR levels. In line with psychobiology models (Hostinar, 2015; Hostinar & Gunnar, 2013), these results support an alternative pathway to biological embedding, indicating that peer experiences may predict elevated inflammation through health behaviors, consistent with findings emerged in adult samples (e.g., Raposa et al., 2014).

Overall these findings seem to suggest that there are at least two pathways that can lead to dysregulation of immune system functioning: 1) a direct pathway from peer experiences to inflammation, perhaps suggesting biological embedding, and 2) an indirect pathway through health-related factors or behaviors (e.g., BMI and smoking).

Aim 3: The independent and interactive effects of peer experiences with early-life adversity

Although the current dissertation's focus was on peer experiences in adolescence, it also considered how these peer experiences might interact with other early life experiences. Indeed, the role that peer experiences play for adolescents' health might only be fully understood if put into the context of other adversities known to impact adolescents' physical health. Cumulative and interactive effects have been previously suggested in adversity and health research (Hostinar et al., 2015). Therefore, the current dissertation made some preliminary steps to see for which adolescents peer experiences might predict physical health the most, by examining the independent and interactive effects of peer experiences with early life adversity, a known factor to influence physical health outcomes (Chapter 3 and 4).

Independent effect of peer experiences above and beyond the effect of early childhood adversity

In the current dissertation, some first steps have been made to investigate the importance of peer experiences in adolescence by disentangling the effects of

peer experiences in adolescence from early-life adversity in childhood. Early life adversity, such as childhood trauma, lack of maternal warmth, or low childhood SES, has been consistently shown to affect later health outcomes, and this might also modify how other social experiences influence health across the life course (Cole, 2014; Hostinar et al., 2017; Nusslock & Miller, 2016). However, most prior research has typically examined the effect of early-life adversity by combining different types of social stressors across childhood (and sometimes even adolescence), thus preventing the possibility to investigate the type and timing of stressors. The results from Chapter 3 and Chapter 4 added to this line of research by revealing an independent effect of peer experiences in addition to the one of early childhood adversities. In line with other studies that supported the impact of peer experiences on inflammation (Copeland et al., 2014; Takizawa et al., 2015), we found a significant association between peer preference and hsCRP in the TRAILS sample while taking early childhood adversities into account. Additionally, we found an effect of peer victimization on inflammation (suPAR) after adjusting for low SES and (lack of) maternal warmth (see supplemental material Chapter 4). Although the measure of early life adversity in the TRAILS sample was not associated with inflammation, these results together indicate that peer experiences can have an independent effect (over and above early life adversity) on adolescents' levels of inflammation.

The interplay between peer experiences and early childhood adversity

The current dissertation also examined the extent to which peer experiences interacted with early life adversities, as would be predicted by the sensitization model (Miller et al., 2011). According to this model, individuals exposed to adversity in early life may be more sensitive to experiences of stress that occur later in their life, resulting, for instance, in more pronounced physiological reactions. Previous studies have tested this model with stressors at different developmental stages (e.g., early childhood, adolescence, adulthood) and have

found mixed support (Hostinar et al., 2015; Simons et al., 2019). Overall, these studies suggest that sensitization effects could be domain-specific, meaning that individuals may be sensitive primarily to similar experiences later in life (Simons et al., 2019). For example, when people experience rejection early in life (e.g., lack of maternal warmth), they may be more likely to show elevated inflammatory responses to similar rejection experiences later in adulthood.

In this dissertation, we further explored this research line by focusing specifically on the effects of peer experiences on inflammation in adolescence. However, early adversity did not enhance the impact of peer experiences on systemic inflammation. In the TRAILS sample (Chapter 3), no interaction was found between a cumulative score of early childhood adversity (e.g., parental psychopathology, out-of-home placement, hospitalization) and peer preference. Moreover, preliminary findings showed a pattern that is opposite to sensitization for peer popularity. For those adolescents who experienced *little* early childhood adversity, being popular was associated with higher systemic inflammation levels. In Chapter 4, we examined whether peer victimization interacted with multiple domain-specific childhood adversities in the E-Risk sample. For example, we investigated childhood SES, which has been often associated with inflammation levels later in life (Miller et al., 2011; Hostinar et al., 2015) and is indicated as one of the strongest predictors of biological risk (Friedman et al., 2015). Although childhood SES was associated with inflammation levels (suPAR), no stronger association between peer victimization and inflammation levels was observed for youth who came from low SES families. The same pattern was found for maternal warmth: lack of maternal warmth (measured before the age of 5) was associated with higher inflammation levels but did not sensitize youth to react more strongly to peer victimization. Thus, overall, both chapters did not provide support for the sensitization hypothesis.

However, it should be acknowledged that both studies had some limitations to test the sensitization model. Specifically, although in Chapter 3 we were able to disentangle specific sensitive developmental periods in life (early childhood and

adolescence), some relevant early childhood adversity, such as physical abuse and childhood poverty, could not be examined. The opposite might be true for SES in Chapter 4. Although low SES is suggested to be one of the strongest predictors of biological risk factors (Brummett et al., 2013; Friedman et al., 2015), it is relatively stable across childhood and adolescence and might not be specifically related to early childhood as a sensitive period. Therefore, it will be important for future research to further explore the sensitization hypothesis, for example, by testing competing models that examine multiple sensitive periods while also comparing domain-specific stressors versus broad cumulative stressors.

General reflections and implications

These findings provide three main insights related to the three aims addressed in this dissertation. I will discuss each of them in detail below.

Aim 1: Peer experiences can matter for adolescent health

This dissertation indicated that all three peer experiences can have, to at least some extent, unique effects on adolescents' physical health (see for peer victimization Chapter 2 and 4; peer popularity Chapter 3; peer preference, Chapter 3). Even though effect sizes were small, they were comparable to effect sizes found for other adversities (Baumeister et al., 2016), and three types of peer experiences can provide insight into adolescents' health. Interestingly, the results indicate that it might be useful to consider both severe peer stressors, such as peer victimization, and seemingly less intense experiences related to peer status (e.g., low peer preference).

Because these peer experiences could lead to potential health problems, it is essential to monitor problems in the peer domain and discuss them with

professionals in order to prevent this. For example, a peer-victimized adolescent who stays at home because of headaches and stomach aches might avoid negative peer experiences at school. However, this dissertation's results indicate that likely those health symptoms are not just somatic (see also Schacter, 2021. Therefore, medical practitioners could consider negative peer experiences, such as peer victimization and low peer status, when adolescents come to them with health problems without apparent medical cause (Schacter, 2021). Teachers and parents should also become more aware of both the negative consequences of peer victimization and low peer status on adolescents' health. This awareness could also create a more open and understanding atmosphere for adolescents to communicate about their problems. Overall, this information could be of help to prevent that exposure to negative peer experiences would lead to (longer-term) health consequences.

Aim 2: Distinguishing peer experiences from early life adversity

Negative peer experiences in adolescence have often been integrated into broader early life adversity (Baumeister et al., 2016). However, this dissertation indicates that they can play an independent role next to other early life adversities (see Chapters 3 and 4), so it might be worth looking at peer experiences separately. These results can be discussed in light of two theoretical hypotheses found in the developmental literature. First, there are multiple sensitive developmental periods (e.g., prenatal, early childhood, adolescence) that are important for understanding health trajectories (Del Giudice et al., 2011). In Chapter 4 both early life adversity in childhood (maternal warmth) and peer victimization later in life predicted inflammation. This is in line with research showing that likely early childhood (the first few years of life) and adolescence are both periods that are important for predicting inflammation (see meta-analysis, Kuhlman et al., 2020).

Second, results are in line with the notion that at each developmental period, different experiences may be more relevant for understanding individual

well-being (Sroufe & Rutter, 1984). For example, finding a position in the peer group is a primary developmental task in adolescence, while forming a relationship with a caregiver is a primary developmental task in early childhood (Sroufe, 1979). Thus, peer experiences could impact health, particularly in adolescence, given the key importance of peers during this period of life, just like child-parent relationships (e.g., an attachment, Belsky & Rovine, 1988) are important for predicting childhood health. Unsurprisingly, therefore, early life stressors that have been shown to affect health across life mostly have been related to children's relationships with their parents (e.g., separation from a parent; Baumeister et al., 2016; Lacey et al., 2013). In a similar way, this disseration has shown that peer experiences in adolescence predict physical health. This is overall in line with the hypothesis that especially developmental salient stressors will affect health across life.

Overall, findings that peer experiences can impact health in addition to early life adversities have relevant practical implications. Although they might not interact with earlier experiences, negative peer experience can independently add to the negative effects of early life adversities. Alternatively, positive peer experience might counteract some of the effects of previous experiences in life due to their positive effects. Thus, for those adolescents who experienced early life adversities, it would be good to pay extra attention to stimulate positive peer experiences. This is particularly important as adolescence has been indicated as a period in which the stress system might recalibrate (Dahl, 2014; Romeo & McEwen, 2006). Therefore, stimulating positive peer experiences could help parents, teachers, and health-practitioners to prevent health difficulties later in life.

Aim 3: Different routes to adolescents physical health

Finally, the findings of the current dissertation suggest that there are multiple pathways from peer experiences towards adolescents' health. Specifically, the effects on health may occur by influencing inflammation, directly or

indirectly. Where peer preference emerged to affect levels of hsCRP directly, peer victimization was found to influence suPAR levels only indirectly by increasing the odds of smoking and having a higher BMI. This is in line with multiple theoretical hypotheses, such as the neuroimmune network hypothesis (Nusslock & Miller, 2016; see also Hostinar et al., 2015; Uchino, 2006) that predict both direct and indirect pathways.

Prior work has most often discussed a direct path between adversity exposure and inflammation markers (Baumeister et al., 2016; Nusslock & Miller, 2016; Slavich & Cole, 2013). Like other social experiences, peer experiences could directly affect inflammation through activation of the central nervous system (CNS) and of physiological stress systems (Glaser & Kiecolt-Glaser, 2005; Kiecolt-Glaser et al., 2010). Specifically, CNS activity triggered by peer experiences could activate physiological stress pathways (e.g., HPA-axis & SNS) that regulate multiple internal physiological processes, including broad transcriptional activity patterns in innate immune cells and activation of pro-inflammatory gene expression (Irwin & Cole, 2011).

Health factors and behaviors, including BMI and smoking, have been considered crucial cofounders when examining the association between peer experiences and inflammation path (Horn et al., 2018). However, in line with a growing line of evidence, this dissertation indicates that health-related factors, such as BMI and smoking, can be pathways through which social stressors affect health outcomes. Moreover, this dissertation reveals that such indirect pathways may already manifest in adolescence, perhaps due to the fact that in this development period the self-regulatory abilities needed to resist engaging in health-risk behaviors (e.g., smoking, unhealthy eating) are likely to be challenged (see also Moffitt et al., 2011).

Notably, peer victimization and peer status predicted different inflammation markers. This is in line with stress research that shows that, although the experience of stress is commonly regarded as non-specific, different types of stressors can be related to different biological profiles (Pacák &

Palkovits, 2001). Stress can activate a combination of systems, among which the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, but this does not always happen in the same way. The way in which the central nervous system interacts with both these systems and the immune system is complex, and it includes many configurations of co-regulation processes (Glaser & Kiecolt-Glaser, 2005). Each peer experience could set in motion a slightly different biological response with varying interactions between the central nervous system, HPA-axis, and immune system, for example. Multiple studies have shown that specific stressors might be related to some markers of inflammation but not others (Baumeister et al., 2016; Rasmussen et al., 2019). For example, a meta-analysis by Baumeister and colleagues (2016) showed that parental absence in childhood mainly predicted CRP but not IL-6 or TNF-α. These differences might arise from the different roles and characteristics these markers have (e.g., activate other cells and proteins) in the overall inflammatory response and their roles outside of the inflammation process (Del Giudice & Gangestad, 2018). For example, effects of parental absence might only be visible in CRP because CRP is a more stable marker (Pradhan et al., 2001) than IL-6 and TNF-α, and thus, it is less susceptible to short time environmental changes. Something similar could apply to the different peer experiences as well; peer status may predict a different biomarker than peer status. However it should be noted that because peer victimization and low peer status are both similar sources of social stress (i.e., both signal a weaker group position), it is likely that the physical processes they affect are very similar.

The health behavior pathway has clear, practical implications as the behaviors provide malleable targets for intervention. Existing interventions targeting smoking and obesity could be used to improve health and specifically target adolescents who experience problems with their peers. Making teachers and parents aware that negative peer experiences can increase the odds of smoking and developing a higher BMI could further motivate them to prevent

these stressors (in addition to taking into account the immediate psychological pain that these stressors evoke).

Future directions

The current dissertation has several strengths, amongst which the examination of multiple frameworks and peer experiences, the use of various markers of inflammation, the longitudinal designs that limited recall biases of adversity, and, in some cases (see Chapter 2), allowed the examination of within-person processes. However, the studies also had limitations that leave possibilities for future research. As research on peer experiences and physical health outcomes is still relatively new, there is much yet to be explored. Below, I elaborate on four main future directions that deserve particular attention when it comes to peer experiences and physical health.

Chronicity of peer experiences

To start, much remains unclear about the timing of effects of peer experiences on adolescent health. All three peer experiences uniquely predicted adolescent health, but for how long, or how often, should an adolescent experience peer victimization or a low peer status before these experiences affect health? The studies within this dissertation all examined different timeframes and different periods of exposure, which could have led to some of the differences in results. However, the timing, frequency, and duration of peer victimization and peer status in adolescence are important avenues to consider for at least two reasons.

First, it may be important to distinguish between acute types of peer stressors and chronic types of peer stressors (Segerstrom & Miller, 2004), especially when examining health outcomes such as inflammation. Acute stressors have been related to different stress responses (e.g., HPA-axis activation) than chronic stressors (Rohleder, 2019). On the one hand, acute stressors have been

characterized by increased heart rate and cortisol increases (Dickerson & Kemeny, 2004). Acute stressors are also related to acute inflammatory responses, such as the production of pro-inflammatory cytokines (e.g., Il-6, IL-1β, TNF Rohleder, 2019; Segerstrom & Miller, 2004). On the other hand, chronic stressors have been characterized by loss of circadian rhythm and lower overall cortisol output throughout the day (Rohleder, 2019). Additionally, chronic stressors activate other inflammatory processes next to those triggered by acute stressors: Exposure to chronic stressors has been related to low-grade systemic inflammation and elevated pro-inflammatory gene activity (Segerstrom & Miller, 2004).

Second, the dichotomy between acute stressors and chronic stressors is very relevant for peer experiences, although not one that is easily made. Low peer status, for example, is more likely a more mild chronic stressor than an acute stressor because it is based on a group position across a period of time and is not bound to a single occurrence (Bukowski et al., 2016). Yet, peer victimization can be both an acute stressor as well as a chronic experience (Biggs et al., 2010; Bogart et al., 2014; Sheppard et al., 2019). This distinction between acute, proximal peer victimization experiences and chronic victimization may matter for adolescents' well-being. For example, chronic peer victimized-adolescent are at increased risk for psychopathology than those who get victimized sporadically (Biggs et al., 2010; Bogart et al., 2014; Sheppard et al., 2019). Overall, the difference in acuteness and stress severity between peer status and peer victimization, but also between different measures of these constructs, could be worth exploring further as they might explain different results.

Notably, it may be challenging to distinguish between acute and chronic experiences of peer victimization. For example, peer victimization is often measured with instruments that combine the severity and the frequency of peer victimization (Fisher et al., 2015; Mynard & Joseph, 2000). This was also the case in the E-Risk study (Chapter 4 of this dissertation): peer victimization scores were a combination of the repetition across childhood and adolescence and the severity of peer victimization within those periods. In this chapter, although we

were able to differentiate victimization in childhood and in adolescence, within these periods it was impossible to distinguish between acute and chronic peer victimization. Another challenge may be that research of chronically victimized youth has relied on cutoffs that are not consistent across studies (e.g., belonging to the highest quartile of victimized children) or across varying periods (e.g., three-year period Sheppard et al., 2019 vs. six-year period Brendgen et al., 2016). Therefore, because chronic peer victimization is operationalized differently across studies, it also means that each study does not necessarily capture the same experience. Overall, these difficulties make it hard to compare the effects of peer victimization, so future research could benefit by standardizing the measurement of both acute and chronic peer victimization.

Third, it would be useful for future research to try to examine when (i.e., at which point) smaller acute forms of negative peer experiences may accumulate into chronic stressors (see Rohleder, 2019). Specifically, seemingly small or less severe instances of peer victimization might not have immediate direct effects on adolescent health. However, a repeating of something small, like being joked about for being short, might build up over time and become a chronic form of peer victimization. This is a relevant direction for future work. Using mixed design studies that combine experiences sampling methods with more standard longitudinal designs (e.g., measurements with a few months interval) could help indicate when acute peer experiences can become more chronic. When setting up such a design, researchers should be aware of the time resolution (e.g., daily, weekly, monthly, etc.) to assess the particular peer experiences they would like to investigate. For example, it would probably not be worth asking an adolescent daily about peer victimization and peer status (Pouwels et al., 2016). Additionally, it would be good to explore and compare different lengths of chronic exposure within one study. What are the effects of peer experiences repeated over a couple of months, compared to a year or two years on the same health outcome?

Finally, considering that peer experiences can be chronic (Ehrlich et al., 2015; Sheppard et al., 2019) but also mild stressors (Ehrlich et al., 2015), future

research might also build on the mild chronic stress (MCS) model (Willner, 1997). This model, which emphasizes the role of MCS, has been used to explain the development of depression in animals and has been related to the expression of inflammatory cytokines (You et al., 2011). Although the MCS model is still most often applied to animal research, there is support that this framework can be helpful to gain new insight when examining social stressors in humans (Viena et al., 2012). More specifically, Viena and colleagues (2012) have shown that individuals who experience mild chronic stress (e.g., during an exam period) can react more strongly to an acute stressor than those who have not. Based on this finding, it might be interesting to explore how peer preference and peer popularity might interact with acute peer victimization forms.

Measurement of physical health-related outcomes

In this dissertation, the physical health of adolescents was examined by assessing subjective physical health symptoms and biomarkers of systemic inflammation. These are two different but equally important ways to examine and understand adolescents' physical health. While subjective health measures are well established and commonly used in developmental research (Schacter in press), biomarkers represent a novel and potentially more objective approach to assess physical health in adolescents. Therefore a primary strength of the current dissertation is that we were able to examine the effects of peer experiences on two different biomarkers, which are well-known to be involved in the development of both physical and mental health problems (Scrivo et al., 2011; Slavich & Irwin, 2014).

However, a difficulty with examining the effects of social-environmental influences on biomarkers is that a chain of processes has to be initiated before we may be able to measure inflammation in the blood. This chain starts in the outside environment with the peer experience itself and ends with the production of proteins (e.g., cytokines) in the immune cells of the body. As a result, effect sizes are commonly small, and therefore hard to identify. However,

as argued in other fields, small effects can have large consequences (Cortina & Landis, 2010). The small effects of peer experiences on adolescent health might grow in strength over time, as indicated by the long-term effect of childhood adversity on makers of inflammation decades later (Danese et al., 2007). Effect sizes are generally even smaller in childhood and adolescence, and null effects and mixed findings are more common (Kuhlman et al., 2020).

The small effect size of social stressors on health might be explained by several reasons. First, these effects might have an incubation period and only manifest later in life (Hostinar et al., 2018). Second, childhood and adolescence are healthy periods of life in which baseline inflammatory markers are particularly low, which can cause significant difficulties for research. For example, assays might have difficulty picking up the fine-grained differentiations in inflammation markers. It is not uncommon that 50% of a sample may have levels of systemic inflammation markers (e.g., hsCRP) below the limit of detection (Schlenz et al., 2014). Also, when collecting the data for the Peer Power Project used in this dissertation, this was the case: A large percentage of adolescents (based on a subsample) in the PPP sample had levels below the limit of detection of hsCRP. If these markers are not identifiable in adolescence, they might not be the best measure to investigate inflammation during this period. Therefore, it can be wise for research with children and young adolescent samples to focus on more sensitive approaches to assess inflammation or immune system functioning than hsCRP.

Therefore, other biomarkers or a combination of biomarkers could be considered. The significant suPAR associations reported in the current dissertation, although measured at age 18, suggest that compared to hsCRP, suPAR might be more suitable for younger populations. suPAR shows more variability and seems to be more normally distributed in the population, and therefore it is likely that fewer adolescents would score below the levels of detection. An alternative approach that has been recently proposed would be to make inflammatory phenotypes based on multiple inflammatory markers (e.g., CRP,

suPAR, IL-6, TNF-α; see, for example, Hartwell et al., 2013; Rasmussen et al., 2019). All these markers of inflammation represent a slightly different aspect of the inflammatory response. Making profiles based on a combination of biomarkers might be a more reliable and valid way to identify individuals at risk of developing health problems after experiencing adversity (Rasmussen et al., 2019).

In alternative to biomarkers, there are at least two other ways to assess inflammatory activity in childhood and adolescence. First, in vitro stimulation of immune cells such as with bacteria (e.g., lipopolysaccharide) could be a better measure to understand younger samples' immune system functioning. Because this method measures the phenotypic potential for inflammatory reactivity within an individual's immune system, it could show pro-inflammatory tendencies of cells that would only be visible later in life in levels of biomarkers (Kuhlman et al., 2020). Currently, this method has only been used a few times in young samples (e.g., Ayaydin et al., 2016; Chen et al., 2017; Ehrlich et al., 2016; Miller & Chen, 2010). These studies suggested that in vitro stimulation could be a good alternative. Studies using this approach have consistently found associations between early life adversity and inflammatory reactivity, although the direction of effects is still mixed (Kuhlman et al., 2020).

Second, research could focus on identifying the expression of pro-and anti-inflammatory genes. The effects of social stress on immune system functioning partly rely on gene expression (Cole et al., 2015; Levine et al., 2015; Powell et al., 2013). Research has revealed that exposure to social stressors may regulate gene expression resulting in a profile characterized by increased pro-inflammatory gene expression and decreased antiviral and antibody-related gene expression (Cole, 2019). Similar results have also been found for social stress in adolescence (Murphy et al., 2013, 2015). For example, Murphy and colleagues (2013) have found that adolescents at risk for depression who experience rejection had up-regulated inflammatory gene expression. Remarkably, this relationship was found especially for adolescents who perceive themselves to be high in social status, which is consistent with the results found in this dissertation

Both these alternatives could identify inflammatory activity before commonly examined biomarkers (e.g., hs-CRP) become elevated. For example, in vitro stimulation could show inflammatory reactivity even in adolescents who do not necessarily have detectable biomarker' levels because bacterial agents are used to guarantee an inflammatory response, where an inflammatory response may not be triggerd in the external environment. Therefore using these alternative approaches could give the opportunity to increase the reliability and validity of the conclusions that could be drawn when investigating the role of peer experiences on inflammation in adolescence. More broadly, these alternative methods suggest the possibility of exploring the biological underpinnings of elevated levels of inflammation and diseases already at a relatively young age. This is important as research indicates that immune and inflammatory correlates of chronic diseases emerge decades earlier than when they become visible in adulthood (Cole et al., 2020). However, it is crucial to identify these processes as soon in life as possible to be able to intervene.

Furthermore, to adequately investigate how these peer experiences could lead to inflammatory-based diseases in adulthood, future studies should examine inflammation across multiple time points. This will make it possible to investigate how changes in peer experiences are related to changes in objective predictors of physical health.

Different pathways to health

As stated, peer experiences may affect health through different pathways. This dissertation's findings indicate that peer experiences could become biologically embedded, influencing hsCRP and suPAR levels, and that it is likely that both direct and indirect routes play a role. I will discuss two possible alternative pathways through which peer experiences may lead to inflammation, or more generally physical health. First, I will discuss (un)healthy behaviors such as eating habits, exercise habits and poor sleep. Second, I will discuss how poor mental health may provide an alternative pathway. Additionally, I will discuss across

these points how some of these effects could reinforce one other in a reciprocal manner over time.

First, this dissertation supports the hypotheses that BMI and smoking are possible pathways through which peer experiences could lead to higher levels of inflammation. Future research should further explore this line of research because other health-related behaviors, such as eating habits, exercise habits, sleep and more generally self-regulation skills, could also play a role in this. For example, eating habits could explain why peer victimization is associated with a higher BMI, as victimization is associated with binge eating or emotional eating for comfort (Copeland et al., 2015; Salvy & Bowker, 2013). Similarly, negative peer experiences are associated with less physical activity and more sedentary activities (Salvy & Bowker, 2013), which also could lead to a higher BMI. Alternatively, negative peer experiences could lead to sleep problems (Herge et al., 2016; Tu et al., 2019) which has been considered part of poor physical health (Herge et al., 2016). These poor health behaviors could be the result of victimization interfering with self-regulatory processes (A. L. Miller et al., 2018). Similarly, these behaviors may serve, at times, as maladaptive coping strategies (for example, emotional eating). Overall, these health-related behaviors represent particular interesting pathways that could be modified to help improve adolescents' health.

Research is needed to better understand the links between peer experiences, health behaviors, and health outcomes. All these mediation pathways should first be tested separately. However, the co-dependency and interplay of these constructs should also be considered. The interplay between these constructs is complex and likely bi-directional in nature. Peer experiences could lead to inflammation through changes in health behaviors, but it is also possible that health behaviors, in turn, lead to increased negative peer experiences. For example, an unhealthy diet could lead to higher BMI and, in turn, a higher risk of being bullied (Puhl et al., 2013). Health behaviors such as diet, exercise, and sleep can become interwoven with physiological processes

involved in frequently activated stress responses (Nurius et al., 2016). For example, poor sleep can alter neuro neuroendocrine systems, stress responsivity as well as immune system functioning (Irwin et al., 2016; Meerlo et al., 2008). Therefore, it is necessary to assess peer experiences, health behaviors, and health outcomes at multiple time points. This would allow the researcher to investigate the direction of the associations by using random intercept cross-lagged path analysis (Hamaker et al., 2015; Huang et al., 2019). It would also allow the opportunity to examine which pathways could make the most difference in improving health in adolescence. Only when considering all possible directions with cross-lagged paths, it would be possible to fully understand if peer experiences lead to higher inflammatory levels through health behaviors and/or vice versa.

A second pathway to consider is through poor mental health. Moreover, a vicious cycle between mental and physical health could be triggered by negative peer experiences. Negative peer experiences can lead to poorer mental well-being (see meta-analysis; Reijntjes et al., 2010) and, as also highlighted in this dissertation, to poorer physical health (Schacter, 2021). Physical health and mental health are closely interlinked, and they can influence each other both directly as indirectly (Nabi et al., 2008; Ohrnberger et al., 2017). This link is vital in adolescence, as this is when several psychological disorders emerge (Kessler et al., 2005). Therefore, future research could consider iterative cycles of effects between mental health and physical health that are the result of negative peer experience.

Notably, one particular mechanism linking mental and physical health could be elevated inflammation. Inflammation is a predictor of both physical health and mental health (e.g., depressive symptoms; Slavich & Irwin, 2014). Thus, the influence of peer experiences on inflammation could be a mechanism to explain the link between peer experiences and both physical health (symptoms) and mental health problems, such as depression. Additionally, accumulating evidence suggests that inflammation could play a role in explaining

the bidirectional links between mental and physical health (Messay et al., 2012). Both physical health (e.g., tissue damage, chronic diseases) and mental health (e.g., depressive symptoms) can lead to increased inflammatory cytokines that in their turn can lead to more physical health problems and mental health problems (Scrivo et al., 2011; Slavich & Irwin, 2014). The role of inflammation in both types of health could also explain the comorbidity of mental health and physical health problems in adolescents that undergo negative peer experiences (Dyb et al., 2015). This would be a promising avenue for future research, especially as many psychological disorders emerge in adolescence (Kessler et al., 2005). In sum, inflammation might play a salient role in explaining how peer experiences can lead to a negative spiraling loop of mental and physical health problems.

Interplay with psychological factors

Finally, the association between peer experiences and adolescents' physical health can be influenced by a variety of factors at many different levels of functioning. For example, some of those factors could act as moderators (Karunamuni et al., 2020; Lehman et al., 2017). This dissertation has taken into account variables from different domains (e.g., socio-demographic variables, health-related factors, cognitive factors and temperament); still many other factors could play a role in explaining individual differences in how peer experiences in adolescence are associated with health-related outcomes. Although the findings overall supported a direct role for many of these factors (e.g., SES and maternal warmth), none of the factors taken into account in the current dissertation moderated the association between peer experiences and inflammation. Thus, although the findings from this dissertation are in line with a biopsychosocial model (Karunamuni et al., 2020; Lehman et al., 2017) in which social dynamics (e.g., peer experiences), psychological dynamics (e.g., anxious depressed disposition), and biological dynamics (e.g., inflammation) all play a role in shaping (adolescents') health, it did not find support for an interaction between these factors. These results suggest that peer experiences play an

equally important role for each adolescent in predicting their physical health. However, the factors examined in this dissertation represent a limited number of possibilities and are only the beginning of examining the complex interplay between social, psychological, and biological factors.

One of the primary candidates would be to consider the effect of cognitive processes, such as appraisal and attributions, which may alter the way in which individuals experience the social environment. These cognitive processes have been suggested to play a dominant role in the biopsychosocial framework because the extent to which social situations influence individuals may largely depend on how these situations are subjectively experienced (i.e., information from the situation has to be processed; Karunamuni et al., 2020). Especially in adolescence, the role of appraisals and attributions would be interesting to investigate because adolescence brings about an increase in sensitivity to social information from peers (Crone & Dahl, 2012; Somerville, 2013). This would be in line with the accumulating research on the link between inflammation and loneliness, which represents the subjective appraisal of not having satisfying social contact (Hackett et al., 2012; Jaremka et al., 2013; Vingeliene et al., 2019). Thus, it would be important to study the effect of cognitive processes, such as appraisal, as these could be possible moderators of the association between peer experiences and adolescents' levels of inflammation.

A second likely moderator would be friendships. In this dissertation, I have focused on group-based peer experiences and therefore I did not investigated this important dyadic peer experience. However, friendships are equally important to adolescents as peer victimization and peer status. Moreover, dyadic peer experiences have been suggested to buffer against negative peer experiences (Bollmer et al., 2005; Hodges et al., 1999; Schmidt & Bagwell, 2007). Stress buffering models propose that the social support received in friendships can be used to cope with the social stress of negative peer experiences (Bollmer et al., 2005; Hodges et al., 1999; Schmidt & Bagwell, 2007). Prior research has supported this hypothesis, for instance showing that adolescents with supportive friends

experience less negative effects of peer victimization (Bollmer et al., 2005; Hodges et al., 1999; Schmidt & Bagwell, 2007) - althouhg recent meta-analytic work reported mixed-findings (see Schacter et al., 2021). Therefore, a final line of research to explore would be to examine if friendships could buffer against the negative effects of peer victimization and peer status on health-related outcomes.

Concluding statements

Overall, this dissertation shows that group-level peer experiences are important social dynamics for understanding adolescents' health trajectories. This work represents first steps in integrating peer relations research with biological stress research. It underlines the need to combine social, psychological and biological knowledge to understand health in adolescence. Of course, many other factors (outside of the ones discussed in this dissertation) influence adolescents' health and are worth considering (see, for example, biosocial models of Harris & McDade, 2018; Lehman et al., 2017).

This dissertation demonstrated that it is essential to distinguish between types of peer experiences (i.e., peer victimization, peer preference, and peer popularity) and to consider health factors (i.e., BMI and smoking) as pathways through which peer experiences can lead to negative health-related outcomes. Moreover, it showed that peer experiences could predict adolescents' levels of inflammation, a key part of immune system functioning. Currently, poor physical health in adolescents, who are victimized or low in peer status, is still often attributed to psychosomatic causes. However, this dissertation demonstrates that these peer experiences should also be considered for health-outcomes at the biological level. This finding might open up the conversation with parents, teachers, and health-professionals about which factors might underly adolescents' poor physical health.

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Appendix

Summary

In adolescence, belonging to the peer group is vital for wellbeing. When adolescents face negative peer experiences, such as peer victimization or low peer status, they are at increased risk for experiencing lasting health consequences. Thus far, existing research, however, has mainly examined how these peer experiences may predict poor mental health outcomes. However, to get a holistic view of how peer experiences at the group level could affect adolescents' wellbeing, it is crucial to understand to which extent different peer experiences could also influence adolescents' physical health. Although support exists that peer experiences negatively impact physical health, it remains unclear what biological processes, if any, give rise to this link and which particular peer experiences may be driving forces. Moreover, to fully understand the role that peer experiences play in influencing adolescents' physical health, these associations should be considered in the context of other early life adversities,

which are known to impact adolescents' physical health negatively. Therefore this dissertation aims to contribute to this area of research by investigating three aims: 1) the extent to which different types of peer experiences can affect adolescents' health-related outcomes, 2) specifically, the extent to which peer experiences influence adolescent levels of systemic inflammation, and 3) how peer experiences interact with other early life experiences.

Three main group-based peer experiences have been identified in prior research: peer victimization and two types of peer status (i.e., peer preference and peer popularity). In line with *Aim 1*, **Chapter 2** examined the unique, interactive, and cumulative effects of these three types of peer experiences on poor physical health in a sample of Dutch adolescents who were followed over the first two years of secondary school. This chapter considered the possibility that all three peer experiences independently predict adolescent physical health and the alternative that no given type of peer experience but the sum of different negative peer experiences predict adolescents' physical health (i.e., cumulative effect). Moreover, it explored the possibility that both low and high levels of peer popularity negatively predict physical health. Findings from multilevel analysis showed that poor physical health was mainly influenced by peer victimization. Adolescents who experienced higher levels of peer victimization than their peers had poorer physical health (i.e., between-person effect). Additionally, when adolescents experienced more peer victimization, as compared to their own average levels, they also reported poorer physical health (i.e., within-person effect). No effects of peer status (low or high) on adolescents' poor physical health were found, and a cumulative effect of negative peer experiences emerged to be driven by peer victimization. These findings highlight that it is essential to differentiate between the effects of peer victimization, peer preference, and peer popularity. Additionally, they indicate that peer victimization plays a predominant role in predicting (self-reported) poor physical health in adolescence.

This dissertation further explored the different effects of peer victimization, peer preference, and peer popularity on adolescents' physical

health in **Chapter 3.** In this chapter, the effects of these three different types of peer experiences on high sensitive C-reactive protein (hs-CRP), a marker of systemic inflammation (*Aim 2*), were examined in a large sample of Dutch adolescents from the Tracking adolescents Individual Lives Survey (TRAILS). This chapter's findings showed that *peer preference* at age 13 predicted lower levels of hsCRP three years later. This effect remained after controlling for several covariates, including age, sex, smoking behavior, SES, fat percentage, physical activity, and temperament. Conversely, neither peer popularity nor peer victimization were associated with hsCRP three years later (age 16). This chapter also examined the extent to which the association between peer experiences and hsCRP was moderated by early childhood adversity (*Aim 3*). Preliminary findings showed that *peer popularity* at age 13 interacted with early childhood adversity (< age 5) in predicting hsCRP (age 16), suggesting that adolescents with high levels of popularity had higher levels of CRP if they had experienced little early childhood adversity. Overall, this chapter's findings support the idea that negative peer experiences may predict systemic inflammation. This evidence may in turn suggest that inflammation is one possible biological process through which peer stressors predict poor physical health. Moreover, extending prior work on social status and inflammation, this chapter underlines the importance of distinguishing between the two types of peer status as they may differentially predict systemic inflammation during adolescence.

Finally, the extent to which peer experiences can influence systemic inflammation was explored further in **Chapter 4.** Specifically, in this chapter, we examined the effect of *peer victimization* on the biomarker of systemic inflammation soluble urokinase plasminogen activator receptor (suPAR; *aim 2*). This chapter investigated the possibility that the effects of peer victimization on inflammation are partly driven by health-related factors (i.e., BMI and smoking). Findings showed that cumulative peer victimization during childhood and adolescence predicted suPAR entirely through higher BMI levels and smoking. Furthermore, this chapter explored if two early life adversities, low childhood socioeconomic status

(SES) and lack of maternal warmth (both measured before the age of 5), and two individual characteristics, IQ and an anxious depressed disposition, moderated the association between peer victimization and inflammation (*Aim 3*). In contrast to the expectations, the effects of peer victimization on suPAR did not vary as a function of SES, maternal warmth, IQ, and anxious depressed disposition. Overall, the findings in this chapter underscore that special attention should be directed to the health behaviors of victimized youth as these could be targeted to prevent them from developing higher levels of systemic inflammation.

Together, the findings discussed in these chapters show that group-level peer experiences are important social dynamics to consider for understanding adolescents' health trajectories. First, they indicate that in addition to other early life adversities (e.g., low childhood SES), peer experiences are essential to consider when predicting adolescents' physical health. Second, these findings suggest that it might be useful to consider both severe peer stressors, such as peer victimization, and seemingly less intense experiences related to peer status (e.g., low peer preference) as effects were found for both. A more broad awareness of the adverse effects of peer victimization and peer status could help identify adolescents most at risk for physical health problems. Third, the findings indicate that there could be multiple pathways that lead to poorer adolescent physical health. Specifically, they suggest that the effects of peer victimization and peer status on adolescents' health may occur by influencing inflammation, directly or indirectly. Specifically, increases in smoking and BMI might explain how negative peer experiences could lead to higher levels of systemic inflammation. For adolescents who encounter negative peer experiences, physical health symptoms might have a psychosomatic etiology. Thus, medical practitioners would do well to consider the negative peer experiences of adolescents who report health complaints without apparent medical cause.

Overall, this dissertation takes the first steps in integrating peer relations research with psychoneuroimmunological research. Results underline the need to combine social, psychological, and biological knowledge to understand health in adolescence.

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