Hostility: A prospective study of the genetic and environmental background and associations with cardiovascular risk

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Abstract

Hostility is a multidimensional construct having wide effects on society. In its different forms, hostility is related to a large array of social and health problems, such as criminality, substance abuse, depression, and cardiovascular risks. Identifying and tackling early-life factors that contribute to hostility may have public health significance. Although the variance in hostility is estimated to be 18-50 percent heritable, there are significant gaps in knowledge regarding the molecular genetics of hostility. It is known that a cold and unsupportive home atmosphere in childhood predicts a child’s later hostility. However, the long-term effects of care-giving quality on hostility in adulthood and the role of genes in this association are unclear.

The present dissertation is part of the ongoing population-based prospective Young Finns study, which commenced in 1980 with 3596 3-18-year-old boys and girls who were followed for 27 years. The specific aims of the dissertation were first to study the antecedents of hostility by looking at 1) the genetic background, 2) the early environmental predictors, and 3) the gene–environment interplay behind hostility. As a second aim, the thesis endeavored to examine 4) the association between hostility and cardiovascular risks, and 5) the moderating effect of demographic factors, such as gender and socioeconomic status, on this association.

The study found potential gene polymorphisms from chromosomes 7, 14, 17, and 22 suggestively associated with hostility. Of early environmental influences, breastfeeding and early care-giving were found to predict hostility in adulthood. In addition, a serotonin receptor 2A polymorphism rs6313 moderated the effect of early care-giving on later hostile attitudes. Furthermore, hostility was shown to predict cardiovascular risks, such as metabolic syndrome and inflammation. Finally, parental socioeconomic status was found to moderate the association between anger and early atherosclerosis.

The new genetic and early environmental antecedents of hostility identified in this research may help in understanding the development of hostility and its health risks, and in planning appropriate prevention. The significance of early influences on this development is stressed. Although the markers studied are individual- and family-related factors, these may be influenced at the societal level by giving accurate information to all individuals concerned and by improving the societal circumstances.
**Tiivistelmä**


Löysimme muutamia potentiaalisia geenialueita kromosomeista 7, 14, 17 ja 22, jotka saattavat olla yhteydessä vihamielisyteen. Myös varhaiset ympäristötekijät, kuten imetys ja hoiva, ennustivat aikuisuuden vihamielisyyttä. Serotoniinireseptori 2A:n polymorfismin rs6313 havaittiin muokkaavan varhaisen hoivan yhteyttä myöhempään vihamielisiin asenteisiin. Lopuksi, vihamielisyys ennusti sydän- ja verisuonitautiin riskitekijöihin ja 5) muokkaavatko väestötieteelliset tekijät, kuten sukupuoli tai sosioekonominen asema, tätä yhteyttä.

Nämä löydökset vihamielisyyden taustalla vaikuttavista geneettisistä ja varhaisista ympäristötekijöistä voivat auttaa vihamielisyyden ja sen terveysriskien kehittymisen ymmärtämisessä ja mahdollisessa ennaltaehkäisyssä. Vihamielisyys juontaa juurensa jo varhaiseen kehitykseen. Vaikka kyse on yksilö- ja perhetason tekijöistä, niihin voidaan yhteiskunnan tasolla vaikuttaa oikealla tiedonannolla ja ympäröiviä olosuhteita parantamalla.
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List of original publications


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“False facts are highly injurious to the progress of science, for they often long endure; but false views, if supported by some evidence, do little harm, as every one takes a salutary pleasure in proving their falseness; and when this is done, one path towards error is closed and the road to truth is often at the same time opened.”

**Darwin, C. (1871)** *The Descent of Man, and Selection in Relation to Sex*, ch. XXI.
**Abbreviations**

- AHA = anger, hostility, aggression –syndrome
- BP = base pair
- BDI = Beck Depression Inventory
- C = cytokine
- CHD = coronary heart disease
- CHR = chromosome
- CRP = C-reactive protein
- DNA = deoxyribonucleic acid
- EAS = emotionality, activity, sociability –temperament theory
- EGIR = the European Group for the Study of Insulin Resistance
- GWAS = genome-wide association study
- HDL = high-density lipoprotein
- HF = high-frequency power of systolic arterial pressure,
- HRV = heart rate variability
- HTR1A = serotonin receptor 1A
- HTR2A = serotonin receptor 2A
- IDF = the International Diabetes Federation
- IMT = intima-media thickness
- LDL = low-density lipoprotein
- LF = low-frequency power of systolic arterial pressure,
- MAF = minor allele frequency
- MetS = metabolic syndrome
- MI = myocardial infarction
- MMPI = Minnesota Multiphasic Personality Inventory
- NEO-PI = neuroticism, extraversion, openness to experience –personality inventory
- NCEP = the National Cholesterol Education Program (of USA)
- SNP = single nucleotide polymorphism
- SES = Socioeconomic status
- T = thymine
- YF = Young Finns study
1 INTRODUCTION

Hostility is a personality construct having wide effects on society. Irritability and paranoia, which are part of the hostility construct, are major symptoms of many psychiatric diagnoses, such as depression and generalized anxiety disorder (Stringaris, Cohen, Pine, & Leibenluft, 2009). In addition, hate, suspiciousness and aggression in an individual have significant consequences on interpersonal relationships and the physical health of others, as well as the individual himself. Irritability is estimated to be prevalent among 3-20% among of children and adolescents (Stringaris, 2011), therefore affecting a considerable portion of the population. Hostility in its different forms is related to a wide array of social problems such as isolation (Vandervoort, 1999) and criminality (Soyka, Graz, Bottlender, Dirschfeld, & Schoech, 2007), psychiatric symptoms such as substance abuse (Everson et al., 1997; Pulkki, Kivimäki, Elovainio, Viikari, & Keltikangas-Järvinen, 2003) and depression (Heponiemi et al., 2006), as well as somatic problems such as cardiovascular risk (Chida & Steptoe, 2009). In addition to personal suffering and feelings of insecurity, hostility places a large burden on healthcare and social affairs systems as a result of violence and somatic and psychiatric health problems. Thus the costs of hostility may be far greater than assumed. Studying the early roots of hostility and its consequences is important for early prevention and intervention efforts aimed at reducing hostility’s adverse consequences. Identifying and tackling early-life factors that contribute to hostility may have public health significance and the present study was undertaken with this view in mind.

1.1. Definition of hostility

The current view on the role of hostility in the etiology, onset, and prognosis of somatic diseases emerged in the 1970s, and since then the research has been extending rapidly. Some concepts, such as anger-in and anger-out, have been adopted from previous Freudian psychosomatic theories, but the concept of hostility has mostly been based on empirical findings with no strong links to psychological ground theories.

A good example of an empirically based concept is Type A behavior which has been characterized by hard-driving competitiveness, a preoccupation with time, acting quickly, and impatience (Jenkins, Rosenman, & Friedman, 1967; Rosenman et al.,
The concept was developed upon pure empirical observations with no connection to personality theories. The potential for anger, aggression, and hostility were also seen as components of Type A behavior (e.g. Diamond, 1982; Matthews, Glass, Rosenman, & Bortner, 1977; Siegman, 1994).

Voluminous research on the role of Type A behavior in the pathogenesis of coronary artery disease has resulted in a more detailed identification of the above-mentioned components. The constructs of anger, hostility, and aggression are related, but not interchangeable. Thus contemporary psychology makes a distinction between these concepts. Usually anger refers to affect, hostility to attitudes, and aggression to behavior (Parrott & Giancola, 2007; T. W. Smith, 1994; T. W. Smith, Glazer, Ruiz, & Gallo, 2004).

The literature on the topic is contradictory, however, and uses a variety of different definitions and conceptual hierarchies. Buss (1991), for example, sees anger as an independent emotion, and considers hostility to be a cognitive subcomponent of anger. To the contrary, anger has also been considered as an affective subcomponent of a multifactorial hostility construct (Barefoot, 1992). According to this view, hostility is composed of cognitive, affective, and behavioral components. Further Greenglass and Julkunen (1989) see the term ‘hostility’ as referring primarily to cynical attitudes. As a rule, researchers agree that anger, aggression and hostility are distinct although closely related concepts, but disagree on which concepts are the main ones and which are subordinate.

For simplicity, here the concept of hostility is used as the main construct and it includes anger (i.e. irritability), hostile attitudes (i.e. cynicism and paranoia), and aggression (i.e. the way hostility is expressed) – AHA (anger, hostility and aggression) phenomenon. If we refer specifically to one of these ‘subcomponents’ of hostility, we will use its precise term: 1) ‘hostile attitudes’ = cynicism + paranoia/distrustful attitudes when referring to the cognitive component of hostility, 2) ‘anger’ when referring to the affective component, and 3) ‘aggression’ or ‘anger expression’ (including anger-out and anger-in) when referring to the behavioral component. Only cognitive (measured with cynicism and paranoia scales = hostile attitudes) and affective (measured with an irritability scale = anger) components are empirically tested here, thus the focus is on these and not on aggression.
We use the term ‘hostility’ because it is located in the middle of the AHA phenomenon. Anger may be seen as the primary construct describing the physiological reactivity which emerges first in the developmental perspective in childhood, while hostile attitudes are a more developed version of learned or inherited reactions to environmental distractions or to emotional anger sensations. Aggression, on the other hand, may be seen as a way of reacting to these feelings and attitudes on a behavioral level. However, we could also use the term ‘anger’ or ‘agression’ as a ground concept, as Buss (1991; A. H. Buss & Perry, 1992) does when referring to this broad phenomenon. Perhaps it does not matter which term we use as long as our usage of the words and understanding of their meaning are mutually close enough. As we know, it is difficult to draw boundaries for closely related concepts (Wittgenstein, 1981 [1953], §67-70). This is especially true with psychological concepts, such as emotions (Averill, 1983; Russell & Fehr, 1994). In addition, the same underlying constructs may vary in their phenotype in different cultural contexts (Norenzayan & Heine, 2005), albeit clarifying the core concepts definitions might reduce misunderstandings and bring more cohesive understanding of this subject.

Hostility may be measured by a variety of means ranging from self-reports to structured interviews and observations. Although structured observations and interviews and the use of different informants enable capturing the nuances of the reality more reliably, for large epidemiological studies covering thousands of participants and involving several follow-ups, self-report questionnaires are the most convenient way to assess personality (C. Eckhardt, Norlander, & Deffenbacher, 2004; A. Haukkala, Konttinen, Laatikainen, Kawachi, & Uutela, 2010), therefore they are used in the present study.

1.1.1 Characteristics related to hostility

Hostility is closely related to many concepts of personality psychology driven by trait theory and by psychoanalytic theory. Hostility might be assumed to have a shared variance at least with depression, neuroticism, low agreeableness, temperamental negative emotionality, harm avoidance and low reward dependence, as well as character traits such as low self-directedness and low cooperativeness.
The concept of anger is an essential part of temperament theories. According to the temperament theory on emotionality-activity-sociability (EAS) by Buss anger forms a part of the temperament trait of emotionality (A. H. Buss & Plomin, 1975). There is innate individual variability in dispositions to experience anger, which is not a consequence of experienced frustrations or environmental provocations. This view emphasizes that in the same environmental situation individuals vary as regards their thresholds for anger and the intensity of the experience (A. H. Buss & Plomin, 1975).

Hostility has been associated with high neuroticism and low agreeableness in the neuroticism-extraversion-openness personality inventory (NEO-PI) (Harkness, Bagby, Joffe, & Levitt, 2002; Watson & Clark, 1992). Within the psychoanalytic tradition, depression may be seen as hostility turned inwards, conceptually resembling the anger-in construct of hostility. However, hostility is a wider construct and is usually understood to be directed more towards the external world and social interactions. Hostility and depression may share similar roots in negative emotionality. While depressive symptoms may be more oriented towards one’s inner world (i.e. internalizing, e.g. “I am the one to blame”), hostility might be directed more towards other people (externalizing, e.g. “It is their fault”). Although theoretically distinct concepts, it is worth noting that hostility and depression are closely connected.

1.2. The development of hostility

1.2.1 Genetic effects

Both genetic and environmental factors affect hostility, and twin as well as family studies have shown heritability estimates of different hostility constructs to range between 0.18-0.50 (Coccaro, Bergeman, Kavoussi, & Seroczynski, 1997; Hur, 2006; Rebollo & Boomsma, 2006; Weidner et al., 2000), depending on the measure used. Although hypotheses exist on the location of ‘hostility genes’ the specific regions of the genome that underlie hostility have not been identified. The only previous attempt to capture more widely the human genome for hostility covered 387 autosomal short-tandem-repeat polymorphisms and found no significant linkage to hostility (Knox, Wilk, Zhang, Weidner, & Ellison, 2004). Currently, strong candidate genes for hostility are those that regulate the brain’s serotonin production.
The etiological role of serotonin deficit in depression has been studied extensively (Carr & Lucki, 2011; Jans, Riedel, Markus, & Blokland, 2007; Jokela, 2007) and serotonin levels have also been related to aggression (Booij et al., 2010; Coccaro, Kavoussi, Sheline, Berman, & Csernansky, 1997; Lesch & Merschdorf, 2000; Takahashi, Quadros, de Almeida, & Miczek, 2011). As serotonin-related genes regulate the brain’s serotonin system, which is essential in regulation the emotions and interpreting the environment (Lesch, 2007), the serotonin receptor and transporter genes are strong candidates for affecting hostility levels as well (Lesch & Merschdorf, 2000). This possibility is supported by findings showing that a low serotonin level in the central nervous system is related to high hostility (R. B. Williams et al., 2010). More specifically, serotonin 1A receptor (HTR1A) polymorphism rs6295, for example, putatively regulates serotonin signaling and has been linked to neuroticism and amygdala reactivity (Fakra et al., 2009; Strobel et al., 2003). As well, the T allele in the rs6313 polymorphism of the serotonin 2A receptor (HTR2A) gene has been associated with an ability to maintain high serotonin levels in the brain (Turecki et al., 1999), and the expression of HTR2A has been found to be regulated by allele-specific methylation (Polesskaya, Aston, & Sokolov, 2006). Animal models again show that environmental effects, such as prenatal stress and postnatal caregiving, also may change the functioning of the serotonergic system (Jans et al., 2007; Shannon et al., 2005). Thus there is potentially a complex interplay between genetic and environmental factors behind the development of hostility, but the longitudinal evidence is still limited.

1.2.2. Influences of the childhood environment

The quality of the rearing environment during childhood is known to affect a child’s later development and wellbeing. Repetti et al. (2002) characterize ‘risky families’ as being aggressive and conflictive, living in cold, unsupportive, and neglectful relationships which disturb children’s emotion control and expression, social competence, as well as physiological and neuroendocrinal systems. For example, Lehman et al. (Lehman, Taylor, Kiefe, & Seeman, 2005) show that retrospective self-reports of risky family environments correlate with depression and hostility in adulthood. In addition, prospective studies show that neglected or abused children have a higher risk for depression, antisocial personality disorder, and intimate partner

1.2.2.1. The early care-giving family environment

In cross-sectional and retrospective studies hostility has been associated with a family environment low in warmth, supportiveness, and cohesion (Houston & Vavak, 1991; Woodall & Matthews, 1989). However, retrospective designs make no conclusions about the direction of causation. Moreover, they may be compromised by a respondent’s poor memory, current life situation, or personality factors that may distort recollections of the past. The available prospective studies, however, support the findings of the retrospective studies. For example, government officials’ reports on child neglect/abuse predict later hostility, personality disorder, and intimate partner violence in young adulthood (White & Widom, 2003). Milder forms of negative family interactions, such as hostile maternal child-rearing attitudes have also been shown to predict hostile attitudes in adolescents (Keltikangas-Järvinen & Heinonen, 2003; Matthews, Woodall, Kenyon, & Jacob, 1996; Rääkkönen, Katainen, Keskivaara, & Keltikangas-Järvinen, 2000), while family SES, parental Type A behavior, parental life satisfaction, and Type A behavior in children has been shown to predict hostility in adulthood (Keltikangas-Järvinen & Heinonen, 2003). In the present study, maternal care-giving attitudes are used as one measure of the childhood environment when predicting later hostility.

In early infancy, mother-child interactions are mostly limited to fulfilling the infant’s biological needs, such as providing warmth, nourishment, and sleep. Breastfeeding is a significant component of early interaction between the mother and child, and may be a marker of family functioning and maternal nurturing during the very early months of life. Breastfeeding is recommended because of its wide-ranging and long-lasting health effects on offsprings’ somatic health (Eglash, Montgomery, & Wood, 2008). In addition, breastfeeding is also hypothesized to affect a child’s psychological development. Breastfeeding may have a beneficial effect on the mother-child attachment, which, in turn, could influence the child’s personality development. Although empirical evidence in humans of the effect of breastfeeding on mother-child bonding and attachment has been inconclusive (Jansen, de Weerth, & Riksen-Walraven,
some indirect evidence does exist. One study showed an association between longer duration of breastfeeding and higher adolescent perceptions of maternal care during childhood (Fergusson & Woodward, 1999). Breastfeeding can protect against maternal neglect in the long run (Strathearn, Mamun, Najman, & O’Callaghan, 2009), as it has been shown to predict less negative parental behavior (including negative affects, parental intrusiveness) and less irritable and unregulated children as well as better mother-infant interaction at one year-of-age (Bystrova et al., 2009; Else-Quest, Hyde, & Clark, 2003). Breastfeeding may also affect hormonal and neurobiological functioning in both the mother and the child. One of the hormones involved is oxytocin, which may decrease aggression and have many other related physiological and behavioral effects (Pedersen, 2004; Uvnäs-Moberg, 1996; Uvnäs-Moberg, 1998).

Previous studies on the effects of breastfeeding on a child’s later behavior or personality are few and contradictory (Batstra, Neeleman, Elsinga, & Hadders-Algra, 2006; Kramer et al., 2008; Oddy et al., 2010; Räikkönen et al., 2008; Sorensen, Mortensen, Reinisch, & Mednick, 2005; Taylor & Wadsworth, 1984). A large retrospective study showed that breastfeeding predicted a lower level of behavioral problems at age 5 (Taylor & Wadsworth, 1984) and a prospective cohort study showed that breastfeeding decreased the likelihood of behavioral problems at 2 to 14 years of age (Oddy et al., 2010). However, in a large randomized controlled trial prolonged, exclusive breastfeeding did not predict behavioral problems at age 6.5 (Kramer et al., 2008). Another cohort study showed no association between breastfeeding and hostility at age 63 (Räikkönen et al., 2008). There is also evidence of breastfeeding having a protective role as regards later mental health, i.e. lower levels of depression (Batstra et al., 2006) and schizophrenia (Sorensen et al., 2005) in young adulthood. However, we are not aware of studies examining the association between early-life breastfeeding and adult levels of hostility in a well-characterized, nationally representative sample of young adults, and this was one goal of the present study.

1.2.2.2 The role of socioeconomic status

Socioeconomic status (SES) is widely known to relate to stress and health problems (Adler, Boyce, Chesney, & Cohen, 1994; Lehman et al., 2005), and people with lower SES tend to have higher hostility levels (Gallo & Matthews, 2003; Pulkki et al., 2003).
A model proposed by Gallo and Matthews (2003) suggests that negative emotions are a pathway connecting low SES with ill health. According to this model, low SES fosters cynical attitudes because individuals with low SES encounter more frequent and more severe stressors than individuals in more favorable socioeconomic circumstances. Negative emotions and cynical attitudes are a response of the individual to a constantly taxing environment. The strongest association has been found between low SES (education, household income and occupational group) and hostile attitudes, supporting the model above, while high SES has been related to higher outwardly expressed anger, possibly because of more social power and freedom to emotional expression in high SES individuals (A. Haukkala, 2002).

The pathway also includes other factors: at lower levels of the social hierarchy people have less access to goods, facilities and other benefits of society compared with individuals at higher levels. These deficits are material, such as poorer nutrition, less exercise options and poorer schooling, as well as psychological, such as a lower ability to control emotions and less social support. Low SES parents may also create a hostile family atmosphere by being more punitive and stricter toward their children (Repetti et al., 2002). Because of the stressfulness related to the environment, low SES children may learn cynical attitudes and perceive the world as a threatening place, as well as react to future stressors more strongly (Matthews, Gump, Block, & Allen, 1997). Thus lower SES children may be less resilient to stress and more prone to interpreting situations negatively or in a hostile manner. Such reactions may be adaptive in the original surroundings, but maladaptive later in life. Therefore hostility may be one link between low SES and poor health. In addition, a risky family environment is associated more strongly with adulthood SES than with childhood SES (Lehman et al., 2005) which highlights the possibility that a stressful early family environment may result in moving downwards in social ranking perhaps due to emotional or physiological problems. Then, the adverse and stressful SES environment in which the person has ended up may increase hostility in that person because he perceives the situation as unfair.
1.2.3. The interactions between genes and environment

Personal factors (such as temperament) and environmental factors (maternal caregiving, for instance) may work together in producing vulnerability to hostility. However, little is known about the interactive effects between childhood environment and genetic constitution with regard to hostility, although the interface between nature and nurture is one of the most important themes in genetic research on personality (Lesch & Merschdorf, 2000). Vulnerability to environmental adversities may be conditional depending on an individual’s genetic susceptibility (Kendler, 2001; Rutter & Silberg, 2002). This has been convincingly demonstrated for instance in the Dunedin study by Caspi et al. (2002) and in the Virginia Study by Foley et al. (2004). These studies showed that some but not all maltreated children developed conduct disorders later in life. Whether they developed behavioral problems as a response to childhood adversities depended on a specific genetic component. The significance of these findings has been disputed in a meta-analysis which found no association of the interaction between the 5-HTT and stressful life events when predicting the risk of depression (Risch et al., 2009). However, in a recent review by Caspi (2010) and a meta-analysis by Karg et al. (2011) this meta-analysis was disputed backing the relevance of this gene-environment interaction. Thus, this issue is widely debated.

On the whole, majority of research community believes that both genes and environment affect the development. However, there is dispute about what kind of the methodology and proof are needed for verifying gene-environment interactions (Dick, 2011). The most recent evidence proposes that also the environment, in turn, modifies the expression of genes (Fraga et al., 2005). This may be explained by epigenetics, the idea that the functioning of genes is altered by environmental factors or other genes without changes occurring in the DNA sequence (Kappeler & Meaney, 2010; Meaney, 2010). This might at least partly explain the mechanism of how gene-environment interactions might work in practice.

It has been previously shown that HTR2A rs6313 polymorphism, a base pair in the HTR2A gene, modifies earlier environmental effects on adulthood outcomes such as depressive symptoms and harm avoidance (Jokela et al., 2007; Jokela, Lehtimäki, & Keltikangas-Järvinen, 2007b). An rs6313 polymorphism consists of two alleles, T (thymine) and C (cytocine), one of which is inherited from the mother and one from the
father, making the possible genotypes of the offspring T/T, T/C and C/C. The T allele in this polymorphism has been associated with an ability to maintain high serotonin levels in the brain (Turecki et al., 1999). Carriers of the T allele of the HTR2A rs6313 respond in adulthood to the protective aspects of high maternal nurturance with low depressive symptoms (Jokela et al., 2007), to high parental SES with low harm avoidance (Jokela, Lehtimäki, & Keltikangas-Järvinen et al., 2007b), and to urban residency with low depressive symptoms (Jokela, Lehtimäki, & Keltikangas-Järvinen, 2007a). Thus it has been suggested that carriers of the T allele in the HTR2A polymorphism rs6313 are susceptible to environmental effects, and that they are particularly likely to respond favorably to benign environments.

A serotonin-related mechanism might be one factor explaining the development of hostility and the wide interplay between the genetic and environmental factors behind emotion regulation and personality development (Way & Taylor, 2010). Certain environmental vulnerability factors may determine whether specific genotypes are ultimately manifested as hostile attitudes or behaviors. Alternatively, personal resilience may provide hardness vis-a-vis the environment, which may explain why some individuals thrive in sub-optimal environments while others do not.

1.3. Cardiovascular consequences of hostility

1.3.1 History of the hostility-disease link

The role of negative emotions in the transformation of psychological events into somatic disease is well-known. Of three major negative emotions, i.e. anger, fear, and depression, anger and depression have most convincingly been associated with physiological processes leading to somatic disease. Anger and hatred as obstacles to mental or somatic well-being have been mentioned already in the Old Testament as well as in ancient oriental philosophy and traditional Chinese medicine. The holistic approach suggesting a close mind-body interaction, usually attributed to the Freudian scientists of the 30s and 40s, was actually discovered in the ancient world and prevailed throughout Antiquity. During the Renaissance and the later rise of modern scientific medicine this approach, however, was lost, and only physical factors were seen as initiating physical diseases. In spite of this, some researchers at that time acknowledged the role of psychological factors in somatic disease. William Harvey, the discoverer of
blood circulation, wrote in 1628 (Harvey, 1628/1928; in Siegman, 1994) about the association between emotions and heart functions, while Heberden (1772), Fothergill (1781), Wardrop (1851), and Trousseau (1882) implicated anger in particular in coronary heart disease (references taken from Siegman, 1994).

At the beginning of 20th century Lange and James (Lange & James, 1922) saw anger as a mental expression of an originally physiological state, i.e. a mental expression of high physiological arousal. According to this theory, negative or frustrating experiences evoke a physiological reaction, and anger is the mental expression of this reaction. Thus the intensity of anger may represent innate or early individual differences in physiology. Later, findings in molecular genetics suggested that certain genetic combinations affecting central nervous system serotonin levels may predispose an individual to both hostility as well as metabolic and cardiovascular disturbances (Franchi, Lazzeri, Barletta, Ianni, & Mannelli, 2001; Giegling, Hartmann, Möller, & Rujescu, 2006; Rujescu, Giegling, Gietl, Hartmann, & Möller, 2003; R. B. Williams et al., 2010). Hostility might therefore be a marker of high physiological sensitivity and, as such, susceptibility to disease.

Recognizing negative emotions as contributors to somatic disease has usually been attributed to Freudian psychoanalysts, especially Dunbar (1947), Menninger (1936), Alexander (1939; 1950), and French (F. G. Alexander, French, & Pollack, 1968). While, “the holistic approach” claimed that psychological conflicts that include negative emotions can trigger somatic processes leading to disease, the “specificity theory” suggested a link between specific conflict and certain diseases, so that by knowing the somatic symptom of the disease, one might identify the underlying mental problem or conflict. This theory was widely accepted at first, but has been strongly criticized later.

The specificity theory in modern psychosomatics associated anger with heart disease for the first time. In the 1930s, Menninger and Menninger (1936) supposed that repressed aggressive tendencies might affect the heart, and Alexander (1939) suggested that the continuous suppression of rage may lead to a chronic elevation of blood pressure. These suggestions referred to the underlying psychoanalytic theory stating that “impulses which are inhibited in their expression sustain a chronic tension which is apt to have a permanent effect upon certain physiological functions” (F. Alexander, 1939).
Hence, intense anger and especially the inability to express it (i.e. suppression or repression of anger) were seen as being most harmful to health. It was also suggested that repressing anger had its roots in a conflict between passive dependent tendencies and compensatory aggressive hostile impulses. The more an individual gives in to his/her dependent compliant tendencies, the greater becomes his/her anger or hostility toward those to whom he submits, and a vicious, repetitive circle is formed (F. Alexander, 1950).

1.3.2. Hostility as a risk factor for cardiovascular outcomes

Coronary artery disease comprises several forms of pathology which ultimately lead to the manifestations of coronary heart disease (CHD), i.e. sudden death, myocardial infarction (MI), or stroke. The most important cause of coronary artery disease is atherosclerosis. The formation of atherosclerotic plaques contributes to the stenosis and calcification of arteries which, in the long run, decrease oxygen flow to the heart. A cardiac event may occur as a result. Atherosclerosis develops silently over a long period, beginning from childhood, and is usually rather advanced before clinical symptoms appear (S. Li et al., 2003; Raitakari et al., 2003). CHD is the most common of cardiovascular diseases and the leading cause of illness and death in most industrialized countries (World Health Organization, 2006), hence recognizing the risk factors and understanding the processes that contribute to cardiovascular diseases is very relevant to public health.

1.3.2.1. Coronary heart disease

Contemporary science considers hostility to be an independent risk factor for coronary heart disease (CHD) (Chida & Steptoe, 2009; Miller, Smith, Turner, Guijarro, & Hallet, 1996) although conflicting findings do exist (Rozanski, Blumenthal, & Kaplan, 1999; Rozanski et al., 2011; T. W. Smith et al., 2004). These findings may be due to the fact that some components of hostility are more harmful than others regarding CHD risk. Compelling evidence has recently emerged to support an association between incident CHD events and experiencing and expressing hostility (Chang, Ford, Meoni, Wang, & Klag, 2002; Chida & Steptoe, 2009; Everson et al., 1997; Kawachi, Sparrow, Spiro, Vokonas, & Weiss, 1996; J. E. Williams et al., 2000). Moreover, the mixed findings
may be masked by different associations between hostility and CHD in various subpopulations, such as different age, gender, ethnic or SES groups.

1.3.2.2. Atherosclerosis

Atherosclerosis is a process of coronary calcification resulting from plaque on the walls of arteries. Low-density lipoprotein (LDL) cholesterol attaches to the walls of arteries, gradually forming plaques and atheromas on the arterial walls. As a result, calcification and stiffening of the walls occurs, which restricts blood flow and oxygen to the vital organs. Elevated level of high-density lipoprotein (HDL) cholesterol, in turn, is known to prevent cardiovascular disease because it inhibits cholesterol from attaching to the arteries. Preclinical atherosclerosis is a risk factor for cardiovascular disease, possibly leading to myocardial infarction (MI) or stroke.

Sub-clinical atherosclerosis measured by carotid artery intima-media thickness (IMT) is related to vascular risk factors, the extent of coronary atherosclerosis, and the occurrence of coronary events (Bots, Hoes, Koudstaal, Hofman, & Grobbee, 1997; Burke et al., 1995; Heiss et al., 1991). The advantage of measuring IMT by ultrasound is that it can be safely applied to asymptomatic people, allowing for studies of atherosclerosis among healthy young people who do not yet have clinically manifested disease. Exposure to risk factors in youth is associated with increased IMT in adulthood (Juonala et al., 2010; Koivistoinen et al., 2011; Raitakari et al., 2003).

Anger and hostile attitudes have been shown to be associated with IMT cross-sectionally (Bleil, McCaffery, Muldoon, Sutton-Tyrrell, & Manuck, 2004; Everson-Rose et al., 2006; Knox et al., 2000; Matsumoto et al., 1993). In prospective studies both anger (Matthews, Owens, Kuller, Sutton-Tyrrell, & Jansen-McWilliams, 1998; Räikkönen, Matthews, Sutton-Tyrrell, & Kuller, 2004) and cynical hostility (Julkunen, Salonen, Kaplan, Chesney, & Salonen, 1994; Pollitt et al., 2005) have been shown to predict increased level of IMT or the further progression of IMT. However, one study found that hostile attitudes and suppression of anger did not predict further progression of IMT (Räikkönen et al., 2004). In summary, the research on the relationship between anger or cynical hostility and IMT has produced mixed findings and has mainly concentrated on either clinical samples or middle-aged populations.
1.3.2.3. Metabolic syndrome

Metabolic syndrome (MetS) presents a great risk for cardiovascular disease, atherosclerosis, diabetes, and myocardial infarction (Lakka et al., 2002; R. Niaura et al., 2002; Ninomiya et al., 2004). MetS was defined by Reaven (Reaven, 1995) as the clustering of central obesity, glucose intolerance, insulin resistance, hypertension and dyslipidemia, although the definitions of MetS have evolved over the past decade. The central components are reduced HDL cholesterol, insulin resistance, high glucose concentration, central obesity, and high blood pressure. The importance of these components varies somewhat depending on which definition is used to describe the MetS. Some definitions require elevated insulin levels as the central component (Balkau & Charles, 1999) while others see obesity as the central abnormality in MetS (Alberti, Zimmet, & Shaw, 2005; Grundy et al., 2005). Prospective data, though limited, suggest that hostility predicts the subcomponents of MetS (Kubzansky, Kawachi, & Sparrow, 1999; R. Niaura et al., 2000; Pulkki-Råback, Elooinio, Kivimäki, Raitakari, & Keltikangas-Järvinen, 2005; Ravaja & Keltikangas-Järvinen, 1995). However, the current literature provides mainly cross-sectional evidence of associations between diagnosis of MetS and hostility (Goldbacher & Matthews, 2007), although Räikkönen et al. (2004) have found that high levels of hostility predict a risk for MetS over 7.4 years in premenopausal, middle-aged women. However, studies examining hostility and MetS prospectively in young adult populations consisting of both genders are lacking. This may have public health relevance, because MetS is rather common already in early adulthood, and preventive efforts are usually most effective when applied early in life (Mattsson, Rönnemaa, Juonala, Viikari, & Raitakari, 2008).

1.3.2.4. Inflammation

Inflammation has been recently suggested as a probable factor explaining at least partly the association between hostility and cardiovascular risk. One of the markers of immune system functioning is systemic inflammation, which has been suggested to be an underlying cause of MetS (Haffner, 2006). It has also been suggested that inflammation plays an important role in the earlier and later stages of atherosclerosis and diabetes, and it has been shown among initially healthy individuals that elevated levels of inflammatory markers, such as C-reactive protein (CRP), predict future CHD and
mortality (Koenig, Khuseynova, Baumert, & Meisinger, 2008; Tuomisto, Jousilahti, Sundvall, Pajunen, & Salomaa, 2006; Yudkin, Kumari, Humphries, & Mohamed-Ali, 2000). The current literature provides mainly cross-sectional evidence of an association between hostility and CRP (Stewart, Janicki-Deverts, Muldoon, & Kamarck, 2008; E. C. Suarez, 2004). The only prospective study that we are aware of (Graham et al., 2006) found that hostility was independently related to circulating levels of CRP among 224 older adults.

1.3.3. Moderators of the hostility-cardiovascular disease link

The association of hostility with cardiovascular risk may depend on characteristics of the population such as sex, age or ethnicity. Recent evidence suggests that hostility may induce different risks in various ethnic groups (E. D. Williams, Steptoe, Chambers, & Kooner, 2011) and in genders (Davidson & Mostofsky, 2010). Further, socioeconomic circumstances may moderate the effects of psychosocial factors as predictors of cardiovascular risk: socioeconomic deprivation may make individuals more vulnerable to CHD (Gallo & Matthews, 2003) due to a lack of protective factors in the environment such as social contacts, trust, financial resources, and/or resources to cope with stress. For instance, Lynch et al. (1998) showed that the effect of cardiovascular reactivity on atherosclerotic progression depended on SES; that is, a stronger association was observed in individuals with low SES. In line with this, Mittleman et al. (1997) found that the risk of episodes of anger triggering the onset of nonfatal myocardial infarction was less in higher SES patients and greater in lower SES patients, suggesting that SES moderated the role of anger as a trigger of MI. Thus one of our hypotheses is that lower SES individuals are more vulnerable to the effects of hostility, and that hostility has more adverse effects on cardiovascular risk in people with lower rather than higher SES.
2 AIMS OF THE STUDY

Little is known about the underlying interplay between genetic background and early environmental factors (G × E interaction) in the development of hostility. Although hypotheses exist on the location of ‘hostility genes’ the specific regions of the genome that underlie hostility have not been identified. At the same time, twin studies show that even half of the differences between individuals in hostility levels may be inherited. Thus there are significant gaps in knowledge regarding the genetic background of hostility. Cold and unsupported home atmosphere in childhood is known to predict later hostility. However, the long-term effects of care-giving quality on hostility in adulthood and the genetic contribution in this association are unclear. As a first purpose, we examined some developmental antecedents of hostility, including parental caregiving attitudes and breastfeeding, as well as the genetic basis of hostility using genome-wide association and gene-environment interaction designs.

The contrary findings on hostility as a cardiovascular risk factor may be due to population-specific factors. Thus the second purpose of the dissertation was to contribute to this debate on the psychosomatics related to hostility and cardiovascular risks. The consequences or correlates of hostility with regards to somatic well-being were examined by studying the relationship between hostility and early atherosclerosis in the form of carotid intima-media thickness, metabolic syndrome, and inflammation, each a risk factor for cardiovascular disease.

The theoretical framework for the present study is presented in Figure 1. Understanding the developmental roots of hostility makes it easier to plan prevention and intervention to reduce it. The prevention of hostility is important because of its wide consequences for both the individual and society. Hostility is associated with social, mental, and physical health problems, thus heavily impacting human life particularly in terms of individual suffering as well as costs to society.
Figure 1. The general theoretical framework suggests that genetic background affects hostility through gene expression as proteins and eventually as hormones, neurotransmitters etc., while environmental factors have a direct effect on hostility as well as an indirect effect through gene expression. The relationship of both the environment and individual physiology to hostility is bidirectional, i.e. hostility also affects these entities thus enabling vicious repetitive cycles. The association of hostility with cardiovascular risks has three possible routes: 1) direct effect of hostility on cardiovascular risk (hostility causing cardiovascular malfunctions); 2) indirect effect through environmental or physiological factors, in which a hostile individual for example has adverse health behaviors which cause the development of cardiovascular problems (hostility indirectly causing cardiovascular malfunctioning); 3) environment or genetic composition causing both hostility and cardiovascular risk (hostility not the cause of cardiovascular risk but rather an indicator of it). In addition to this, interactions between the above-mentioned entities may occur.
The study consisted of two themes, and the specific research questions were as follows:

Theme 1 (Studies I – III): Genes and environment in the development of hostility

1. What are the most significant genetic predictors of hostility in genome-wide association analysis? (Study I)

2. Does the early care-giving environment, as indexed by breastfeeding, predict offsprings’ hostility in adulthood? (Study II)

3. Do certain gene-environment interactions in childhood predict hostility in adulthood: Do serotonin receptor gene polymorphisms moderate the association between parental care-giving attitudes and offsprings’ hostile attitudes in adulthood? (Study III)

Theme 2 (Studies IV – VI): The cardiovascular outcomes of hostility

4. Do hostile attitudes predict later metabolic syndrome or inflammation? (Study IV)

5. Are people raised in lower SES environments more vulnerable to the effects of hostility: Does SES moderate the association of anger or cynicism with early atherosclerosis? (Study V)

6. What is known of the anger-cardiovascular diseases link? A review of previous studies on the relationship between anger and cardiovascular diseases (Study VI).
3 METHODS

3.1. Design of the study and selection of the participants

3.1.1. Design of the Young Finns study

The multicenter study, at first called Atherosclerosis Precursors in Children, and later renamed The Cardiovascular Risk in Young Finns, and nowadays shortly called the Young Finns (YF) study, was launched in Finland in 1979. The YF was designed as a collaborative effort between all university departments of pediatrics and several other institutions in Finland to study the risk factors of cardiovascular diseases and their determinants in children and adolescents of various ages in different parts of the country (Åkerblom et al., 1991). The study was motivated by the World Health Organization Recommendation of 1978 and by earlier studies indicating that atherosclerotic vascular changes start quite early in life (Åkerblom et al., 1991). The main objectives of the YF study have been to: 1) study risk factor levels and their possible regional and socioeconomic differences; 2) study the determinants of CHD risk factors and the mechanisms by which risk factor levels in childhood change into adult levels; 3) explore the tracking and clustering of CHD risk factors; 4) study the behavioral and psychological risk factors for CHD; 5) study the effect of life-style and life-style changes on CHD risk factors; 6) study new risk factors for CHD and genetic variation in CHD risk factors (Raitakari et al., 2008; Åkerblom, Viikari, Raitakari, & Uhari, 1999).

3.1.2. Selection of the study population in the Young Finns study

In order to select participants that were broadly representative of Finnish children and adolescents in terms of living conditions and socioeconomic and demographic background, Finland was divided into five areas according to the location of the university cities with a medical school (Helsinki, Kuopio, Oulu, Tampere and Turku). In each area urban and rural boys and girls were randomly selected on the basis of their personal social security number from the Social Insurance Institution's population register, which covers the whole population of Finland. In four areas (Helsinki, Tampere, Turku and Oulu), 60 girls and 60 boys in the age cohorts of 3, 6, 9, 12, 15, and 18 years in 1980 were selected. To ensure equal numbers of participants from the
east and the west, 120 boys and 120 girls were selected in each cohort in Kuopio, the most eastern area (Åkerblom et al., 1985; Åkerblom et al., 1991). The initially selected sample of the YF consisted of 4320 children and adolescents. The first and second pilot studies were carried out in 1978 and 1979. The first cross-sectional study was performed in 1980, and it included 3596 children and adolescents (83.2% of the invited). These cohorts have had follow-up examinations in 1983, 1986, 1989, 1992, 1997, 2001, 2007, and the latest follow-up will be in 2011.

The examinations took place at the outpatient departments of the Department of Pediatrics in the urban areas, and in the Public Health Centers in the rural areas. A few weeks before the medical examinations, in connection with the invitations for children to participate in the YF, the families received questionnaires by mail covering socioeconomic background of the family, psychological and psychosocial characteristics of the parents and their children, the children’s general health and health behaviors, the parents’ health habits and their state of health, as well as the grandparents’ state of health. The participants brought these questionnaires with them to the medical examination, which included blood tests, measurement of blood pressure, and anthropometric measurements (Raitakari et al., 2008; Åkerblom et al., 1991). Ethical committees of all participant universities accepted the study plan (Åkerblom et al., 1985) and it was in accordance of the Helsinki Declaration.

Compared to those who had dropped out during the follow-up period between 1980 and 2001, the participants were more often women and older (Raitakari et al., 2008). Most common reasons for non-participation in the Young Finns study have previously shown to be lack of time, unknown place of residence, and unwillingness to participate (Raitakari et al., 2003).

3.1.3. Sample selection of the present study

The eligible participants in the present studies were those from whom we had valid data on the main variables of the study in question, i.e. in hostility measures used as well as the independent variables (genetic background and/or early environmental variables) or the dependent variables (cardiovascular risks, such as the metabolic syndrome, inflammation or subclinical atherosclerosis) as well as covariates. The sample sizes in studies I to V are shown in table 1.
Table 1. Number of participants in the individual empirical studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of participants</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>985-1781</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1917 unique individuals, 5501 observations</td>
<td>6-21</td>
</tr>
<tr>
<td>III</td>
<td>819</td>
<td>3-18</td>
</tr>
<tr>
<td>IV</td>
<td>635-973 females, 470-724 males</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>1540</td>
<td>3-18</td>
</tr>
</tbody>
</table>

3.2. Measures

3.2.1. Hostility

Hostility was assessed with three scales in four different examinations in 1992, 1997, 2001, and 2007. Cynicism and Distrustful attitudes/Paranoia scales were used to measure hostile attitudes that is, the cognitive component, and Anger scale was used as an indicator of the affective component. Cynicism was measured with a 7-item cynicism scale derived from the Minnesota Multiphasic Personality Inventory (MMPI) with items such as “It is safer to trust nobody” (Comrey, 1957; Comrey, 1958). Distrustful attitudes, also called paranoia, were assessed with the 6-item paranoid ideation subscale of the Symptom Checklist-90R (e.g. “Others do not give me proper credit for my achievements” (Derogatis & Cleary, 1977). Anger was assessed with a 7-item Irritability Scale of the Buss-Durkee Hostility Inventory (e.g. “I lose my temper easily but get over it quickly”) (A. H. Buss & Durkee, 1957). The items were self-rated by the participants on a 5-point scale, ranging from 1 (totally disagree) to 5 (totally agree), and the mean of each scale was calculated for only those who had responded to at least 50% of the items on the scale. Cronbach’s α being 0.85, 0.84 and 0.82 for cynicism, paranoia and anger scales, respectively. Total hostility score was measured as a mean of the Cynicism, Distrustful attitudes, and Anger sub-scales. Mean of Cynicism and Distrustful attitudes scales were used to characterize Hostile attitudes. The scales used in the separate studies are described in Table 2 and correlations between the scales can be found in Table 4.
3.2.2. Childhood environment

3.2.2.1. Breast-feeding

Breast-feeding (in study II, Table 2) was measured as a parental report of whether the child had been breastfed (1=breastfed, 2=not breastfed, 3=does not remember) and the duration of breastfeeding in months (zero implicating not breastfed). Duration of breastfeeding was used as a continuous variable to measure linear effects and classified as six graded variable to assess the non-linear effects (0=not breastfed, 1=less than 4 months, 2=4-6 months, 3=7-11 months, 4=12 months or more, and 5=not remember). All mothers who had breastfed were categorized as breast-feeders, despite of whether they had used additional milk supplements (partial feeding) or whether the child received all nutrition from breastfeeding (exclusive breastfeeding). Although mothers had to recall their breast-feeding status afterwards, it has been shown that mothers’ reports of breastfeeding history are highly reliable and valid (Kark, Troya, Friedlander, Slater, & Stein, 1984). In Finland, almost all mothers and infants are regularly checked at antenatal clinics during pregnancy and at child health centers after birth from where parents get the child’s personal record card with them. In case of uncertainty regarding breastfeeding, the parent was asked to check the information from these personal records. In a previous study within the present cohort, breastfed men were shown to have better brachial endothelial function than formula fed men (Järvisalo et al., 2009), supporting the validity of the breastfeeding measure as a predictor of health.

3.2.2.2. Child care-giving

Maternal care-giving attitudes (in study III, Table 2) during childhood or adolescence were assessed two times: First at the baseline in 1980 when participants were aged 3-18 and at the first follow-up in 1983 when the participants were 6-21 years. A mean score of these two assessments was calculated to obtain a more permanent measure of maternal attitudes toward the child, and to decrease the influence of transient factors (such as the mother’s difficulty coping with the child due to a rebellious developmental stage). Care-giving measure focused on the child’s emotional significance to the mother (‘My child is emotionally important to me’ and ‘I am emotionally important to my child’) and whether the mother perceived child-caring as enjoyable and satisfying (‘I
enjoy spending time with my child” and “My child allows/enables me to fulfill myself”). Four items were self-rated by the mothers of the participants on a 5-point scale ranging from 1 (totally disagree) to 5 (totally agree), thus a higher score indicates warmer care-giving attitudes. Cronbach’s $\alpha$ was .66 and .77 for maternal care-giving attitudes in 1980 and 1983, respectively.

### 3.2.2.3. Socioeconomic status (SES)

Socioeconomic status (SES) was illustrated as educational years in study V (Table 2). Parental educational years were self-reported by the mother and father in 1980. Educational years of the more highly educated parent were used as an indicator of family socioeconomic status. Childhood SES was classified as low SES (<9 years of education) vs. middle/high SES (≥9 years of education). Participants’ own educational years in 2001 were also used as a representative of adulthood SES classified as low SES (<13 years) vs. middle/high SES (≥13 years). SES measured as education and/or income were also used as a covariate in studies II, III, and IV.

### 3.2.3. Cardiovascular risk factors

#### 3.2.3.1. Metabolic syndrome (MetS)

MetS in study IV was measured in 2001 (See Table 2) using three widely used criteria: the criteria of the National Cholesterol Education Program (NCEP), the European Group for the study of Insulin Resistance (EGIR) and the International Diabetes Federation (IDF). According to NCEP criteria (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001) MetS is diagnosed as 3 or more of the following conditions: waist ≥102 cm in men and ≥88 cm in women, serum triglycerides ≥1.695 mmol/l (150 mg/dl), HDL cholesterol <1.036 mmol/l (40 mg/dl) in men and <1.295 mmol/l (50 mg/dl) in women, blood pressure ≥130 or ≥85 mmHg or treated, and plasma glucose ≥5.6 mmol/l (100 mg/dl). According to the EGIR criteria (Balkau & Charles, 1999), subjects with the MetS were defined as the presence of hyperinsulinemia (defined as non-diabetic subjects having fasting insulin level in the highest quartile, the cut-off point of our study was 9 mU/l), and at least two of the following conditions: fasting blood glucose ≥6.1 mmol/l, blood pressure ≥140/≥90 mmHg or current use of antihypertensive medication, serum triglyceride level >2.0
mmol/l or HDL level < 1.0 mmol/l, and waist at least 94 cm in men and 80 cm in women. The IDF’s criteria (Alberti et al., 2005) for MetS are waist ≥94 cm in men and ≥80 cm in women, fasting plasma glucose ≥5.6 mmol/l, hypertriglyceridemia ≥1.695 mmol/L and HDL-cholesterol levels < 1.036 mmol/L in men and < 1.295 in women and blood pressure ≥130/≥85 mmHg or treatment. A diagnosis requires abdominal obesity and ≥2 of the 4 criteria. Details of analytical procedures used in the Cardiovascular Risk in Young Finns follow-up study in 2001 are reported previously (Raitakari et al., 2008).

3.2.3.2. C-reactive protein (CRP)

Inflammation, measured as C-reactive protein (CRP), was one of the outcomes in study IV. Serum high sensitive (hsCRP) was analyzed in 2001 by an automated analyzer (Olympus AU400, Olympus, USA) and a highly sensitive turbidimetric immunoassay kit ("CRP-UL"-assay, Wako Chemicals, Neuss, Germany). The detection limit of the assay was 0.06 mg/L. The inter-assay coefficient of variation was 3.33% at the mean level of 1.52 mg/l (n=116) and 2.65% at the mean level of 2.51 mg/l (n=168).

3.2.3.3. Carotid intima-media thickness (IMT)

Carotid intima-media thickness (IMT) was measured in 2001 with the ultrasound of the left common carotid artery following a standardized protocol (Raitakari et al., 2003). A magnified image was recorded from an angle showing the greatest distance between lumen-intima interface and the media-adventitia interface. From this image, at least four measurements of common carotid far wall were taken approximately 10 mm proximal to the bifurcation to derive a mean carotid IMT, which is used as a sensitive marker of subclinical atherosclerosis, a preclinical state of CHD. Use of cardiovascular outcome measures is shown in table 2.
Table 2. The research questions of the individual empirical studies and measures used

<table>
<thead>
<tr>
<th>Study</th>
<th>Research Question</th>
<th>Anger</th>
<th>Anger</th>
<th>Anger</th>
<th>Cynicism</th>
<th>Cynicism</th>
<th>Cynicism</th>
<th>Cynicism</th>
<th>Cynicism</th>
<th>Paranoia</th>
<th>Paranoia</th>
<th>Paranoia</th>
<th>Paranoia</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>What are the most significant genetic predictors of hostility in genome-wide analyses?</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Genotyping and imputating around 2.5 million SNPs in 2007</td>
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<td></td>
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<tr>
<td>II</td>
<td>Does breastfeeding predict offspring hostility in adulthood?</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>III</td>
<td>Is the association between maternal care-giving in childhood and hostile attitudes in adulthood moderated by serotonin receptor SNPs? Maternal care-giving quality</td>
<td>Maternal care-giving quality</td>
<td>Hostile attitudes</td>
<td>HTR2A rs6313</td>
<td>HTR1A rs6295</td>
<td></td>
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<tr>
<td>IV</td>
<td>Do hostile attitudes predict inflammation and metabolic syndrome?</td>
<td>Hostile attitudes</td>
<td>MetS</td>
<td>CRP</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>V</td>
<td>Is the association of anger or cynicism with carotid IMT in adulthood modified by socioeconomic exposures during the lifecourse? SES: Parental educational years; &lt;9 vs. ≥9 years</td>
<td></td>
<td>Anger</td>
<td>Cynicism</td>
<td>Participant’s own educational years; &lt;13 vs. ≥13 years</td>
<td>Carotid IMT</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

SNP = Single nucleotide polymorphism; HTR2A = Serotonin receptor 2A gene polymorphism; HTR1A = Serotonin receptor 1A gene polymorphism; MetS = Metabolic syndrome; CRP = C-reactive protein; IMT = Intima-media thickness; SES = Socioeconomic status

3.3. Genotyping

The genome-wide single nucleotide polymorphisms (SNP) genotyping of YF-study was done by a custom Illumina BeadChip containing 670000 SNPs and copy-number variant probes (Sanger Institute, UK, (E. N. Smith et al., 2010). A total of 2556 samples were genotyped. After final frequency and genotyping running, there was 546677 SNPs available from a sample of 2442 YF participants (1123 males, 1319 females). Genotype imputation up to 2.5 million SNPs was performed for the YF SNP data using MACH (Y. Li & Abecasis, 2006) with HapMap (phase II) haplotypes as reference.
3.4. Statistical analyses

3.4.1. Study I: What are the most significant genetic predictors of hostility in genome-wide association analyses?

The quasi-continuous mean variables of hostility sub-scales were Box-Cox transformed. Residuals were obtained using the linear regression model in which hostility variables were adjusted for sex and age in order to control the most obvious environmental factors related to hostility. Residuals were standardized (mean 0, s.d. 1) and their distributions were confirmed to be very close to normal by visual QQ-plot analysis. We also verified that the estimates for the beta coefficients from the GWA study are not driven by a few outliers by plotting leverage vs. standardized residuals plots for the residuals.

Tests for additive genetic effects were carried out on a linear scale using linear regression. Genotypes were encoded as 0, 1, or 2 when the SNP was genotyped and by dosage (scale 0-2) when imputed. These tests were performed to assess the association of SNPs with the standardized residuals using PLINK (Purcell et al., 2007) for the genotyped data. ProbABEL (Aulchenko, Ripke, Isaacs, & van Duijn, 2007) was used to fit the model, taking account of the genotype uncertainty at imputed SNPs. P-values were combined from the analysis by favoring genotyped tests over imputed ones. QQ- and Manhattan –plots were drawn for the analysis of the results. The p-value for genome-wide significance was set at $p < 9 \times 10^{-8}$, corresponding to a target $\alpha$ of 0.05 with a Bonferroni correction for 550 000 independent tests with direct genotyping, although associations with $p < 1 \times 10^{-5}$ are shown. Cynicism was normally distributed, while the distributions of paranoia and anger were slightly positively skewed. Thus Box-Cox transformations were used for all the outcomes.

3.4.2. Study II: Does breastfeeding predict offspring’s hostility in adulthood?

The preliminary analyses were conducted using the analysis of covariance (breastfeeding used as a categorical variable) and linear regression analysis (duration of breastfeeding used as a continuous variable) fitted separately for each measurement time of hostility. As the analyses for separate years suggested very similar results (data not shown), they were combined in a single multilevel model in which all the measurement times (observations on each phase) were pooled together and each
participant could contribute 1 to 4 person-observations to the dataset (n=5501 person-observations from 1917 unique participants). The multilevel regression method takes into account the non-independence of the observations in calculating standard errors of the estimates and maximizes the usage of the data using all the person-observations. As a result, the model is able to increase n by analyzing several observations from one individual, thus the same individual contributes more than one observation to the dataset. In the final model, child’s age, sex, birth weight and birth order as well as mother’s age during childbirth, maternal education, hostile child-rearing attitudes, family structure, income, the number of children in family, were used as covariates to assess potential confounding. All continuous variables were standardized into z-scores (SD=1).

3.4.3. Study III: Do serotonin related SNPs moderate the association between parental care-giving attitudes and offspring’s hostile attitudes in adulthood?

We first tested gender differences with three-way interactions (Gender × Gene × care-giving) as a predictor of hostile attitudes. Second, we tested the main effects of the HTR1A rs6295, HTR2A rs6313, and care-giving on hostile attitudes. Third, the interaction effects between SNPs and care-giving on hostile attitudes were tested. When a significant interaction effect was found the population was split in three groups according to the moderator variable (SNP) as recommended by Kraemer et al. (2001). Thus, subsequent analyses of the associations between maternal care-giving and hostile attitudes were performed separately within different genotype carriers with multiple linear regression analysis adjusted for different blocks of covariates. All the analyses were age- and gender -adjusted and conducted with linear regression analyses.

3.4.4. Study IV: Do hostile attitudes predict later metabolic syndrome and inflammation?

We standardized the hostility measure (mean=0, standard deviation=1) and used logistic regression analysis to evaluate the risk of developing MetS (non-cases vs. cases) per one SD increase in the level of hostility. We first controlled the models for the childhood risk factors (socioeconomic status, body mass, HDL cholesterol, triglycerides, blood pressure and insulin) and thereafter, separately for each of adulthood behavioral risk factors (socioeconomic status, smoking, alcohol use, physical
activity), and then separately for each of the heart rate variability (HRV) measures. Finally, we ran a fully-adjusted model where all childhood and adulthood risk factors were included. A separate set of analyses was conducted using each of the metabolic syndrome definitions (NCEP, EGIR, and IDF) as the outcome variable.

The association between baseline hostility and the log-transformed CRP level at follow-up as the dependent variable was tested using linear regression analyses. Also, in these analyses we first controlled the models for childhood CRP and then additionally and separately for each of adulthood behavioral risk factors (socioeconomic status, smoking, alcohol use, physical activity), and then separately for each HRV measures and finally we ran a fully-adjusted model where all childhood CRP and adulthood risk factors were included as predictors.

3.4.5. Study V: Does SES moderate the association of anger or cynicism with early atherosclerosis?

We first tested gender differences with three-way interactions (Gender × SES × hostility measures) as a predictor of carotid IMT. Second, the associations between all the study variables were tested with partial correlation analyses. Third, the interaction effects of SES and hostility measures predicting IMT were tested. When a significant interaction effect was found the population was split in two according to the moderator variable (SES). Thus, subsequent analyses of the associations of hostility with sub-clinical atherosclerosis were performed separately within low and moderate/high SES groups with multiple linear regression analysis adjusted for different blocks of atherosclerosis risk factors. All the analyses were age- and gender-adjusted and conducted with linear regression analyses.

3.5. Methods of the literature review of anger and cardiovascular diseases (Study VI)

Ovid Medline searches with words ‘anger’ and ‘disease’ were done in December 2006 and January 2007 and the relevant articles were chosen according to the titles and abstracts. We restricted to cardiovascular diseases because articles on other diseases were limited. Only those studies covering anger and anger expression were included, thus leaving out studies concentrating on aggression and/or hostile attitudes.
4 RESULTS

4.1. Study I: GWAS of hostility

The average age of the genotyped sample is 37.56 (SD=5.03). The stability of the measures (rs' range .52 to .65) as well as their bivariate correlations (rs' range .37 to .73) are moderate (all ps’ < .001). Cynicism and paranoia correlate higher with each other than with anger. Younger participants scored higher on the three hostility measures (r=-.12, p<.001, r=-.08, p=.01, and r=-.05, p=.123, for mean cynicism, paranoia and anger, respectively). Females scored higher on anger (r=-.20, P<.001) and males on cynicism (r=.18, p<.001) and paranoia (r=.09, p<.01). All the subsequent models were therefore adjusted for sex and age.

We tested 2,577,640 SNPs for association with the three hostility scales measured in four different time points. Chromosome 14 at 99 cM (SNPs rs3783337, rs7158754, rs3783332, rs2181102, rs7159195, rs11160570, rs941898) predicted suggestively the mean paranoia score [(phase 1 + phase 2 + phase 3 + phase 4 / 4)] during the 15 years at the genome-wide statistical significance level (p < 9 × 10\(^{-8}\)). However, this suggestive association did not replicate at each single measurement point over time. The most significant SNP suggestively associated with anger was found on chromosome 17 at 11 cM SNP rs11656526 (p < 9 × 10\(^{-8}\)) for anger measured in 1992.

Replications of the genetic linkage between different measurement of hostility and different measurement years are presented in Table 3. The most systematic replicating evidence for suggestive genetic effects was found for cynicism, although the significance levels (p < 1 × 10\(^{-5}\)) did not reach the Bonferroni corrected genome wide significance level (p < 9 × 10\(^{-8}\)). Promising SNPs suggestively predicting cynicism were found on chromosome 7 at 86 cM (rs802047, rs802028, rs802030, rs802026, rs802036, rs802025, rs802024, rs802032, rs802049, rs802051), which replicated on two different measurements of cynicism (1992 and 1997) as well as the first four of the SNPs above on the mean of all four measurements of cynicism (Table 3). In addition SNPs in chromosome 22 at 43 cM (rs7510759, rs7510924) were associated with cynicism in 1997 and the mean of all four measurements of cynicism. The genetic background of different components of hostility appears to be largely distinct from each other, although a group of SNPs from chromosome 17 at 2.8 cM (rs12936442,
rs894664, rs6502671, rs7216028) and from chromosome 22 at 43 cM (rs7510759,
rs7510924, rs7290560) and at 36 cM (rs8136107) were suggestively associated with
both cynicism and paranoia.

Table 3. SNPs replicating (p<10\(^{-5}\)) in different years or different hostility scales

<table>
<thead>
<tr>
<th>CHR</th>
<th>SNP</th>
<th>BP</th>
<th>Minor allele</th>
<th>MAF</th>
<th>(P^a)</th>
<th>Replication</th>
<th>Closest gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>rs802047</td>
<td>86795721</td>
<td>C</td>
<td>0.12</td>
<td>&lt; 3 \times 10^{-7}</td>
<td>Cynicism in 1992, 1997 and mean cynicism score</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>rs802028</td>
<td>86829611</td>
<td>T</td>
<td>0.10</td>
<td>&lt; 2 \times 10^{-6}</td>
<td>Cynicism in 1992, 1997 and mean cynicism score</td>
<td>CROT</td>
</tr>
<tr>
<td>7</td>
<td>rs802030</td>
<td>86831487</td>
<td>G</td>
<td>0.10</td>
<td>&lt; 2 \times 10^{-6}</td>
<td>Cynicism in 1992, 1997 and mean cynicism score</td>
<td>CROT</td>
</tr>
<tr>
<td>7</td>
<td>rs802026</td>
<td>86826975</td>
<td>A</td>
<td>0.10</td>
<td>&lt; 4 \times 10^{-6}</td>
<td>Cynicism in 1992, 1997 and mean cynicism score</td>
<td>CROT</td>
</tr>
<tr>
<td>7</td>
<td>rs802036</td>
<td>86815830</td>
<td>G</td>
<td>0.09</td>
<td>&lt; 7 \times 10^{-6}</td>
<td>Cynicism in 1992 and 1997</td>
<td>CROT</td>
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<tr>
<td>7</td>
<td>rs802025</td>
<td>86824568</td>
<td>T</td>
<td>0.07</td>
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<td>Cynicism in 1992 and 1997</td>
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</tr>
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<td></td>
</tr>
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<td>Cynicism in 1992 and 1997</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>rs12936442</td>
<td>2879859</td>
<td>A</td>
<td>0.10</td>
<td>&lt; 6 \times 10^{-6}</td>
<td>Cynicism and paranoia in 2007</td>
<td>RAP1GAP2</td>
</tr>
<tr>
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<td>rs894664</td>
<td>2857234</td>
<td>A</td>
<td>0.13</td>
<td>&lt; 8 \times 10^{-6}</td>
<td>Cynicism and paranoia in 2007</td>
<td>RAP1GAP2</td>
</tr>
<tr>
<td>17</td>
<td>rs6502671</td>
<td>2852848</td>
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<td>0.13</td>
<td>&lt; 7 \times 10^{-6}</td>
<td>Cynicism and paranoia in 2007</td>
<td>RAP1GAP2</td>
</tr>
<tr>
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<td>rs7216028</td>
<td>2880423</td>
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<td>&lt; 8 \times 10^{-6}</td>
<td>Cynicism and paranoia in 2007</td>
<td>RAP1GAP2</td>
</tr>
<tr>
<td>22</td>
<td>rs7510759</td>
<td>43038359</td>
<td>A</td>
<td>0.16</td>
<td>&lt; 5 \times 10^{-6}</td>
<td>Cynicism in 1997 and mean cynicism and mean paranoia score</td>
<td>KIAA1644</td>
</tr>
<tr>
<td>22</td>
<td>rs7510924</td>
<td>43039988</td>
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<td>0.16</td>
<td>&lt; 5 \times 10^{-6}</td>
<td>Cynicism in 1997 and mean cynicism and mean paranoia score</td>
<td>KIAA1644</td>
</tr>
<tr>
<td>22</td>
<td>rs8136107</td>
<td>35697254</td>
<td>A</td>
<td>0.10</td>
<td>&lt; 5 \times 10^{-6}</td>
<td>Mean cynicism and paranoia score</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>rs7290560</td>
<td>43036573</td>
<td>A</td>
<td>0.15</td>
<td>&lt; 6 \times 10^{-6}</td>
<td>Mean cynicism and paranoia score</td>
<td>KIAA1644</td>
</tr>
</tbody>
</table>

*a the highest p-value (least statistically significant) for the SNP concerned*
4.2. Study II: Breastfeeding and hostility

Most of the mothers had breastfed their child (88.2%), but 4.9% had not and 6.9% did not remember whether they had breastfed or not. The average duration of breastfeeding was 3.79 months with a range between 0 and 36 months. These figures are high in comparison with those in the 1970s United States where less than 30% of infants were breastfed (K. W. Eckhardt & Hendershot, 1984). On average, mothers were 27 years old at childbirth and had ten years of education. Most of the children were born on nuclear families with two to three children. The offspring were more often women (54.5% women, 45.5% men) with a mean age around 29 years during the hostility measurement and hostility score 2.53.

The bivariate correlations between the study variables are shown in Table 4. Older mothers were somewhat less likely than younger mothers to breastfeed (r=-.10) but if they did breastfeed, it lasted for a longer period of time (r=.19). A longer duration of breastfeeding was related to less hostile child-rearing practices (r=-.10), lower family income (r=-.06), higher amount of children in the family (r=.11) and later birth order of the child (r=.14). High hostile child-rearing (r=.13), low maternal education (r=-.05) and low family income (r=-.10) correlated with child’s hostility in adulthood. All ps’ <.001.

In age- and sex-adjusted multilevel models breastfeeding status predicted total hostility (p=.007), cynicism (p=.013), and distrustful attitudes (p=.013) but not anger (p=.169). Table 5 (model 1) shows that those who had not been breastfed had higher levels of hostility (2.69 vs. 2.49), especially cynicism (2.91 vs. 2.70) and distrustful attitudes (2.51 vs. 2.29) than their four to six months breastfed peers. Further adjustment for birth weight, maternal age in childbirth, maternal education, hostile child-rearing attitudes, family structure and income, the number of children in family and birth order affect only little these associations (Table 5, model 2). The association between the duration of breastfeeding and later hostility was not linear, but rather U-shaped (Figure 2). Hostility levels declined steadily up to 4-6 months of breastfeeding, but started to rise with longer breastfeeding durations. Those who were breastfed over a year did not differ from those who were not breastfed. However, the group size of those who were breastfed 12 months or more was small, consisting of 56 participants (158 participant-observations).
Table 4. Correlations between study variables (hostility and age are means derived from one to four different measurement years from the 1917 unique individuals complying up 5501 person-observations.

<table>
<thead>
<tr>
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<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Breastfeeding status ( ^a )</td>
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<tr>
<td>2. Duration of breastfeeding (months) ( ^b )</td>
<td></td>
<td>.26***</td>
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<tr>
<td>3. Mother's age at childbirth</td>
<td>-.10***</td>
<td>.19***</td>
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<tr>
<td>4. Maternal educational years</td>
<td></td>
<td>.05***</td>
<td>.02</td>
<td></td>
<td>-.03*</td>
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<tr>
<td>5. Hostile child-rearing (Z-score)</td>
<td>-.05***</td>
<td>-.10***</td>
<td>-.10***</td>
<td>.06***</td>
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<tr>
<td>6. Family structure ( ^c )</td>
<td></td>
<td>-.00</td>
<td>-.02</td>
<td>.02</td>
<td>.00</td>
<td>.02</td>
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<tr>
<td>7. Family income ( ^d )</td>
<td></td>
<td>.01</td>
<td>-.06***</td>
<td>.02</td>
<td>.40***</td>
<td>-.03*</td>
<td>.23***</td>
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<tr>
<td>8. Number of children in the family</td>
<td></td>
<td>.01</td>
<td>.11***</td>
<td>.38***</td>
<td>-.20***</td>
<td>.07***</td>
<td>.05***</td>
<td>-.14***</td>
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<td>9. Birth order</td>
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<td>.14***</td>
<td>.58***</td>
<td>-.23***</td>
<td>-.11***</td>
<td>.03*</td>
<td>-.14***</td>
<td>.83***</td>
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<td>10. Birth weight</td>
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<td>.01</td>
<td>.10***</td>
<td>-.04**</td>
<td>.00</td>
<td>.04*</td>
<td>.01</td>
<td>.03*</td>
<td>.08***</td>
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<td></td>
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<td>11. Gender ( ^e )</td>
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<td>-.05***</td>
<td>-.04*</td>
<td>.05***</td>
<td>.07***</td>
<td>.09***</td>
<td>-.03*</td>
<td>.04***</td>
<td>-.05**</td>
<td>-.03*</td>
<td>.15***</td>
<td></td>
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<td>12. Age</td>
<td></td>
<td>-.04***</td>
<td>-.02</td>
<td>.02</td>
<td>-.17***</td>
<td>-.11***</td>
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<td>.17***</td>
<td>.10***</td>
<td>-.04**</td>
<td>-.06***</td>
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<tr>
<td>13. Total hostility</td>
<td></td>
<td>-.06***</td>
<td>.00</td>
<td>-.05**</td>
<td>-.05***</td>
<td>.13***</td>
<td>-.01</td>
<td>-.10***</td>
<td>-.03*</td>
<td>-.02</td>
<td>.03*</td>
<td>.01</td>
<td>-.16***</td>
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<tr>
<td>14. Cynicism</td>
<td></td>
<td>-.05***</td>
<td>.01</td>
<td>-.04**</td>
<td>-.08***</td>
<td>.10***</td>
<td>-.02</td>
<td>-.11***</td>
<td>-.03*</td>
<td>-.01</td>
<td>.05***</td>
<td>.12***</td>
<td>-.18***</td>
<td>.84***</td>
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<tr>
<td>15. Distrusful attitudes</td>
<td></td>
<td>-.07***</td>
<td>-.01</td>
<td>-.03*</td>
<td>-.03*</td>
<td>.13***</td>
<td>.00</td>
<td>-.08***</td>
<td>-.02</td>
<td>-.02</td>
<td>.04**</td>
<td>.06***</td>
<td>-.14***</td>
<td>.87***</td>
<td>.70***</td>
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<td>16. Anger</td>
<td></td>
<td>-.04***</td>
<td>.00</td>
<td>-.05**</td>
<td>-.02</td>
<td>.09***</td>
<td>-.01</td>
<td>-.07***</td>
<td>-.02</td>
<td>-.02</td>
<td>-.02</td>
<td>-.16***</td>
<td>-.08***</td>
<td>.78***</td>
<td>.41***</td>
</tr>
</tbody>
</table>

*** <.001; ** <.01; * <.05

\( ^a \) 0=not breastfed, 1=breastfed; n=5130 observations

\( ^b \) 0=not breastfed; n=5130 observations

\( ^c \) 1=nuclear family 0=single or stepparent family

\( ^d \) 1=low, 2=medium, 3=high

\( ^e \) 0= female, 1= male
Table 5. Statistical significance of breastfeeding predicting hostility in repeated measures multilevel model and post hoc covariate-adjusted estimated means of hostility by groups of different breastfeeding durations (n=5501 person-observations; 1917 unique individuals)

<table>
<thead>
<tr>
<th>Breastfeeding</th>
<th>Total hostility</th>
<th>Cynicism</th>
<th>Distrustful attitudes</th>
<th>Anger</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (CI)</td>
<td>p</td>
<td>Mean (CI)</td>
<td>p</td>
</tr>
<tr>
<td>Model 1. a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>not breastfed (n=264)</td>
<td>2.69 (2.58-2.79)</td>
<td>.007</td>
<td>2.91 (2.79-3.03)</td>
<td>.013</td>
</tr>
<tr>
<td>less than 4 months (n=2979)</td>
<td>2.53 (2.50-2.56)</td>
<td>.004 c</td>
<td>2.76 (2.72-2.79)</td>
<td>.017</td>
</tr>
<tr>
<td>4 to 6 months (n=1147)</td>
<td>2.49 (2.44-2.53)</td>
<td>.001</td>
<td>2.70 (2.64-2.76)</td>
<td>.002</td>
</tr>
<tr>
<td>7 to 11 months (n=582)</td>
<td>2.52 (2.45-2.59)</td>
<td>.007</td>
<td>2.76 (2.68-2.84)</td>
<td>.046</td>
</tr>
<tr>
<td>12 months or more (n=158)</td>
<td>2.60 (2.47-2.73)</td>
<td>.312</td>
<td>2.86 (2.71-3.02)</td>
<td>.652</td>
</tr>
<tr>
<td>not remember (n=371)</td>
<td>2.60 (2.52-2.69)</td>
<td>.216</td>
<td>2.84 (2.74-2.94)</td>
<td>.395</td>
</tr>
<tr>
<td>Model 2. b</td>
<td></td>
<td>.016</td>
<td></td>
<td>.024</td>
</tr>
<tr>
<td>not breastfed (n=264)</td>
<td>2.67 (2.57-2.78)</td>
<td></td>
<td>2.89 (2.77-3.02)</td>
<td>.024</td>
</tr>
<tr>
<td>less than 4 months (n=2979)</td>
<td>2.53 (2.48-2.57)</td>
<td>.007 c</td>
<td>2.75 (2.70-2.81)</td>
<td>.025 c</td>
</tr>
<tr>
<td>4 to 6 months (n=1147)</td>
<td>2.49 (2.43-2.55)</td>
<td>.002</td>
<td>2.71 (2.64-2.77)</td>
<td>.005</td>
</tr>
<tr>
<td>7 to 11 months (n=582)</td>
<td>2.53 (2.45-2.60)</td>
<td>.021</td>
<td>2.77 (2.69-2.86)</td>
<td>.098</td>
</tr>
<tr>
<td>12 months or more (n=158)</td>
<td>2.63 (2.50-2.68)</td>
<td>.623</td>
<td>2.89 (2.74-3.05)</td>
<td>.987</td>
</tr>
<tr>
<td>not remember (n=371)</td>
<td>2.59 (2.50-2.68)</td>
<td>.233</td>
<td>2.82 (2.71-2.92)</td>
<td>.340</td>
</tr>
</tbody>
</table>

* Adjusted for age and sex

*c Post hoc p-values: other groups compared to not breastfed group

b Adjusted for age, sex, mother's age at childbirth, maternal education years, hostile child-rearing, family structure, family income, number of children in family, birth order, birth weight

---

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Figure 2. Age- and sex- adjusted mean scores of hostility measures according to different durations of breastfeeding.
4.3. Study III: The interaction between maternal care-giving and serotonin receptor SNPs predicting hostile attitudes

Interactions assessing gender differences were non-significant (all \( p’ > .12 \)). Thus, males and females were analyzed together in subsequent analyses. Females were somewhat over-represented in the sample (58.6%). The mean score for hostile attitudes was \( M = 2.55 \) and for depressive symptoms \( M = 2.04 \). At the same time, mothers reported on average to have warm and caring attitudes toward their children (\( M = 4.41 \) on a scale from 1 to 5).

Neither care-giving attitudes of the mothers nor hostile attitudes of the offspring differed according to the HTR2A or HTR1A SNPs (all \( p > .30 \)). The age- and gender adjusted association of mean maternal care-giving attitudes with mean offspring’s hostile attitudes in adulthood was statistically significant (\( \beta = -0.07, p = .047, \eta^2 = 0.01 \)) implying that warm and nurturing care-giving attitudes during childhood or adolescence might result in less hostile attitudes of the offspring in adulthood.

The interaction effect HTR1A rs6295 × maternal care-giving attitudes did not predict hostile attitudes, \( F (2, 811) = 0.88, p = .417, \eta^2 = 0.00 \). However, the HTR2A rs6313 × maternal care-giving attitudes interaction predicted statistically significantly hostile attitudes, \( F (2, 811) = 7.25, p = .001, \eta^2 = 0.02 \). To illustrate this interaction in Figure 3, we categorized the participants according to a median split of maternal care-giving attitudes. Figure 3 shows that T allele carriers have lowest level of hostile attitudes in highly nurturing environment while in less nurturing environment they were the most hostile. The hostile attitudes of the CC genotype carriers were not affected by the care-giving environment.

In the analyses within the genotypes in Table 6, the association between a high score on maternal care-giving attitudes and low hostile attitudes was at least borderline statistically significant among carriers of the T/T or T/C genotype explaining 6.3 and 3.3 percent of the variance, respectively (\( \beta = -0.26, p = .02 \), and \( \beta = -0.18, p = .001 \)), and this association was independent of parental education, mother’s age at childbirth, and childhood activity (\( \beta = -0.27, p = .02 \), and \( \beta = -0.16, p = .004 \)). Among carriers of the C/C genotype there was no association between maternal care-giving and hostile attitudes (\( \beta = 0.07, p = .19 \)), suggesting that CC carriers may be less affected by the care-giving environment than carriers of the other genotypes.
Figure 3. The interaction of maternal child care-giving and serotonin receptor 2A SNP rs6313 predicting hostile attitudes of children at 21 to 39 years-of-age.
Table 6. Maternal care-giving during childhood as a predictor of hostile attitudes in adulthood in different serotonin receptor 2A rs6313 genotype carrier groups

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Mean Hostile attitudes in 1997 and 2001</th>
<th>β</th>
<th>p</th>
<th>(\eta^2)</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T/T Genotype (N=83)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother's nurturance adjusted for in addition to age + gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td>-0.257</td>
<td>0.024</td>
<td>0.063</td>
<td>0.063</td>
</tr>
<tr>
<td>Childhood factors³</td>
<td></td>
<td>-0.272</td>
<td>0.018</td>
<td>0.072</td>
<td>0.119</td>
</tr>
<tr>
<td>Adulthood depressive symptoms</td>
<td></td>
<td>-0.046</td>
<td>0.627</td>
<td>0.003</td>
<td>0.413</td>
</tr>
<tr>
<td>All of the above</td>
<td></td>
<td>-0.060</td>
<td>0.525</td>
<td>0.005</td>
<td>0.463</td>
</tr>
<tr>
<td>T/C Genotype (N=358)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother's nurturance adjusted for in addition to age + gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td>-0.182</td>
<td>0.001*</td>
<td>0.033</td>
<td>0.045</td>
</tr>
<tr>
<td>Childhood factors³</td>
<td></td>
<td>-0.160</td>
<td>0.004*</td>
<td>0.023</td>
<td>0.057</td>
</tr>
<tr>
<td>Adulthood depressive symptoms</td>
<td></td>
<td>-0.071</td>
<td>0.097</td>
<td>0.008</td>
<td>0.386</td>
</tr>
<tr>
<td>All of the above</td>
<td></td>
<td>-0.050</td>
<td>0.268</td>
<td>0.003</td>
<td>0.396</td>
</tr>
<tr>
<td>C/C Genotype (N=378)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother's nurturance adjusted for in addition to age + gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td>0.067</td>
<td>0.191</td>
<td>0.005</td>
<td>0.020</td>
</tr>
<tr>
<td>Childhood factors³</td>
<td></td>
<td>0.069</td>
<td>0.184</td>
<td>0.005</td>
<td>0.044</td>
</tr>
<tr>
<td>Adulthood depressive symptoms</td>
<td></td>
<td>0.052</td>
<td>0.229</td>
<td>0.004</td>
<td>0.322</td>
</tr>
<tr>
<td>All of the above</td>
<td></td>
<td>0.051</td>
<td>0.234</td>
<td>0.004</td>
<td>0.347</td>
</tr>
</tbody>
</table>

* \(p < 0.017\) (stricter p-value 0.05/3)

\(\eta^2\) = partial Eta squared

R² is for the whole model

³ Childhood factors include mother's age at childbirth, parental SES, and participant's own childhood activity
4.4. Study IV: Hostile attitudes, inflammation and metabolic syndrome

Women had higher levels of serum triglycerides (0.61 vs. 0.57, \( p = .013 \)), serum insulin (10.1 vs. 8.7, \( p < .001 \)) and CRP (1.2 vs. 0.9, \( p = .038 \)) levels in childhood compared with men. Men were more often than women smokers (27 vs. 19 %, \( p < .001 \)), used alcohol more heavily (3.1 vs. 2.1, \( p < .001 \)), had more often MetS as defined by the EGIR (13 vs. 8\%, \( p < .001 \)) and the IDF criteria (18 vs. 12\%, \( p < .001 \)) in adulthood. C-reactive protein levels were higher in women also in adulthood (2.13 vs. 1.48, \( p < .001 \)). Women had higher high-frequency (HF) power of systolic arterial pressure, lower low-frequency (LF) power of diastolic arterial pressure and lower LF/HF ratio compared with men (\( ps' < .001 \)). Men were slightly more hostile than women in 1992 (2.6 vs. 2.5, \( p = .008 \)).

All MetS indicators, NCEP, EGIR and IDF were associated with CRP at follow up in women (\( r = 0.23, r = 0.26, r = 0.29 \), respectively) and men (\( r = 0.19, r = 0.26, r = 0.30 \), respectively, \( ps' < .001 \)). In women, hostile attitudes was associated with less physical activity (\( r = -0.08, p = 0.015 \)), low education (\( r = -0.18, p < 0.001 \)), higher alcohol consumption (\( r = 0.13, p < 0.001 \)), more prevalent smoking (\( r = 0.13, p < 0.001 \)), higher HF (\( r = 0.10, p = 0.005 \)) and higher LF (\( r = 0.08, p = 0.02 \)). In men, hostile attitudes was associated with low education (\( r = -0.13, p < 0.001 \)), higher alcohol consumption (\( r = 0.08, p = 0.02 \)), more prevalent smoking (\( r = 0.08, p = 0.04 \)) and higher HF (\( r = 0.09, p = 0.03 \)).

The risk for having MetS, as indicated by the EGIR and the IDF definitions, was almost 1.4-fold in women for each 1 standard deviation increase in standardized hostile attitudes score (Table 7). Adjustments for health risk behaviors and cardiac control had a little effect on this association. In men, no associations were found between hostile attitudes and MetS indicators. CRP as the outcome showed a similar pattern (Table 8).

Among women association between hostile attitudes and MetS indicated by IDF was additionally adjusted for CRP at follow-up as well as the association between hostile attitudes and CRP for the MetS indicated by IDF. The association between hostility and MetS attenuated somewhat (OR from 1.45 to 1.30) being no longer statistically significant (95% CI 0.98 - 1.74, \( p = 0.075 \)) after adjustment to CRP, suggesting that CRP might be a partial mediating factor between hostile attitudes and MetS. Although there was a marginal attenuation between hostility and CRP (\( \beta \) from 0.115 to 0.094) after adjustment to MetS, the association remained statistically significant (\( p = 0.011 \)).
Table 7. The relationships (Odds ratios and 95% CI) between one standard deviation increase in hostile attitudes and the risk of having metabolic syndrome in women. Adjusted for childhood metabolic risk factors, adulthood health risk behavior and indicators of heart rate variability.

<table>
<thead>
<tr>
<th>Adjusted in addition to age:</th>
<th>N/Cases</th>
<th>OR (95% CI)</th>
<th>N/Cases</th>
<th>OR (95% CI)</th>
<th>N/Cases</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>912/56</td>
<td>1.21 (0.92 – 1.58)</td>
<td>916/75</td>
<td>1.34 (1.05 – 1.68)</td>
<td>916/110</td>
<td>1.35 (1.11 – 1.65)</td>
</tr>
<tr>
<td>Childhood risk factors</td>
<td>763/49</td>
<td>1.19 (0.97 – 1.62)</td>
<td>766/63</td>
<td>1.33 (1.02 – 1.75)</td>
<td>766/96</td>
<td>1.37 (1.09 – 1.72)</td>
</tr>
<tr>
<td>Childhood risk factors and adulthood SES</td>
<td>760/49</td>
<td>1.16 (0.85 – 1.59)</td>
<td>763/63</td>
<td>1.31 (1.00 – 1.73)</td>
<td>763/96</td>
<td>1.35 (1.07 – 1.70)</td>
</tr>
<tr>
<td>Childhood risk factors and alcohol consumption</td>
<td>750/48</td>
<td>1.29 (0.93 – 1.79)</td>
<td>753/63</td>
<td>1.38 (1.04 – 1.81)</td>
<td>753/94</td>
<td>1.44 (1.14 – 1.82)</td>
</tr>
<tr>
<td>Childhood risk factors and smoking status</td>
<td>744/48</td>
<td>1.26 (0.92 – 1.73)</td>
<td>747/62</td>
<td>1.40 (1.06 – 1.86)</td>
<td>747/94</td>
<td>1.44 (1.14 – 1.82)</td>
</tr>
<tr>
<td>Childhood risk factors and physical activity</td>
<td>696/45</td>
<td>1.20 (0.85 – 1.68)</td>
<td>699/59</td>
<td>1.27 (0.94 – 1.71)</td>
<td>699/87</td>
<td>1.40 (1.08 – 1.81)</td>
</tr>
<tr>
<td>Childhood risk factors and all adulthood risks</td>
<td>696/45</td>
<td>1.20 (0.85 – 1.68)</td>
<td>699/59</td>
<td>1.27 (0.94 – 1.71)</td>
<td>699/87</td>
<td>1.40 (1.09 – 1.81)</td>
</tr>
<tr>
<td>Childhood risk factors and HF</td>
<td>694/37</td>
<td>1.37 (0.96 – 1.95)</td>
<td>697/53</td>
<td>1.41 (1.05 – 1.89)</td>
<td>697/82</td>
<td>1.46 (1.14 – 1.87)</td>
</tr>
<tr>
<td>Childhood risk factors and LF</td>
<td>694/37</td>
<td>1.37 (0.98 – 1.95)</td>
<td>697/53</td>
<td>1.42 (1.06 – 1.90)</td>
<td>697/82</td>
<td>1.46 (1.15 – 1.87)</td>
</tr>
<tr>
<td>Childhood risk factors and LF/HF</td>
<td>694/37</td>
<td>1.33 (0.93 – 1.91)</td>
<td>697/53</td>
<td>1.38 (1.03 – 1.86)</td>
<td>697/82</td>
<td>1.42 (1.11 – 1.81)</td>
</tr>
<tr>
<td>All</td>
<td>635/37</td>
<td>1.35 (0.91 – 2.01)</td>
<td>638/51</td>
<td>1.33 (0.96 – 1.84)</td>
<td>638/77</td>
<td>1.45 (1.10 – 1.91)</td>
</tr>
</tbody>
</table>

SES = socioeconomic status; HF = high-frequency (HF) power of systolic arterial pressure; LF = low-frequency (LF) power of diastolic arterial pressure.
Table 8. The relationships (standardized regression coefficients ($\beta$)) between hostile attitudes and CRP in women and men. Adjusted for childhood CRP, adulthood health risk behavior, and indicators of heart rate variability.

<table>
<thead>
<tr>
<th>CRP</th>
<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>$\beta$</td>
<td>N</td>
<td>$\beta$</td>
</tr>
<tr>
<td>Adjusted in addition to age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>973</td>
<td>0.094**</td>
<td>724</td>
<td>0.026</td>
</tr>
<tr>
<td>Childhood CRP</td>
<td>961</td>
<td>0.085**</td>
<td>710</td>
<td>0.017</td>
</tr>
<tr>
<td>Childhood CRP and adulthood SES</td>
<td>958</td>
<td>0.084*</td>
<td>705</td>
<td>0.009</td>
</tr>
<tr>
<td>Childhood CRP and alcohol consumption</td>
<td>945</td>
<td>0.083*</td>
<td>698</td>
<td>0.010</td>
</tr>
<tr>
<td>Childhood CRP and smoking status</td>
<td>938</td>
<td>0.103**</td>
<td>689</td>
<td>0.011</td>
</tr>
<tr>
<td>Childhood CRP and physical activity</td>
<td>897</td>
<td>0.074*</td>
<td>670</td>
<td>0.034</td>
</tr>
<tr>
<td>Childhood CRP and all adulthood risks</td>
<td>877</td>
<td>0.092**</td>
<td>651</td>
<td>0.009</td>
</tr>
<tr>
<td>Childhood CRP and HF</td>
<td>871</td>
<td>0.112**</td>
<td>630</td>
<td>0.041</td>
</tr>
<tr>
<td>Childhood CRP and LF</td>
<td>871</td>
<td>0.109**</td>
<td>630</td>
<td>0.036</td>
</tr>
<tr>
<td>Childhood CRP and LF/HF</td>
<td>871</td>
<td>0.105**</td>
<td>630</td>
<td>0.032</td>
</tr>
<tr>
<td>All</td>
<td>796</td>
<td>0.115**</td>
<td>577</td>
<td>0.031</td>
</tr>
</tbody>
</table>

***p < 0.001, **p < 0.01, *p < 0.05.
4.5. Study V: The moderating effect of socioeconomic status on the relationship between hostility and early atherosclerosis

Low socioeconomic status (SES) in childhood was associated with high cynicism ($r=-0.06, p<0.05$) and low SES in adulthood ($r=0.20, p<0.001$). Low SES in adulthood was related to high cynicism ($r=-0.15, p<0.001$) and anger ($r=-0.07, p<0.05$). Cynicism correlated with anger, $r=0.39, p<0.001$, and cynicism, anger, or SES were not associated with IMT.

Adulthood SES had no interactive effects with either indicator of hostility in predicting subclinical atherosclerosis, as indexed by carotid artery intima-media thickness (IMT) ($p>0.23$). Childhood SES did not moderate the relationship between cynicism and IMT ($\beta=-0.06, p=0.14$). However, the Childhood SES $\times$ Anger interaction was statistically significant ($\beta=-0.13, p=0.001$), and Table 9 clarifies the interpretation of this interaction.

As shown in Table 9, anger was positively associated with IMT in participants with low childhood SES ($\beta=0.16, B=0.02, p<0.001$), suggesting that a one-point increase in the anger scale corresponds to a 0.02 mm increase in IMT among participants coming from low childhood SES background. In contrast, anger had no significant association with IMT in participants having medium/high childhood SES ($p=0.33$). The observed association between hostility and IMT in low-SES-participants remained significant after adjusting for the participants’ adulthood SES, health-related behaviors, physiological risk factors, and social support ($\beta=0.15, B=0.02, p=0.001$). In an additional analysis where only anger was used as an explanatory factor of IMT, anger explained 1.6% of the variance in IMT among low-childhood-SES participants.
Table 9. Anger predicting IMT when adjusted for different blocks of atherosclerosis risk factors separately with low and medium/high childhood SES groups

<table>
<thead>
<tr>
<th></th>
<th>Low childhood SES N=507</th>
<th>Medium/High childhood SES N=1033</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R²</td>
<td>β</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.13</td>
<td>0.16</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.13</td>
<td>0.16</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.13</td>
<td>0.16</td>
</tr>
<tr>
<td>Model 4</td>
<td>0.17</td>
<td>0.14</td>
</tr>
<tr>
<td>Model 5</td>
<td>0.13</td>
<td>0.16</td>
</tr>
<tr>
<td>Model 6</td>
<td>0.18</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*** p<0.001, ** p<0.01, * p<0.05, † R² is for the whole model

a Model 1: Anger adjusted for age and gender.

b Model 2: Anger adjusted for age, gender, and adulthood SES.

c Model 3: Anger adjusted for age, gender, and health related behaviors (smoking, alcohol consumption, and physical activity index).

d Model 4: Anger adjusted for age, gender, and physiological risk factors (LDL-cholesterol, HDL-cholesterol, systolic blood pressure, diastolic blood pressure, and BMI).

e Model 5: Anger adjusted for age, gender, and social support.

f Model 6: Anger adjusted for all covariates (age, gender, adulthood SES, health related behaviors, physiological risk factors, and social support).
4.6. Study VI: Anger and cardiovascular disease

According to the literature reviewed in Tables 10 and 11, anger both as a state and as a trait and the way anger is expressed can have detrimental effects on cardiovascular health. Cross-sectional evidence on high-risk samples in Table 11 supports the view of the harmfulness of both extreme suppression and outward expression of anger. These studies imply that anger expressed outwards may serve as a final trigger of CHD, especially in individuals otherwise vulnerable or who usually do not show angry outbursts. Prospective studies in Table 10 are rather unanimous by showing that suppression of anger (i.e., not showing it) predicts subsequent CHD. This appears to be true for both men and women at varying ages, although the studies are slightly biased towards middle-aged male samples. It seems that those who experience high levels of anger but are unable to express it are at greatest risk for subsequent CHD.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Participants &amp; Design</th>
<th>Anger Measure</th>
<th>Result</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyle, Michalek &amp; Suarez, 2006</td>
<td>2,105 male Air Force veterans of the Vietnam War aged 35-78 years. Average follow-up 15 years.</td>
<td>Trait anger (MMPI-2)</td>
<td>+</td>
<td>CHD</td>
<td>Hazard ratio 1.24 for developing CHD comparing a person at the 75th percentile of the scale to the 25th percentile.</td>
</tr>
<tr>
<td>Chang et al., 2002</td>
<td>1,055 male medical students. Median follow-up 36 years.</td>
<td>3-item anger questionnaire: expressed or concealed anger, irritability, and gripe sessions</td>
<td>+</td>
<td>CHD</td>
<td>Significant associations found only in premature cardiovascular disease, CHD and MI (onset before age 55 years).</td>
</tr>
<tr>
<td>Eaker et al., 2004</td>
<td>3,873 men and women aged 18-77 years. 10-year follow-up.</td>
<td>Framingham scale: anger symptoms anger-out anger-in anger-discuss Spielberger Trait Anger</td>
<td>ns ns ns ns ns</td>
<td>CHD</td>
<td>No associations with CHD. In men trait anger and anger symptoms predicted atrial fibrillation and trait anger predicted total mortality. In women anger-out predicted atrial fibrillation.</td>
</tr>
</tbody>
</table>

* List is not necessarily exhaustive
+ = positive relationship
- = negative relationship
ns = non-significant relationship
### Table 10. Longitudinal studies of anger and CHD (continued)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Participants &amp; Design</th>
<th>Anger Measure</th>
<th>Result</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eng et al., 2003</td>
<td>23,522 male health professionals aged 50-85 years. 2-year follow-up.</td>
<td>Spielberger Anger-Out</td>
<td>ns</td>
<td>total CHD</td>
<td>Non-significant for total CHD. However, moderate levels of anger-out were protective against MI and high levels of anger-out were protective against stroke.</td>
</tr>
<tr>
<td>Gallacher et al., 1999</td>
<td>2,388 men aged 49-65 years. 9-year follow-up.</td>
<td>Framingham scale: anger symptoms</td>
<td>ns</td>
<td>IHD</td>
<td>Developed new “suppressed anger” scale from 3 items of Framingham scale. Men with evidence of ischemia at baseline were not excluded, but this was used as a covariate.</td>
</tr>
<tr>
<td>Haynes, Feinleb &amp; Kannel, 1980</td>
<td>1,674 men and women aged 45-77 years from the Framingham heart study. 8-year follow-up.</td>
<td>Males: 55-64 years old anger symptoms</td>
<td>ns</td>
<td>CHD</td>
<td>Significant associations found only in 55-64 years age group. Associations most evident among white-collar workers.</td>
</tr>
<tr>
<td></td>
<td>Females: 55-64 years old anger symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>anger-out</td>
<td>ns</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>anger-in</td>
<td>ns</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>anger-discuss</td>
<td>ns</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kawachi et al., 1996</td>
<td>1,305 men aged 40-90 years. Average follow-up 7 years.</td>
<td>Anger Content scale of MMPI-2</td>
<td>+</td>
<td>CHD</td>
<td>High anger is associated with 2- to 3-fold increase in risk of CHD compared to low anger score.</td>
</tr>
<tr>
<td>Koskenvuo et al., 1988</td>
<td>3,750 men of which 2,885 healthy &amp; 104 with both previous CHD and hypertension. Age 40-59 years. 3-year follow-up.</td>
<td>3-item hostility questionnaire: anger-arousal, irritability, and argumentativeness</td>
<td>+</td>
<td>ns</td>
<td>IHD</td>
</tr>
<tr>
<td>Stürmer, Hasselbach &amp; Amelang, 2006</td>
<td>5,114 men and women aged 40-65. Median follow-up 8.5 years.</td>
<td>Anger control</td>
<td>ns</td>
<td>MI</td>
<td>No association with MI, stroke or cancer.</td>
</tr>
<tr>
<td>Williams et al., 2000, 2001</td>
<td>12,986 black and white men and women aged 45-64 years. Average follow-up 4 years.</td>
<td>Spielberger Trait Anger</td>
<td>+</td>
<td>CHD</td>
<td>Relationship found in total population and among normotensives, but not among hypertensives.</td>
</tr>
<tr>
<td></td>
<td>Angry temperament</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angry reaction</td>
<td>ns</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* List is not necessarily exhaustive  
+ = positive relationship  
- = negative relationship  
ns = non-significant relationship  
CHD = coronary heart disease; IHD = ischemic heart disease; MI = myocardial infarction
### Table 11. Cross-sectional studies of anger and CHD among patient samples

<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects</th>
<th>Anger Variable</th>
<th>Result</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dembroski et al., 1985</td>
<td>131 patients, 98 men and 33 women</td>
<td>Structured Interview</td>
<td>+</td>
<td>number of MI</td>
<td>Only patients with no or severe CAD were included.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anger-in</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potential for hostility</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kneip et al., 1993</td>
<td>185 cardiac patients, 112 men and 73 women aged 25-87 years</td>
<td>Multidimensional Anger Inventory (MAI):</td>
<td>.</td>
<td>Thallium scan measured CHD status</td>
<td>Significant associations found only in spouse-rated MAI. Self-ratings were nonsignificant.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anger arousal</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range of situations</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hostile outlook</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anger-in</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mendes de Leon, 1992</td>
<td>31 MI patients, 26 unstable angina patients, and 26 hospital controls.</td>
<td>Spielberger STAXI:</td>
<td>MI</td>
<td></td>
<td>Anger-out and impatience/irritability were significantly higher among MI patients than among controls.</td>
</tr>
<tr>
<td></td>
<td>White, low SES males aged 40-65 years</td>
<td>Trait anger</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anger-out</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anger-in</td>
<td>ns</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jenkins Activity Survey:</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Impatience/irritability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mittleman et al., 1995, 1997</td>
<td>1,623 patients, 1,122 men and 501 women aged 20-92 years</td>
<td>Onset anger scale</td>
<td>+</td>
<td>MI</td>
<td>Anger acts as a trigger and doubles the onset of MI for subsequent 2-hours. The trigger effect was modified by educational status, use of ß-blockers or aspirin, and history of a previous MI.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>State anger from the Spielberger's State-Trait Personality Inventory (STPI)</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Möller et al., 1999</td>
<td>660 patients aged 45-70 years with a first event of nonfatal MI</td>
<td>Onset anger scale</td>
<td>+</td>
<td>MI</td>
<td>9-times greater risk of MI during 1 hour after anger episode. Among those without premonitory symptoms, the relative risk was 15.7. The risk was higher among usually nonhostile cases and those with less frequent outbursts of anger.</td>
</tr>
<tr>
<td>O'Connor et al., 1995</td>
<td>340 first MI patients and 340 controls</td>
<td>Framingham anger scale sum score of suppressed/expressed anger</td>
<td>ns</td>
<td>MI</td>
<td>Suppressed anger marginally, but not significantly related to MI.</td>
</tr>
<tr>
<td>Siegman et al., 1998</td>
<td>196 patients, 101 men and 95 female</td>
<td>Spielberger STAXI:</td>
<td>+</td>
<td>Thallium stress testing measured CHD or previous MI</td>
<td>Significant associations found mainly in spouse-rated anger scores and only in males. Self-ratings were nonsignificant with the exception of anger-out.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trait anger</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anger-out</td>
<td>ns</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Anger-in</td>
<td>ns</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Anger control</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Impulsive anger-out</td>
<td>+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* List is not necessarily exhaustive  
+ = positive relationship  
- = negative relationship  
ns = non-significant relationship
5 DISCUSSION

5.1. Summary of main findings

5.1.1. The development of hostility

Both genetic and environmental factors affect the development of hostility (Coccaro et al., 1997; Hur, 2006; Rebollo & Boomsma, 2006; Weidner et al., 2000). This is true for most of the psychological constructs, although the heritability of hostility related concepts however seems to be weaker than heritability of several other personality traits, such as Big Five for example (Loehlin, McCrae, Costa, & John, 1998). In spite of the possible heritability, the molecular genetics of hostility is still widely unknown. A genome-wide association study (GWAS) on hostility was done showing some suggestive preliminary linkages to hostility in chromosomes 7 at 86 cM, 14 at 99 cM, 17 at 2.8 cM, as well as 22 at 36 cM and 43 cM; these areas seem worthy of further examination.

Paranoia was tentatively linked to a group of SNPs in chromosome 14 at 99 cM, which is near regions previously associated with neuroticism and anxiety (Middeldorp et al., 2008; Wray et al., 2008) as well as bipolar disorder (Burton et al., 2007). The closest gene for these SNPs is the EVL gene in chromosome 14, which has been proposed as a possible candidate gene for colorectal cancer (Sjöblom et al., 2006). Also both paranoia and cynicism were tentatively associated with an area in chromosome 17 at 2.8 cM. For which the closest gene is RAP1GAP2, which affects the GTPase-activating protein and has a role in regulating platelet aggregation; it is particularly expressed in heart, testis and blood leucocytes, but also in stomach, pancreas, and intestines, and to a small degree in the brain (Schultess, Danielewski, & Smolenski, 2005). Therefore this may also be a possible link between hostility and health problems. Cynicism and paranoia were as well related to areas in chromosome 22 at 36 cM and 43 cM for which the closest gene is KIAA1644. Chromosome 22 at 36 cM has been linked previously to bipolar disorder and schizophrenia (Badner & Gershon, 2002). Cynicism was also tentatively associated with areas on chromosome 7 at 86 cM. The nearest gene for this area is the CROT, which affects fatty acid functioning at the cellular level and is expressed at least in mice almost everywhere in the body, particularly strongly in liver and intestines, but also slightly in the heart and brain (Westin, Hunt, & Alexson, 2008).
Due to lack of statistical power, the observed associations are only suggestive, and consequently need replication in other datasets. However, these suggestive associations if replicated may have theoretical implications. The same locations in chromosome 17 at 2.8 cM as well as in chromosome 22 at 36 cM and 43 cM were associated with both cynicism and paranoia, which may imply a shared genetic background with these aspects of hostility. Such hostile attitudes might be seen as the core of the hostility construct (Greenglass & Julkunen, 1989; Miller et al., 1996). Anger, on the other hand, may be seen theoretically as a separate construct, having its developmental roots in temperament-like characteristics (Nigg, 2006). Anger did not share a similar genetic background with cynicism or paranoia in our study which implies that the consideration of anger as a separate construct might seem justified also from a genetic perspective. In addition, a previous study showed lower heritability estimates for hostile affect, than for cynicism or aggressive behavior (Weidner et al., 2000). These differences in phenotype and genotype of hostility measures may thus in part explain the mixed findings between the wide ‘hostility’ construct and cardiovascular health (Rozanski et al., 1999). However, hostility is a complex phenomenon and there probably are multiple overlapping genetic effects as well as gene×gene, gene×environment, and environment×environment interactions behind hostility.

Serotonin functioning in the brain and serotonin related gene polymorphisms have been widely associated with mental health and personality, like depressive symptoms for example (Jokela, Lehtimäki, & Keltikangas-Järvinen, 2007a; Jokela, Rääkkönen, Lehtimäki, Rontu, & Keltikangas-Järvinen, 2007). Serotonin affects the regulation of emotion as well as the interpretation of the world (Lesch, 2007), suggesting a possible role for it in the development of hostility. In the present study, however, there were no direct links between serotonin receptor polymorphisms and hostility. Instead, the HTR2A rs6313 were found to moderate the effects of childhood environment on offspring’s later hostile attitudes in adulthood similarly as previously shown in the present dataset with depressive traits (Jokela et al., 2007). These findings are in accordance with differential susceptibility hypothesis (Belsky & Pluess, 2009) addressing that the same individuals who are most adversely affected by negative environment may also benefit most in positive environment. Thus some individuals are particularly sensitive to environment. This gene-environment interaction is an example
of how genes indirectly may affect personality, and might possibly explain the contradictory findings concerning genetic effects on personality development, although the importance of gene-environment interactions have been debated widely (Dick, 2011; Karg et al., 2011; Risch et al., 2009). Nonetheless, the findings suggest that the role of genetic effects may depend on environmental exposures (for instance, the quality of the early care-giving environment). Similarly, the same environmental effects may have different outcomes depending on genetic composition, suggesting that individuals differ in their vulnerability to external circumstances. However, the found interactions must be replicated in other studies before firm conclusions can be drawn.

The role of an adverse environment in deteriorating mental health has been widely acknowledged (e.g. Repetti et al., 2002). However, the specific childhood environmental factors affecting hostility in adulthood are widely unidentified. The current findings add evidence to previous research showing that warm and caring childhood environment, such as caregivers having positive feelings and seeing the child being emotionally important to them, are associated with less hostility in the child all the way into adulthood (Houston & Vavak, 1991; Keltikangas-Järvinen & Heinonen, 2003; Matthews et al., 1996). The important finding in the present prospective design was that children’s genes may play a role in determining the extent to which a lack of maternal warmth fosters hostile attitudes. It appears that, on average, non-nurturing environment may be risk for later developing hostile attitudes, but particular genotype carriers might be especially sensitive to the adverse effects of non-nurturing parenting. The functioning of the serotonin system is a one possible mechanism (Way & Taylor, 2010). Less supportive nurturance may decrease the level of serotonin in the brain (Shannon et al., 2005). The T allele carriers in the HTR2A rs6313 SNP may more efficiently bind the available serotonin in the brain (Turecki et al., 1999), and are thus perhaps more dependent on the amount of available serotonin resulting from the quality of care-giving. On the other hand, CC genotype carriers may utilize less of the available serotonin in the brain, resulting in them being less able to benefit from the high nurturance. However, the neurotransmitter functioning in the brain is complicated and several other brain chemicals, such as dopamine, adrenalin, and noradrenalin, may interfere with these processes.
Breastfeeding was another early environmental factor shown in the present study to be associated with hostility in adulthood. We observed that individuals who were not breastfed as infants had higher levels of hostility, particularly cynicism and paranoia, in adulthood than their breastfed counterparts, although the benefits were lost with more than a year’s breastfeeding. This is in accordance with the current official guidelines in Finnish antenatal clinics where the recommendation is 4-6 months exclusive breastfeeding and partial breastfeeding up to 12 months. The observed associations between breastfeeding and hostility may be tentatively explained by at least three different mechanisms. First, a direct nutritional link may exist between breast milk and children’s hormonal and neurotransmitter functioning. Breastfeeding might affect children’s brain development through nutritional processes involving fatty acids (Marszalek & Lodish, 2005), which have been associated with features of mood and behavior such as hostility and depression (Appleton, Rogers, & Ness, 2008). Second, breastfeeding may be a proxy measure of maternal behavior toward the child, or of the family atmosphere (Virden, 1988). A complete absence of breastfeeding may be an indicator of family dysfunction. However, it is also possible that prolonged breastfeeding, lasting longer than what a child physiologically needs, may indicate some form of family dysfunction that ultimately is reflected in the development of hostile attitudes. Third, the shared genetic background between the child and the mother might explain the association.

In summary several both genetic and environmental factors and their interactions seem to play a role in development of hostility. What we know for sure is that the development is complicated and a sum of various interactions is behind it. Here however few potentially affecting factors were covered, hopefully improving our understanding of the subject a little bit more.

5.1.2. Cardiovascular outcomes of hostility

In regards of cardiovascular outcomes of hostility in the present studies of the Young Finns data, hostile attitudes was found to predict a higher risk of metabolic syndrome (MetS) and systemic inflammation (CRP), but these associations were apparent only in women. Our findings are in accordance with the previous studies showing an association between hostility and a higher risk of metabolic syndrome in a sample of
middle-aged, pre- and postmenopausal women (Räikkönen, Matthews, & Kuller, 2002; Räikkönen et al., 2004), and in older men and women (Nelson, Palmer, & Pedersen, 2004). Previous studies on the relationship between hostility and CRP are limited. The few earlier prospective studies have shown that hostility predicted higher CRP levels (Brummett et al., 2010; Graham et al., 2006).

Hostility may produce different cardiovascular outcomes which differ between men and women, and the reasons for this needs to be studied further (E. C. Suarez, 2006). Sex-specific relationships between endogenous sex hormones and psychological states is one possible hypothesis, but evidence for this is still limited (Corcoran et al., 2010). It may also be that girls and young women are not supposed to show their hostility and distrust as openly as is acceptable for their male counterparts, possibly causing more tension in the body. Thus the explanation would be in social power similarly as hypothesized by Haukkala (2002) in relation to anger expression and SES.

When examining subclinical atherosclerosis in early adulthood, anger was associated with it only among participants whose parents had less education, suggesting that the effect of anger on cardiovascular risk may be pronounced in the presence of an unfavorable socioeconomic environment. This finding supports earlier evidence for the increased vulnerability of children living in low SES families as compared to children in higher SES families (Chen, Matthews, & Boyce, 2002). Over time, stressful experiences endured by children living in low SES environments raise their cortisol levels, thus straining their bodies (Chen, Cohen, & Miller, 2010). Low SES children might also have restricted possibilities for coping with their anger and for expressing it in socially acceptable ways, which would also increase the burden on them.

Our review of previous research literature of anger and cardiovascular health risks supports the view that anger as a personality trait is a risk factor for cardiovascular diseases. Most of the prospective studies reviewed show that anger as a personality trait (trait anger) (Boyle, Michalek, & Suarez, 2006; Chang et al., 2002; Kawachi et al., 1996) and suppressing one’s anger (Eng, Fitzmaurice, Kubzansky, Rimm, & Kawachi, 2003; Gallacher, Yarnell, Sweetnam, Elwood, & Stansfeld, 1999; Haynes, Feinleib, & Kannel, 1980) are predictive of subsequent CHD, although inconsistent findings were also found (Eaker, Sullivan, Kelly-Hayes, D'Agostino, & Benjamin, 2004; Stürmer, Hasselbach, & Amelang, 2006), which may depend on the measures of anger and/or
sample used. Also hostile attitudes, which were left out from the original review, have been shown to predict later adverse health in several studies (e.g. Chida & Steptoe, 2009; Everson et al., 1997). In cross-sectional or case-control studies both extreme suppression and overt expression of anger have been associated with adverse cardiovascular health (Dembroski, MacDougall, Williams, Haney, & Blumenthal, 1985; Kneip et al., 1993; Mendes de Leon, 1992; O'Connor, Manson, O'Connor, & Buring, 1995; Siegman, Townsend, Blumenthal, Sorkin, & Civelek, 1998), and intense episode of anger may be a trigger of MI (Mittleman et al., 1995; Mittleman et al., 1997; Möller et al., 1999)

Some subgroups may be more prone to experience adverse health consequences caused by anger as a personality trait, e.g. younger and healthier individuals (Chang et al., 2002; J. E. Williams, Nieto, Sanford, Couper, & Tyroler, 2002). Particularly angry temperament, which comprises anger experienced with minimal or no provocation, seems to confer cardiovascular risk (J. E. Williams, Nieto, Sanford, & Tyroler, 2001). When considering anger as a reaction pattern, that is, anger as an expression style, both extreme expression and suppression may form a risk for health. Implications of anger to health may be different depending on the health status of the individuals under study. Overt expression of anger seemed to be the most harmful to individuals who already are at higher risk (Angerer et al., 2000; Bleil et al., 2004; Everson et al., 1999; Koskenvuo et al., 1988), while expressing ones anger might even benefit healthier, low-risk individuals (Eng et al., 2003; Gallacher et al., 1999; Haynes et al., 1980). In addition, the socioeconomic position of individuals might affect the health risks they have in regards to expression of anger. Overt expression of anger forms greatest risk in individuals from adverse socioeconomic circumstances (Mendes de Leon, 1992; Mittleman et al., 1995; Mittleman et al., 1997), while the same characteristic (anger-out) may even be protective among individuals who are better off in socioeconomic terms (Eng et al., 2003; Haynes et al., 1980). Therefore, angry behavior may lead to different endpoints in different environments depending on the prevailing culture, norms, and values in the population at issue. In some environment anger expression may be acceptable or a beneficial way to communicate, whereas in other environments it might not be tolerated and has adverse consequences. Also the goodness of fit between the
genotype and the environment may be an explanation for the different effects of anger on health.

One interpretation of the findings of anger and CHD in our review is that persons who are not used to express their anger and rather suppress it, may experience expressing anger outwards as more stressful and straining more their bodies than individuals who habitually show angry outbursts. This stressfulness of the experience of expressing anger may trigger myocardial infarction or some other form of CHD. This might explain why not showing anger is a greater risk in the long-run, while intense angry reaction is a risk factor for proximal cardiac events.

Naturally, this does not assure that there is a unidirectional relationship between anger and cardiovascular disease. Having developing CHD may make the individual exhausted and irritable, and thus more prone to experiencing anger. Physiological symptoms of CHD may decline the threshold of experiencing and expressing anger towards others. Thus, there is a possibility that anger is a consequence rather than an antecedent of cardiovascular problems. In this case, it could be used as an early marker of cardiovascular risk.

There might also be genetic explanations for the association between hostility and cardiovascular risks with shared genetic markers by both hostility and cardiovascular risks. Serotonin-related genes might be a missing link relating psychological distress to cardiovascular problems. In addition, areas in the genome that were found to suggestively relate to hostility in our GWA study, if replicated, may deserve further study in order to determine whether they play a role in linking hostility to health risks. However, at the moment it is too early to draw strong conclusions about the role of single polymorphisms for hostility, rather there probably are several genetic markers as well as environmental factors and their interactions affecting hostility and its health risks.

Several attempts have been made to examine the possible pathways through which hostility and psychosocial stress might be related to cardiovascular diseases, but no conclusion has yet been reached (Schulman & Stromberg, 2007; Vitaliano et al., 2002). Both direct and indirect pathways have been suggested, and they are not necessarily mutually exclusive. Probably both genetic vulnerability and early environmental stressors modify the stress sensitivity of an individual, thus engendering vulnerability to
cardiovascular disease especially in stressful environments. Whether hostility is a cause of cardiovascular risks or simply a marker of heightened cardiovascular risk is a question for future research to answer.

5.2. Methodological strengths and limitations of the study

The major strengths of this study were as follows: 1) the measures of hostility used were continuous capturing higher variability than the original measures such as MMPI which use dichotomous items, 2) we were able to establish associations in a prospective cohort which was followed up all the way from childhood or adolescence to adulthood, 3) we were able to consider several possible confounding variables such as socioeconomic circumstances, 4) we had several sources of information (the parents, the participants, and the medical examiners), thereby decreasing common rater variance, and 5) we used an interdisciplinary approach which drew hypotheses from psychology as well as epidemiology and genetics. Our examination of these factors and their interactions is an attempt to understanding the complexity of how psychosocial factors may "get under the skin" and thus be related to somatic illness.

The present study also has limitations. First, operationalization of the construct ‘hostility’ is vague, similarly as several other psychological concepts as well (Norenzayan & Heine, 2005). We used three different measures with the idea to capture more reliably different aspects of the ‘hostility’ construct. However, the measures used were not standardized measures of hostility. In spite of that, the cynicism and paranoia scales which form the hostile attitudes scale, has content similar to sub-scales of the widely used Cook-Medley Hostility Scale (Barefoot, Dodge, Peterson, Dahlstrom, & Williams, 1989; Costa, Zonderman, McCrae, & Williams, 1986). As well, anger scale used in the present study has been shown to correlate with the much utilized Spielberger State-Trait Anger Scale (Moreno, Fuhriman, & Selby, 1993), and which according to Buss (1991) is the most direct and explicit questionnaire of anger. However, the discussion about the meaning of the psychological concepts like ‘hostility’ is still ongoing (Averill, 1983; Norenzayan & Heine, 2005; Russell & Fehr, 1994), thus the relevance and better operationalization of it is left for future research to answer. Second, even though the original study sample was representative of all Finns, it did not remain representative in the follow-up examinations. The large loss of participants that
occurred in some of our studies might have been due to the stringent inclusion requirements: the participants had to be present during all study phases and had to sufficiently answer many questions, which may have left out the most disadvantaged individuals or the most novelty-seeking individuals. Although, this was tried to decrease with the repeated measures multilevel modeling in the study II. Third, the implications drawn from GWAS and gene-environment studies are under serious critic. The effects found in genome-wide association studies are small and are not able to capture reliably all the nuances of complex reality with several gene × gene and gene × environment interactions. This is a general problem in the field, not a problem only in the present study. Hopefully, this may be overcome in future with larger datasets and as the knowledge accumulates. At the moment we are merely gathering small pieces of knowledge, and what we know for sure is that the information will get more complicated as research progresses.

5.3. Conclusions and practical implications

Hostility seems to be an example of a fuzzy concept with fuzzy hierarchy (Russell & Fehr, 1994) thus the borders with closely related concepts and their hierarchies are not clear. Studying different aspects of hostility both together and separately seems important for capturing different nuances of reality more closely. Different constructs of ‘hostility’ concept may have different developmental antecedents and vary on their role as cardiovascular predictors. Our study showed some early antecedents of cognitive aspects of hostility that is hostile attitudes measured as cynicism and paranoia/distrust. Cynicism and paranoia seem to share more similar genetic background than anger. Also early environment in form of close mother-infant contact measured as breastfeeding and child-rearing attitudes seem to be more valid and reliable predictors of these aspects of hostility.

In relation to cardiovascular risks, on the other hand, trait anger and anger expression, particularly suppression of anger, have been shown to predict development of coronary heart disease. Also hostile attitudes were shown to predict metabolic syndrome and inflammation in women. The relationships seem to depend on the population in question and its particular environment. Cynical distrust, i.e. hostile attitudes, have been shown to correlate more highly with trait anger and anger
suppression than outward expression of anger (A. Haukkala, 2002). This shared variance may be the part of hostility that is associated with later health problems. Those who have high anger and/or cynical distrust, perhaps because of lack of basic trust and inequalities in the social surroundings, and who are unable to express it either due biological reasons or due lack of social power, may be in highest risk for poor health.

The early interaction between primary caregiver and child is unique and has long-lasting effects throughout life. Breastfeeding is a unique form of this interaction. In addition to the health effects of breastfeeding, this prospective study shows that breastfeeding may affect the development of personality all the way into adulthood. We observed that those who were not breastfed as infants had higher levels of hostility in adulthood than their four-to-six-months breastfed counterparts. Breastfeeding for longer than a year, on the other hand, was not related to lower hostility in adulthood. Following the breastfeeding recommendations may therefore be recommended for their psychological benefits as well. We also showed that warm and nurturing care-giving received during childhood decreases the probability of having high levels of hostility in adulthood. Thus, we may conclude that close contact with the primary caregiver in an age-appropriate way is essential in preventing the development of hostility. Efforts to enhance warmth and proximity in parent-infant interactions should be a goal of early prevention in antenatal or post-natal clinics.

Exposure to early and long-lasting environmental factors is more likely to have significant effects on an individual, because later experiences accumulate on the basis of earlier ones. As early childhood experiences form the basis for feelings of basic security and later personality development (e.g. Bowlby, 1973) the prevention of mental health problems should be undertaken early in life. Although later interventions may produce important benefits, the most cost-effective way would be to begin prevention as early as possible and to include the entire family's emotional situation within the focus of attention (instead of one individual in isolation). An early and family-based approach might reduce the need for later interventions. Further, this is also a question of economy. A study in the United Kingdom showed that someone with a conduct disorder at age 10 will financially be ten times more costly for society by the age of 28-years than a person without such problems (Scott, Knapp, Henderson, & Maughan, 2001).
With proper prevention or early interventions increasing such individuals’ trust in others, these costs might be reduced.

The development of hostility is also partly dependent on one’s genetic composition, thus individuals with different genetic and environmental backgrounds may require different types of prevention and intervention to reduce hostility and the related social and health problems. Our results here emphasize that the effects of childhood experiences on later hostility may be contingent upon one’s genetic constitution. It seems that some individuals are more resilient with respect to environmental factors (both adverse and benign), while others are more sensitive to environmental exposure (flourishing in optimal environments, but failing in unfavorable ones). The fact that people respond differently to environmental factors according to their genetic background may explain why general intervention programs in some cases might not achieve their ultimate goals. When the same interventions are directed at the entire population, some individuals seem to benefit from them whereas others do not. Therefore choosing suitable target groups as well as recognizing individual differences and taking them into account may be a key element of effectively tailoring psychosocial interventions aimed at reducing hostility and promoting national health.

We showed that hostile attitudes predicted later metabolic syndrome and inflammation among women, and suggested that inflammation might be a potential mechanism linking hostility to cardiovascular diseases. Cardiovascular disease is a significant economic burden on society, thus its prevention by increasing a sense of security and trust among highly hostile individuals might be beneficial for health care systems and national economies as well as the individuals themselves. This increase in social capital may involve, among other things, improving the financial situation of deprived individuals, strengthening their social networks, encouraging further education, and promoting healthy lifestyles.

We found that childhood SES rather than adulthood SES modified the association between anger and preclinical atherosclerosis. This finding supports the idea that the health effects of anger are dependent on the context and have their origins early in life. Our findings also suggest that higher levels of anger are related to higher IMT only among individuals with low SES backgrounds. However the mechanisms underlying the found association are obscure and require further investigation. Individuals with a low
childhood SES background are likely to be particularly sensitive to the effects of anger in terms of cardiovascular health, and perhaps teaching context-appropriate ways to control and express anger might reduce their health risks.

Here, we have looked at only a few early antecedents of hostility and cardiovascular disease. Naturally, many other factors influence this phenomenon. Difficulties in breastfeeding, hostile maternal care-giving attitudes, and low SES, however, may indicate wider difficulties within the family and/or greater stress and demands set by the environment. Family-related factors and individual choices cannot be dictated from the outside. However, individual and even genetic factors can be influenced at the societal level by providing accurate information to all parties as well as assistance when needed, and by improving the social surroundings. Prevention directed toward the entire family, particularly parent-child interactions and the social and economic environment, in early life is recommended in order to mitigate the cumulative life-time effects of an adverse early environment. Increasing the possibilities and trust of the most disadvantaged individuals by giving systematic and long-term help might aid ending vicious cycles of malfunction in the families and increase their faith for a better future.
6 REFERENCES


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