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Maurissa Chapman Mesirow Date

The Role of Polyunsaturated Fatty Acids in Aggression, Antisocial Behaviors, and Crime: A Systematic Review

By

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_____

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By

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An abstract of
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Rollins School of Public Health of Emory University
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Abstract

The Role of Polyunsaturated Fatty Acids in Aggression, Antisocial Behaviors, and Crime: A Systematic Review

By Maurissa Chapman Mesirow

Conduct disorders, oppositional defiant disorders, aggression, and antisocial behaviors are some of the most commonly diagnosed deviant behavioral disorders among children and adolescents today. Youth with these disorders violate societal rules, perform acts of delinquency, and have a greater risk for criminal activity in later adolescence and adulthood. The earlier children start to exhibit these behavioral issues, the more likely they are to become and remain delinquent in their lifetime.

Omega-3 and omega-6 polyunsaturated acids (PUFAs) are important for neural development during fetal stages and in childhood. Deficiencies in omega-3 PUFAs, or high levels of omega-6 PUFAs, can impair neural processes that are important for regulating behaviors, and have been implicated in the etiology of aggression and antisocial behaviors. Dietary trends in the United States has shifted greatly in the last century, introducing high levels of omega-6 PUFAs in to the average diet, which may have attributed to the higher prevalence of deviant behaviors in recent decades.

Observational studies and clinical trials have investigated the effects of omega-3 PUFAs in mediating aggression, antisocial activity, conduct disorders, and similar behaviors commonly associated with juvenile delinquency and criminal activity. While the results are mixed, there is a fair amount of evidence that supplementation with omega-3 PUFAs in childhood, adolescence, and early adulthood may alleviate deviant and antisocial behaviors. This knowledge may be important for understanding the etiologies of delinquent and criminal behavior in the United States.

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I would also like to thank my parents, Florence and Richard Mesirow, who have always believed in me and supported me during my educational pursuits. I would also like to thank my friends, Cari Westbrook, Shelby Farrell, and Jesper Andersson, who always kept me motivated all through my investigation. They have all remained by my side as I grew into the person I am today, and will continue to support me on my journey to become the researcher I know I can be.

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List of Abbreviations

Fatty acids

AA	Arachidonic acid (ω-6)
ALA	Alpha-linolenic acid (ω-3)
DHA	Docosahexaenoic acid (ω-3)
DPA	Docosapentaenoic acid (ω-3 and ω-6)
EPA	Eicosapentaenoic acid (ω-3)
LA	Linoleic acid (ω-6)
ω-3	Omega-3 (fatty acid)
ω-6	Omega-6 (fatty acid)
PUFA	Polyunsaturated fatty acid (refers to either ω-3 and ω-6 unless otherwise specified)

Behavior disorders

ADHD	Attention deficit hyperactivity disorder
APD	Antisocial Personality Disorder
BPD	Borderline Personality Disorder
CD	Conduct disorder
ODD	Oppositional defiant disorder

INTRODUCTION

The prevalence of aggressive and antisocial behaviors in children and adolescents range from 2 to 16%, making them major public health concerns (1). After anxiety disorders, behavioral problems such as conduct disorders, oppositional defiant disorder, and other deviant behaviors characterized by antisocial or aggressive traits, are the most commonly diagnosed behavioral problems among youth (2). Juveniles who display high levels of aggression can exhibit a range of delinquent behaviors consisting of rule violations and hostile actions in additional to behavioral impairments (1). Recently, there has been a growing concern over the rising rates of juvenile delinquency, violence, excessive levels of aggression, and criminal behavior. In the United States, rates of aggression and antisocial behaviors have increased in both severity and frequency in the last few decades (3).

Youth violence and behaviors associated with conduct issues pose societal public health problems. For mental health and juvenile justice workers, aggression is one of the most common and costly behaviors in children and adolescents (1, 4-6). The economic impact of conduct disorders can be more costly than other mental or behavioral disorders. A child with conduct disorder has annual medical costs as high as $14,000 - 3 times greater than the annual medical costs for a child with attention deficit hyperactivity disorder (ADHD) (7, 8). Preventing criminal activity among youth could save society millions of tax dollars for each individual prevented from a life of crime. Saving a14 year-old who is at high-risk for violent behavior from a lifetime of criminal activity could save the public anywhere from $2.6 to $5.3 million in medical, justice system, and mental health service

costs. Preventing someone at birth from becoming a high-risk juvenile offender would save the public between $2.6 to $4.4 million during that person's lifetime (9).

It is imperative to prevent the early onset of delinquent behaviors because the earlier these behaviors emerge, the more crimes are likely to be committed before 18 years of age. As these activities persist, more serious and violence crimes are likely to occur (10). In order to reduce the prevalence of conduct problems and related behaviors, a better understanding of their etiologies needs to explored. To date, there has been a substantial amount of research investigating the genetic and environmental factors that contribute to the development of antisocial behaviors, conduct disorders, violence, and aggression. However, the mechanisms of how these factors influence behavioral outcomes are less well understood (11).

Pre- and post-natal nutrition are important for cognitive and behavioral outcomes, so it would seem as though it would have an important role in modifying maladaptive behavioral outcomes as well. Yet pre- and postnatal nutritive environments are not typically considered a major contributory factor to these abnormal behavioral developments. Fatty acids are of great importance because of their known roles in brain growth and development, reducing depression, and improving cognitive outcomes. Since the fatty acid profiles of our food environment has drastically changed in the last century, as has the prevalence of delinquency and behavioral problems in children, the purpose of this review is to investigate whether or not there is a plausible link between nutrition and conduct problems (aggression, delinquency, conduct disorders, antisocial behaviors, and later criminality).

CHAPTER 1: AGGRESSIVE, ANTISOCIAL, AND DELINQUENT BEHAVIORS

1.1 Defining aggression, behavioral and personality disorders

Aggression is a very broad class of behavior (12) that is normally displayed in young children to some degree. It is consistently more common in boys than girls across almost all cultures (3). Generally, these aggressive displays decrease with age as children learn how to properly socialize with others and learn to channel aggressive impulses into other mediums like sports, social activities, or academia (13). When these behaviors are not channeled into socially acceptable outlets during childhood, there is an increased risk for non-socially acceptable forms of aggression. Aggression can be considered a form of antisocial behavior, which is associated with conduct and oppositional defiant disorders, violence (defined here as a physical force exerted in order to cause physical injury, damage, or physical or mental abuse), and criminal activity in later life (3, 14). Between the mid-1980's and 1998, violent aggression may have caused direct harm to about 10% of adolescents each year in the United States (3, 15).

For the purpose this review, the focus will be on maladaptive types of aggression, which is the exhibition of behaviors outside the rules of society. Excessive or inappropriate aggressive behavior is classified as an emotionally unstable personality disorder, characterized by acting impulsively and without consideration of the consequences of their actions (16). One type is overt aggression (also called oppositional aggression), which is an open act of physical aggression or violence directed against people (fighting, bullying, weapons use in hostile situations, or an open defiance of rules) (17). Another type is covert aggression (also called covert non-aggression), which is a hidden act of aggression, such as

property violations (stealing or fire-starting) or verbal actions (17). Females are less likely to be overtly aggressive or commit violent crimes compared to men (18), but they do commit covert, non-aggressive forms of delinquency like fraud or shoplifting (19). Covert and overt forms of aggression are opposing types on a continuum, and oppositional defiant behavior lies somewhere in the middle (20, 21). Conduct disorders encompass both overt and covert forms of aggression (17), as do antisocial behavioral patterns (17, 22).

1.1.1 Behavioral Disorders

Conduct disorder (CD) is a clinical mental health term that encompasses aggressive and antisocial behaviors in youth under 18 years of age. It is one of the most common complaints in mental health consultations (23), and is characterized by repetitive and persistent violations of age-appropriate societal norms and disregard for the rights of others (24). Defining characteristics of CD include of property destruction (covert aggression), physical (overt) aggression, and deceitfulness (5, 16, 24). Callous-unemotional (CU) traits in childhood have also been proposed as a symptom or subset of CD (25). CU traits are associated with low anxiety in males, but not females (26), even though anxiety is also related to CD (27). Early onset (childhood) CD occurs when behaviors begin to appear in children 10 years or younger. Late onset (adolescent) CD is defined when children first display behaviors at 11 years of age or older (24). Early onset CD is predictive of adult criminal behavior and mental health difficulties in both men and women later in life (5, 28).

The prevalence of CD is related to gender and age (27, 29). While boys have a higher prevalence in their prepubescent years, the prevalence of CD in adolescent girls can approach that of adolescent boys (30). Though CD is generally less prevalent in females, its

symptomology is more severe (31). Sex-related differences of CD can vary based on age. Boys can peak around 10-13 years of age, and girls peak around 16 years (32, 33). In some cases, rates of aggression for boys and girls are equal (32). In both genders, there is an increased risk for later psychiatric disorders with greater severities of CD (23). With increasing age, there is a higher risk for committing non-aggressive acts and status violations, while aggressive acts decrease with age (29). In both boys and girls, conduct disorder is often a precursor to antisocial personality disorder (34).

Characteristics of oppositional defiant disorder (ODD) are different from CD (17). Depending on the diagnostic criteria used, ODD can be classified as a behavioral disorder separate from CD (24), or as a specific type of conduct disorder (16). It is defined by a recurrent pattern of defiant and hostile behaviors towards those in positions of authority (24). In some boys, aggression appears in early life in conjunction with ODD symptoms (35). Persistent ODD symptoms are generally preceded by and can be a predictor of later CD onset in males (36). Children with ODD and ADHD can also be a marker for early-onset CD symptoms (37). ODD is hypothesized to be a precursor to conduct disorder (CD) (37). Those with ODD are 12.6 times more likely to have conduct disorder, and 11.0 times more likely to have a general impulse control disorder, compared to people without ODD (38) throughout their lifetimes. Many youth who are diagnosed with CD often have other psychiatric comorbidities, including ADHD, impulsivity, and early symptoms of antisocial personality disorder (24, 37).

Boys exhibit a higher number of symptoms to meet diagnostic criteria of CD compared to girls. The odds of having CD are three to four times higher among boys (37) than girls, however ODD and CD are still somewhat common diagnoses among girls (39).

Some evidence suggests that sex differences in disruptive behaviors are not apparent until six years of age. Around this time, boys display more overt forms of disruptive behavior than girls (40, 41). In adolescence, age differences in ODD prevalence are inconsistent; rates are shown to be similar between the genders, or slightly higher in males (37).

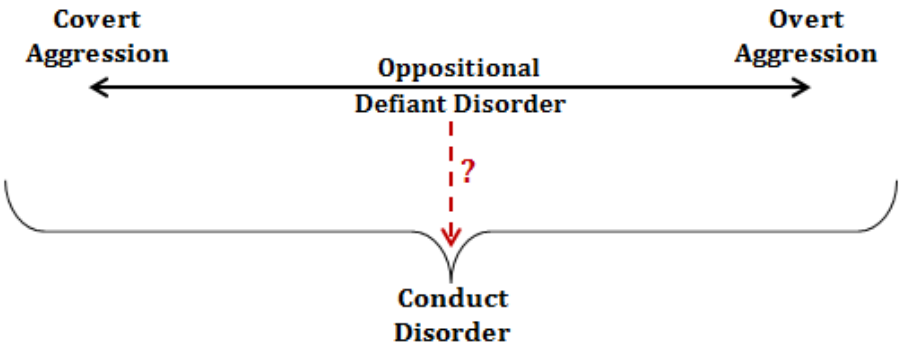

Figure 1.1 Overview of the relationship between types of aggression, oppositional defiant disorder (ODD), and conduct disorder (CD). Direct progression from ODD to CD is still in debate.

1.1.2 Personality Disorders

In the field of criminal justice, antisocial behavior is a broad category that can be defined as any act that violates societal laws, including homicide, theft, and assault, and is harmful to others (3). Antisocial acts are considered to be cumulative in nature, both in frequency and intensity, and include acts of criminality (serious offenses committed by adults over 18 years of age) and delinquency (both serious and less serious antisocial and criminal acts committed by minors) (3). Antisocial behaviors can be categorized into overt and covert dimensions. Overt antisocial behaviors are defined by acts or threats of physical aggression, such as fighting, defiance, and bullying. Covert antisocial behaviors are defined mainly by non-aggressive rule-breaking actions like property violations (theft, fire-setting

vandalism) and status violations (substance abuse, swearing) (22, 42, 43). There are also gender differences in age of onset for antisocial behaviors. The male-to-female ratio for the onset of antisocial behaviors ranges from 10:1 to 15:1 in childhood, but from 1.5:1 to 5:1 in adolescence. While females are less likely to exhibit these behaviors compared to males, whose who do are more likely to continue these behaviors into adulthood (44).

The diagnosis of antisocial personality disorder (APD), and/or psychopathy (those with chronic criminality and recidivistic antisocial behavior), are the most serious outcomes of disruptive behaviors. These are both defined as dissocial personality disorders, characterized by unchangeable disregard for social obligations and blatant unconcern for other's feelings. They have low thresholds for displays of aggression and violence (24). The defining features of APD are the consistent disregard and violation of the rights of others, and large discrepancies between their own behaviors and societal norms. These traits are first observed in early childhood or adolescence, and can persist into adulthood (16, 24, 45). Individuals with APD repeatedly lie, get into fights or assaults, perform actions that are grounds for arrest, mistreat others, fail to maintain proper workplace behavior, and disregard the safety of self and others (24). APD also has high rates of comorbidities with other psychiatric disorders, including anxiety, substance abuse, and psychopathy (45). Psychopathy includes APD-related traits (impulsivity, irresponsibility, and antisocial behavior) and deviant personality traits (lying, interpersonal manipulation, disregard of others, insincerity, lack of remorse, unreliability, and poor insight) (46, 47). Technically, APD cannot be diagnosed until the 18 years of age (24). However, symptoms can be observed at a younger age, and this early in children with CD could help identify those at risk for APD once they become adults (48, 49).

Table 1.1 Summary descriptions of behavioral and personality disorders common in delinquent and criminal behavior, and their defining characteristics. Covert aggression is typically observed in females diagnosed with conduct disorders, but is not part of the current diagnostic criteria in the DSM-IV or ICD-10.

Types of Disruptive Behaviors	Defining characteristics
Personality Disorders	
Aggression 1. Overt aggression 2. Covert aggression (non-aggression)	Exhibits behaviors outside societal rules and acting impulsively 1. Open act of physical aggression or violence directed at others: - Fighting or bullying - Property and/or rule violations - Open defiance of societal rules - Deviant personality traits 2. Hidden, non-confrontational acts of aggression: - Property violations - Deviant personality traits - Indirect/verbal acts of aggression
Antisocial Behaviors 1. Antisocial Personality Disorder (APD) 2. Psychopathy	Violation of societal laws; acts of criminality and delinquency 1. Consistent violation of societal norms and obligations; unconcern for other's feelings (18 years or older) - Antisocial behavior (delinquency, criminality) - Impulsivity and irresponsibility 2. Displays of chronic criminality and recidivistic antisocial behaviors - APD-related traits - Deviant personality traits
Behavioral Disorders	
Conduct Disorder (CD)	Persistent antisocial behavior that violates the rights of others and societal norms: - Overt/Physical aggression (males) - Covert aggression (non-aggression) (females) - General rule violations - Early ($\leq$10 years) or late ($\geq$11 years) onset
Oppositional Defiant Disorder (ODD)	Recurrent defiance and/or hostility towards authority figures - Argumentative with adults - Defies/refuses to comply with authority figures - Spiteful/vindictive - Angry and/or resentful - Blames others for their own mistakes

The various behavioral and personality disorders described above express some degree of overt aggression, covert aggression, and/or antisocial personalities through criminal and delinquent activity. Because of the overlap between these disorders, they are all considered important for exploring possible biological etiologies of criminality and delinquency discussed later in this review.

1.2 Self-reported prevalence of aggression, conduct disorders, violence, and criminal behavior does not correlate with decreasing criminal arrest rates

In the United States, rates of aggression and antisocial behaviors among young people peaked in the late 1980s and early 1990s. While rates have been falling since the turn of the century, they are still high (3). Early signs of aggression and CD are strong predictors for antisocial personality or criminal activity later in life (50). The DSM-IV reports an average prevalence of APD at 2-3% in the general population, with 3% in men and 1% in women (24). Prison inmates have a higher prevalence of APD (47% of men and 21% of women) compared to the general population (51). Lifetime prevalence of ODD among males and females (11.2% and 9.2% respectively), are roughly equal, with the highest prevalence in the 18-24 age group compared to older age groups (13.4% vs 7.5-10.1%) (38).

The worldwide prevalence of Conduct Disorders (CD) among juveniles ranges from 0.9% to 20%. Among U.S. youth, lifetime prevalence can range from 1to 10% (24), and is less common in prepubescent children than in adolescents. Prevalence among males ranges from 2 to 16%, and from 0 to 9% among females (29, 37, 38, 52). There is some evidence that the incidence of CD is increasing in Western societies (53). Additionally, it is one of the most persistent and long-lasting forms of psychological behavior disorders (23). 45-70% of people with CD in childhood or adolescence develop APD in early adulthood (38, 54-57), and up to 70% of children diagnosed with CD will have at least one criminal conviction in adulthood (34). 54% of girls and 26% of boys with CD are likely to have ODD as a co-morbid disorder (36).

1.2.1 Criminal arrest rates

Juvenile violence is usually measured through official police records, court records or self-reports (58). Many acts of aggression, delinquency, or antisocial behaviors are not captured unless there is a crime committed and recorded by authorities. One major issue with using arrest rates to observe delinquent behaviors is that they underestimate the true prevalence of youth violence since they only capture a small percentage of all youths involved in criminal or violent behavior (4). Rates of criminal arrests are not absolute since they reflect temporal changes in how law enforcement handles juvenile violent behavior, and can only report on perpetrators actually caught by law enforcement. Only 6 to 14% of persistent violent offenders are ever arrested for a serious crime (4). Many juveniles who continuously perform crimes only come in contact with the law once, which leads to underestimates in true number of criminal youth (10). While official crime statistics might underestimate the true prevalence of these antisocial behaviors in the population, they can give a rough estimate of more severe forms of delinquency that are exhibited as criminal offences, such as assault (simple, aggravated, and sexual), robbery, and attempted or threatened violence (3).

Crime statistics show conflicting trends in youth violence, as measured by arrest rates for various crimes. Between 1983 and 1993, youth homicide rates increased by 170%, while the total arrest rates for all serious violent crimes increased by 70%. By 1999, these rates dropped again, measuring only 20% higher than they were in 1983. In contrast, self-reports of violent behaviors have shown a 50% elevation in assault and robbery rates between 1983 and 1993, which remained stable through 1999. Both arrest and self-report records indicate that rates of youth violence are higher among males than females (4).

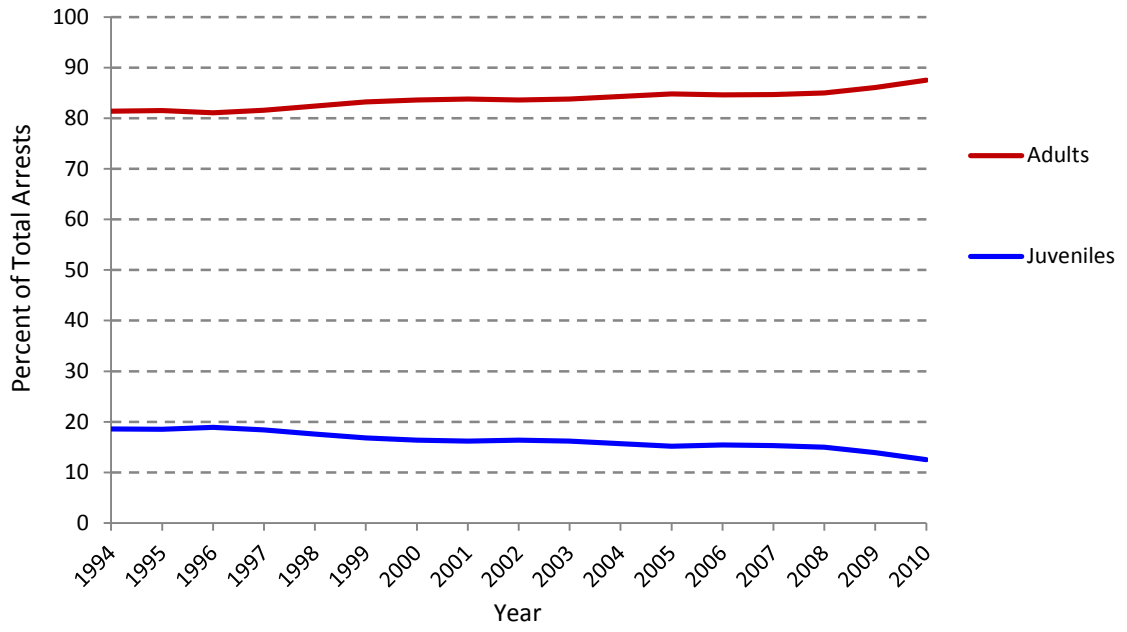

Figure 1.2 Percent of total arrests in the U.S. performed by juveniles (10-17 years) and adults (≥18 years) from 1994-2010. Data source: Puzzanchera, C. and Kang, W., 2013. Easy Access to FBI Arrest Statistics 1994-2010 Online. Available: http://www.ojjdp.gov/ojstatbb/ezaucr/

Between 1994 and 2010 in the U.S., the percent of total adult arrests increased, while percent of total juvenile arrests decreased (**figure 1.2**). In 1994, adults (≥18 years) accounted for 81.4% of total arrests, and juveniles (10-17 years) accounted for 18.6%. By 2010, the proportion of arrests in adults increased to 87.5% (a 7.5% increase), while the proportion of arrests in juveniles decreased to 12.5% (a 32.8% decrease) (59). Even though juvenile arrests have declined, adult arrests have gone up. This is an important observation because almost half of juveniles that begin committing violent crimes before the age of 11 continue to do so into their adult years, whereas youth who start between the ages of 12-17 years have much lower risks of continuing these acts into adulthood (10). The small decrease in juvenile arrest rates seen here does not account for early versus late onset criminal activity in youth, nor does it reflect which of these youth - early- or late-onset - are contributing to the rising adult arrest rates. Additionally, only small proportions

of juveniles who commit crimes are actually arrested. Therefore, this arrest data cannot solely be used as direct evidence for declining juvenile delinquency (10).

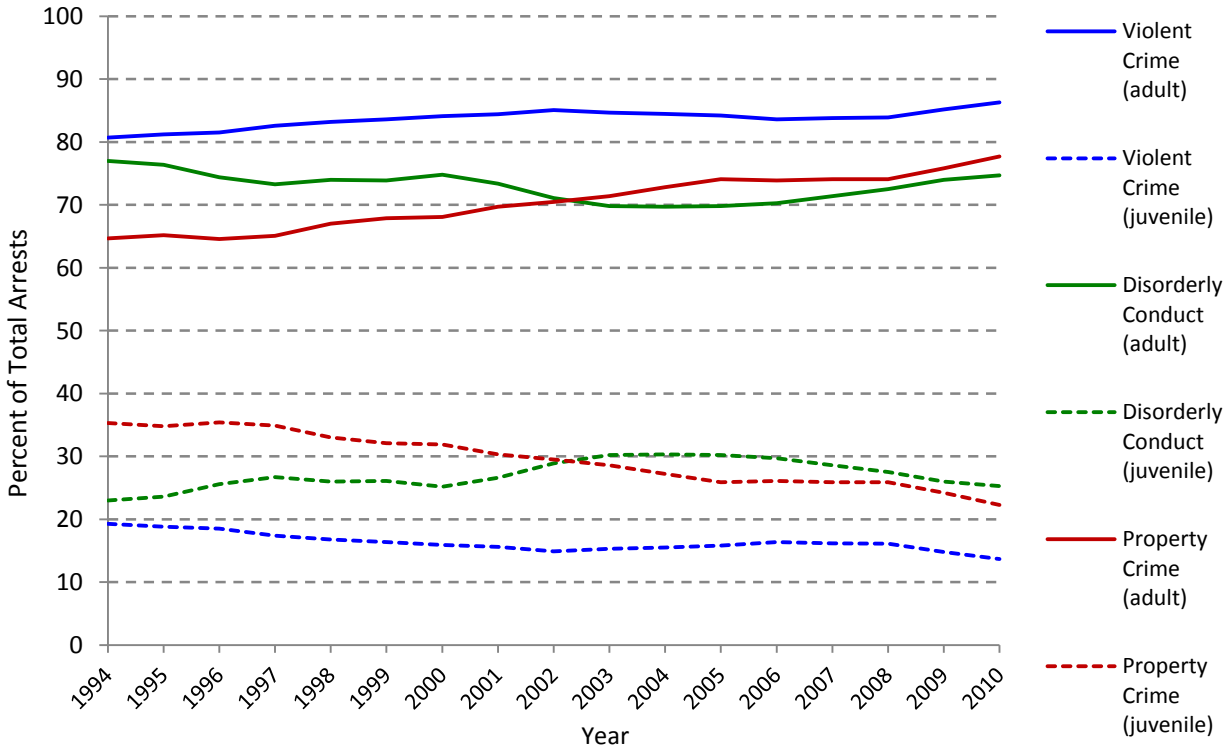

Figure 1.3 Percent of total arrests in the U.S. performed by juveniles (10-17 years) and adults (>18 years) from 1994-2010, by crime type. Violent crime includes murder/non-negligent manslaughter, forcible rape, robbery, and aggravated assault. Property crime includes arson, burglary, motor vehicle theft, and larceny-theft. Data source: Puzzanchera C. and Kang W., 2013. Easy Access to FBI Arrest Statistics 1994-2010 Online. Available: http://www.ojjdp.gov/ojstatbb/ezaucr/

When total arrest rates during this time period are broken down by major category, different patterns emerge for juveniles and adults (**figure 1.3**). The percentage of adult arrests for violent crimes and property crimes increased by 6.9% (from 80.7 to 86.3%) and 20.1% (from 64.7 to 77.7%) respectively, while the percent of adult arrests for disorderly conduct remained fairly constant, decreasing by only 3.0% (from 77.0 to 74.7%). In comparison, the percentage of juvenile arrests for violent crimes and property crimes juveniles decreased by 29.0% (from 19.3 to 13.7%) and 36.8% (from 35.3 to 22.3%)

respectively. However, the percentage of juvenile arrests for disorderly conduct increased by 10.0% (from 23 to 25.3%) (59). It is important to remember that these juvenile arrest records only capture a small percentage of all youth who commit crimes and thus underestimate the true prevalence of conduct and antisocial behavioral issues (4).

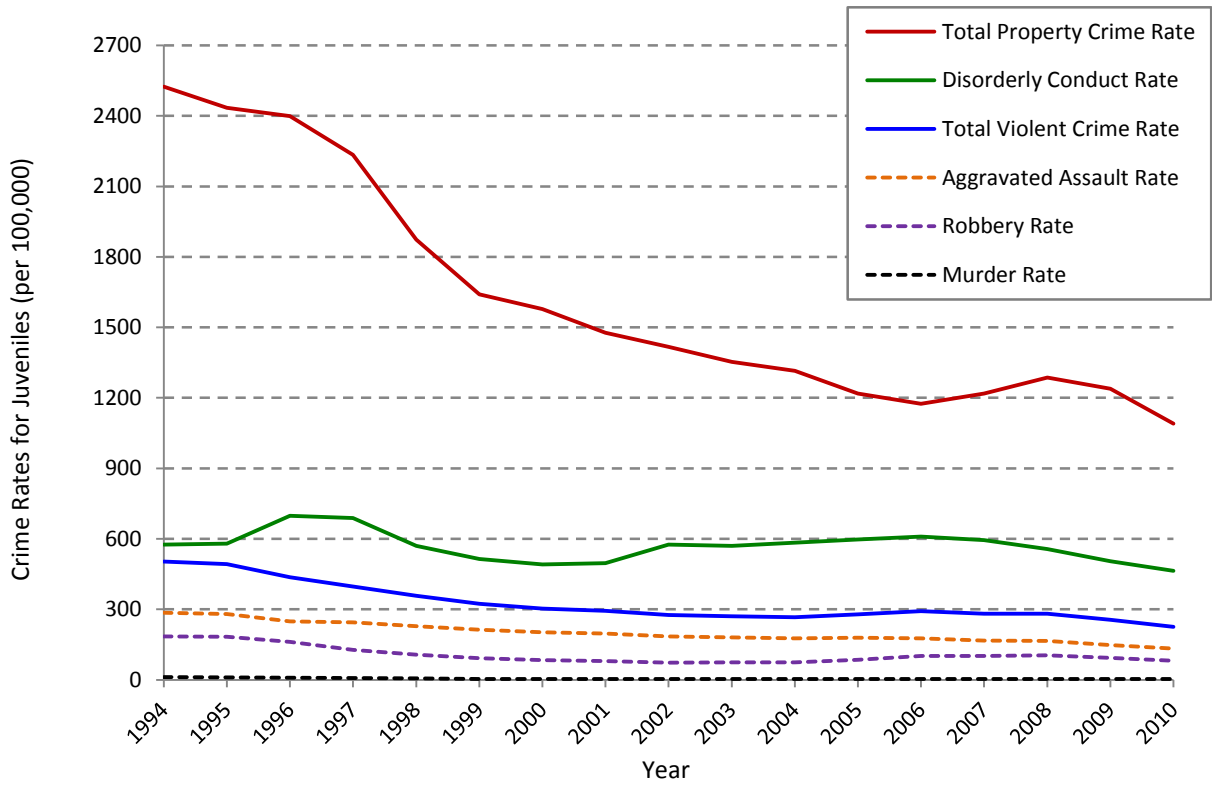

Figure 1.4 Crime rates (per 100,000) in the U.S. performed by juveniles (10-17 years) from 1994-2010, by crime type. Violent crime includes murder/non-negligent manslaughter, forcible rape, robbery, and aggravated assault. Property crime includes arson, burglary, motor vehicle theft, and larceny-theft. Data source: Puzzanchera C. and Kang W., 2013. Easy Access to FBI Arrest Statistics 1994-2010 Online. Available: http://www.ojjdp.gov/ojstatbb/ezaucr/

Figure 1.4 shows the juvenile crime rates for disorderly conduct, property crime, and violent crime. All of these rates show declines between 1994 and 2010. Property crime rates, disorderly conduct rates, and violent crime rates decreased by 56.8% (2,525 to 1,091 per 100,000), 19.3% (575 to 464 per 100,000), and 55.1% (503 to 226 per 100,000),

respectively. Within the total violent crime category, which includes aggravated assault, robbery, and murder, rates for all of these crime types showed declines ranging from 50-75%. Even though the actual crime rates for conduct disorders declined, the proportion of total arrests for conduct disorders have increased among juveniles between 1994 and 2010 (**figure 1.3**).

1.2.2 Self-reported data on conduct issues and criminal activity

Self-reports reveal that a large proportion of male juveniles commit violent acts, but only a small fraction of those result in arrests or convictions (58). Self-reports are important for capturing students performing delinquent acts who might otherwise not be captured by official arrest records (10). According to self-reports, the prevalence of youth violence has been steadily rising since the 1980's, and is still just as prevalent in recent years. In 2000, 10-15% of youth 17-18 years old admitted to having committed a serious act of violence in the last year. Approximately 30% of high school seniors reported committing a violent act in 2000. The reported proportion of 30% has remained fairly stable since the 1980's. This value is higher than expected for this age group, since for males, peaks in violent behavior coincides with the age of high school seniors (17-18 years of age), and because both serious and less-serious violent behaviors are included self-reporting indices (3, 4).

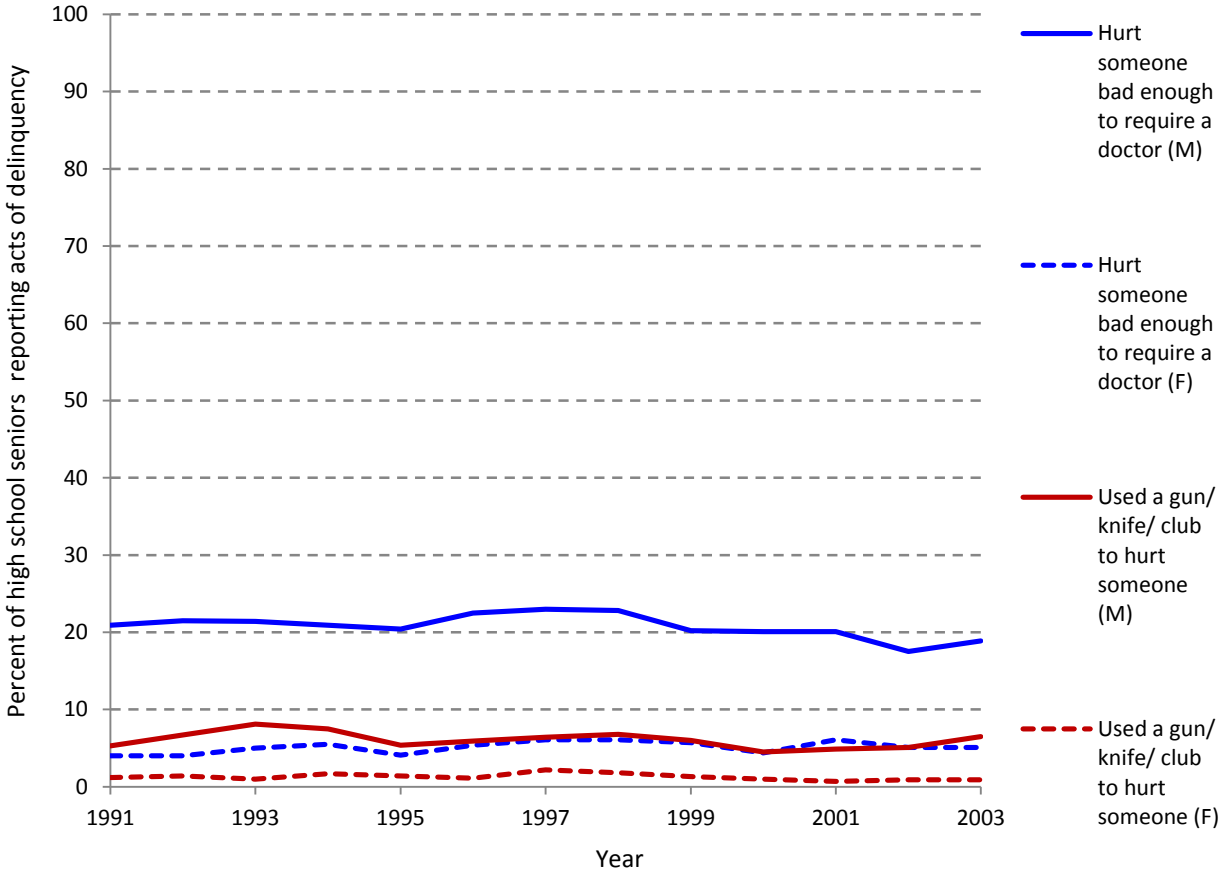

Figure 1.5 Percent of high school seniors who reported involvement in overtly aggressive delinquent activities at least once in last 12 months, by gender, U.S. 1991-2003. Dotted lines denote female students, solid lines denote male students. Data source: Sourcebook of Criminal Justice Statistics 2003, "High School Students: self-reported delinquency." University at Albany, Hindelang Criminal Justice Research Center Available at: http://www.albany.edu/sourcebook/tost_3.htm

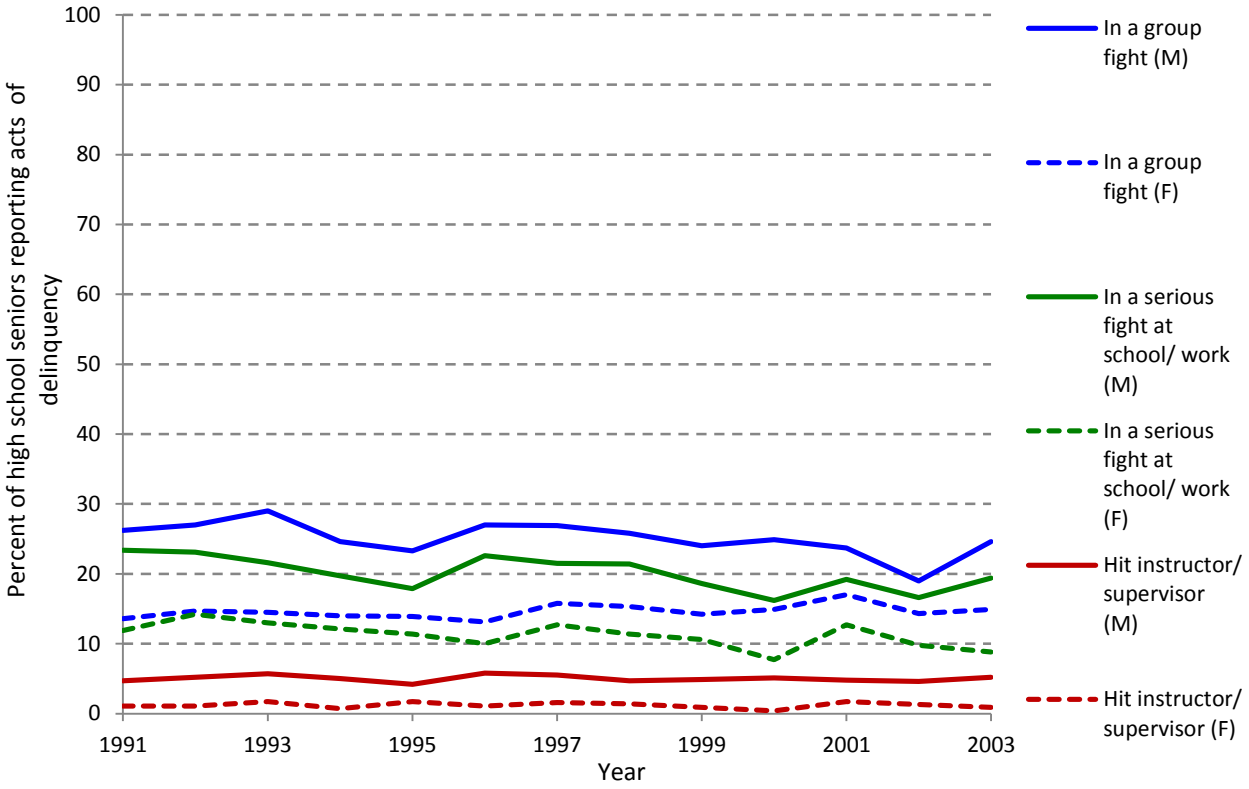

Figure 1.6 Percent of high school seniors who reported involvement in selected overtly aggressive delinquent activities at least once in last 12 months, by gender, U.S. 1991-2003. Dotted lines denote female students, solid lines denote male students. Data source: Sourcebook of Criminal Justice Statistics 2003, "High School Students: self-reported delinquency." University at Albany, Hindelang Criminal Justice Research Center Available at: http://www.albany.edu/sourcebook/tost_3.html

Between 1991 and 2003, the percentage of high school seniors surveyed who admitted to performing at least once act of delinquency in the past 12 months has remained fairly constant during the 12 year period for most acts of physical aggression, theft, and property damage (**figures 1.5-1.8**). The percentage of male and female senior students who performed at least one act of overt/physical aggression, a key trait of conduct disorders, criminality, and antisocial behaviors are shown in **figure 1.5** and **figure 1.6**. Males who reported hurting someone badly enough to require a doctor decreased by 9.6%, but the number of males who reported using a knife, club, or gun to hurt people increased by 22.6%. Females displayed a reverse pattern for these acts, increasing by 27.5% and

decreasing by 25.5%, respectively (**Figure 1.5**). The reported percentage of students hitting instructors or supervisors were roughly equal for males and females, while the percent of students who reported getting into a fight at school or work declined in both genders (**figure 1.6**).

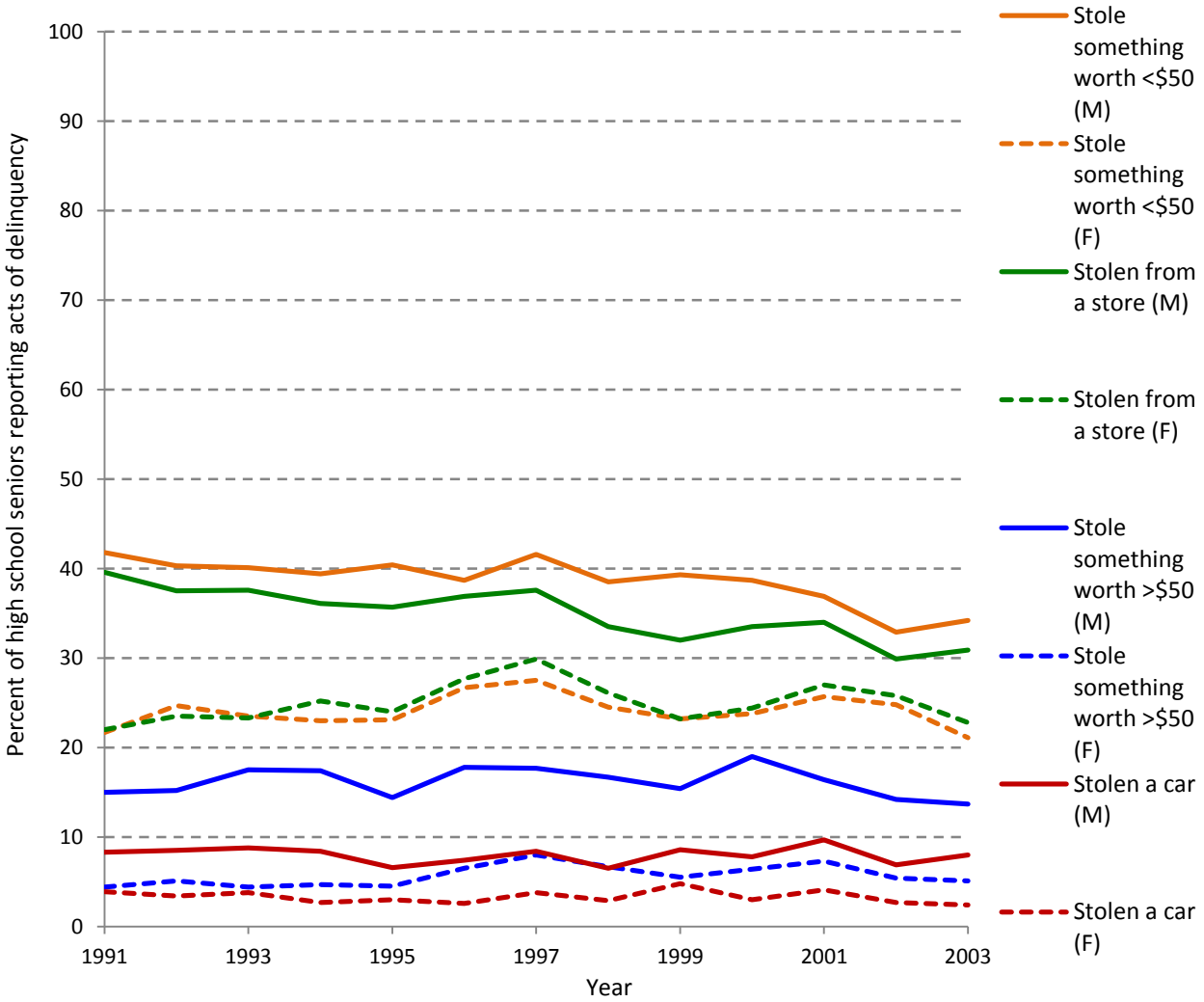

Figure 1.7 Percent of high school seniors who reported involvement in selected delinquent activities related to theft at least once in last 12 months, by gender, U.S. 1991-2003. Dotted lines denote female students, solid lines denote male students. Data source: Sourcebook of Criminal Justice Statistics 2003, "High School Students: self-reported delinquency." University at Albany, Hindelang Criminal Justice Research Center Available at: http://www.albany.edu/sourcebook/tost_3.html

Theft and property damage are also characteristics seen among youth with conduct disorders and antisocial behaviors (APD, psychopathy). The number of high school seniors who performed theft and property damage between 1991 and 2003 can be seen in **figures 1.6 and 1.7**, respectively. Male and female students who reported stealing cars and objects worth more than $50 remained fairly constant (**figure 1.7**). While there was an 18.2% reduction in the percent of male students who reported stealing objects worth less than $50, and a 22% reduction in the percent of males who stole an object from a store, the percent of females who reported committing these acts was nearly the same between 1991 and 2003. Reports of property damage and trespassing are described in **figure 1.8**. The percent of female students who trespassed or damaged school property remained stable during this time, while females had a 50% increase in arson (0.6 to 0.9%) and a 44.4% (1.8 to 2.6%) increase in workplace property damage. The percent of male students who reported property trespassing decreased by 5.5%, males who committed arson increased by 86% (3.6% to 6.7%), and males who committed workplace or school property damage remained fairly constant (**figure 1.8**).

The findings described above in figures 1.4-1.7 do not correlate with decreasing arrest rates for conduct disorder, violent crime, and property crimes described in figures 1.2-1.4. The conflicting findings between arrest statistics and self-reported delinquent acts are consistent with the belief that despite large decreases in arrest rates (**figures 1.2 - 1.4**), youth delinquency as measured by self-report surveys have remained fairly stable through the 1990's and into the beginning of the 21st century. Taken together, this implies that crime rates are not the best indicators for assessing juvenile conduct problems and antisocial behaviors.

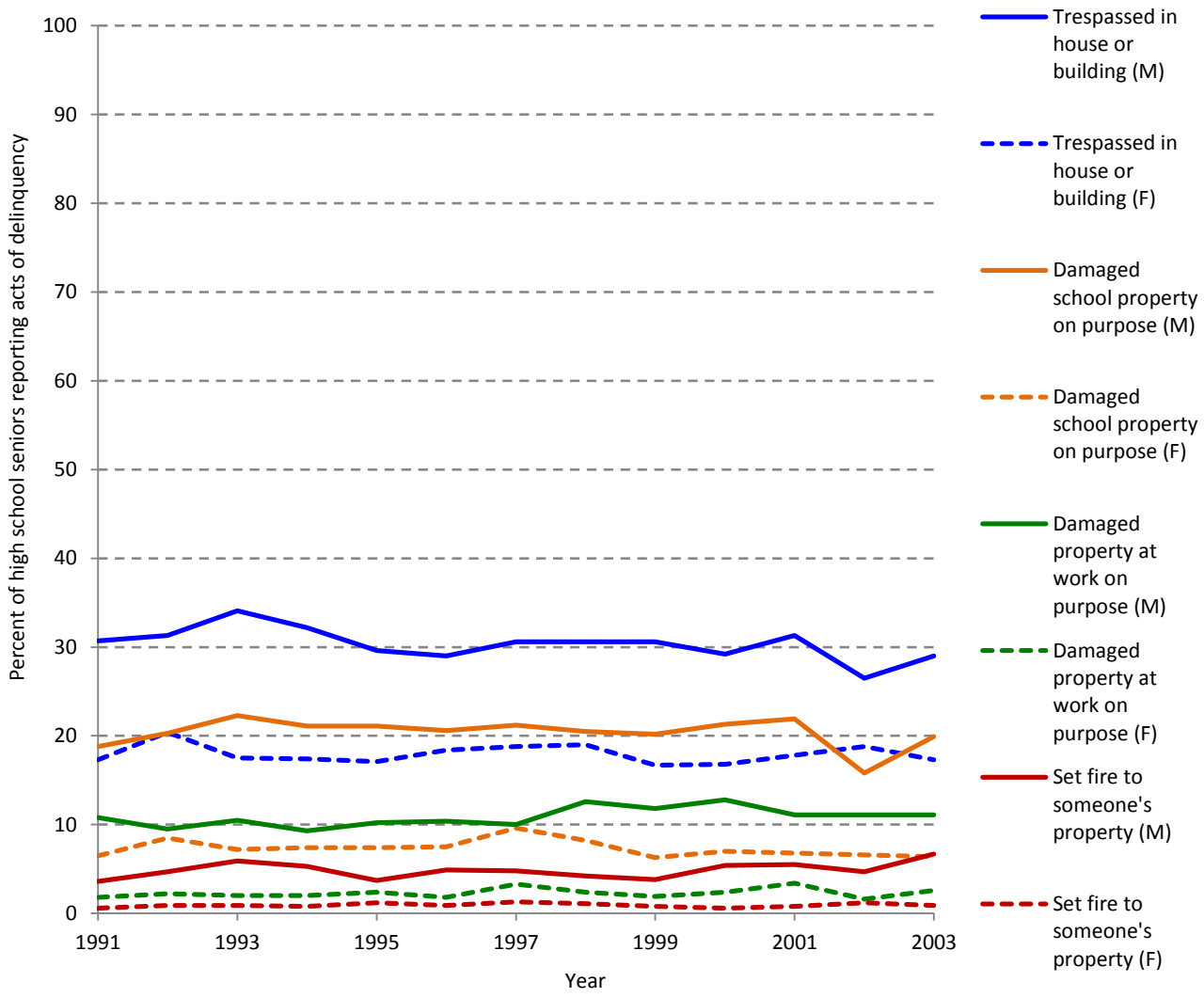

Figure 1.8 High school seniors reporting involvement in selected delinquent activities related to property vandalism or trespassing at least once in last 12 months, by gender, U.S. 1991-2003. Dotted lines denote female students, solid lines denote male students. Data source: Sourcebook of Criminal Justice Statistics 2003, "High School Students: self-reported delinquency." University at Albany, Hindelang Criminal Justice Research Center Available at: http://www.albany.edu/sourcebook/tost_3.html

One important aspect to youth violence is that it is not as lethal in recent years as it was three decades ago. This is in large part due to the decrease in firearms availability and usage in schools, which peaked in the mid 1980's and through the 1990's (4). The decrease in lethal acts is evident by total counts of homicide among male and female juveniles and young adults between 1980 and 2011 (**figure 1.9**). Female counts of homicide are fairly

constant during the 30-year period, and contribute a very small amount (8.5%) to the total number of homicides throughout this timeframe. Male young adults (18-24 years) had higher counts of homicide compared to male juveniles (12-17 years). Total homicide counts for juvenile and young adult males decreased by 44.3% (1,320 to 735) and 26.3% (5,162 to 3,806) respectively. Total homicide counts decreased for both young adults by 28.5% (5,858 to 4,187) and juveniles by 44.1% (1,437 to 803) (60). These higher counts among young adults are consistent with evidence that peak violence occurs around 18 years of age (3, 4), and are consistent with evidence that lethal crimes have been decreasing in recent years due to increased gun control (4).

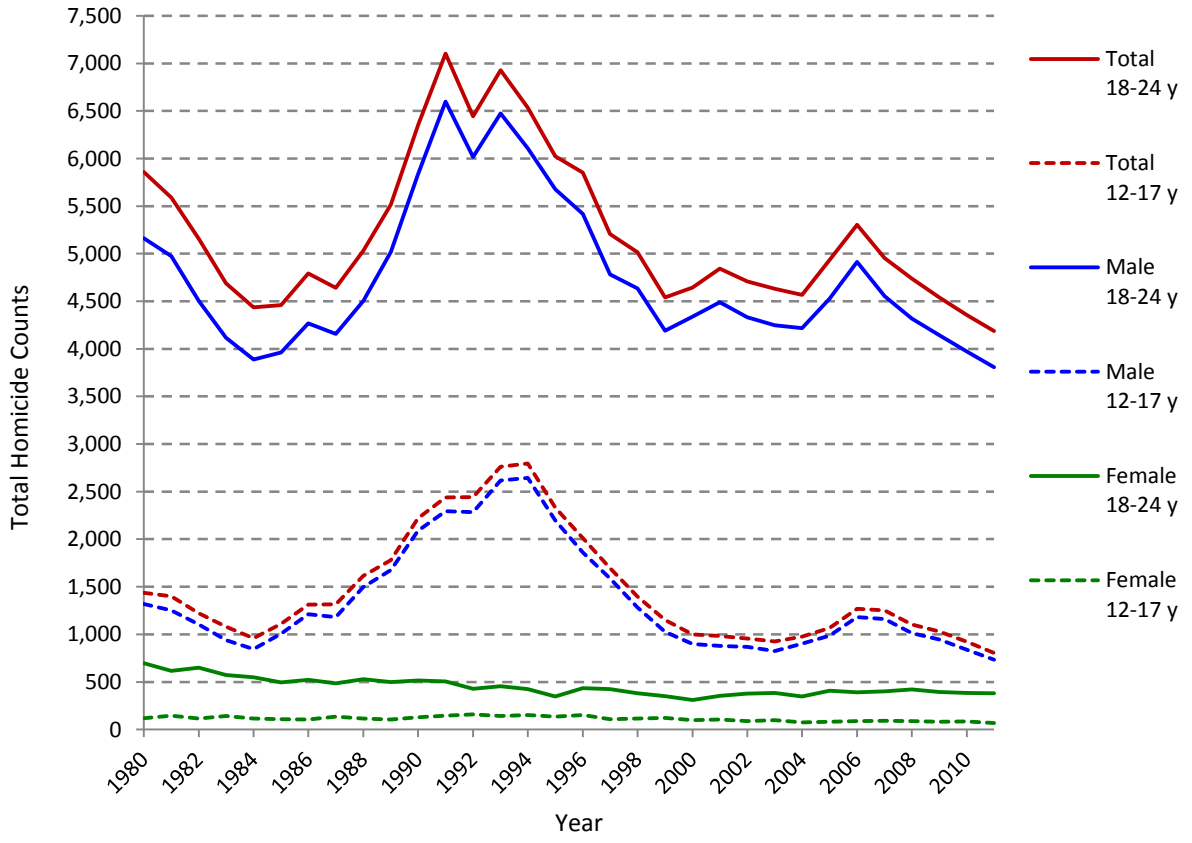

Figure 1.9 Total homicide counts for males, females, and total juveniles (12-17 years) and young adults (18-24 years) in the U.S., from 1980 to 2011. Data source: Puzzanchera C, Chamberlin G, and Kang W., 2013. "Easy Access to the FBI's Supplementary Homicide Reports: 1980-2011." Online. Available: http://www.ojjdp.gov/ojstatbb/ezashr/

1.3 Summary of criminal activities and antisocial behavior in youth

One must keep mind that most juvenile crimes are not reported to authorities, and of those reported, most offenders are not arrested or referred to juvenile court. Official records underrepresent juvenile delinquency for these reasons, even though arrest records imply declining crime rates (10). The statistics presented here only reflect a small percentage of the total youth crime in the United States. The National Youth Survey found that over half of total offenses, and over 80% of serious and/or violent crimes, were committed by 5% of all youth offenders (10). Violent offenders are persistent in their actions, but these repeated offenders are not caught to the same extent as other first-time offenders (58). Despite reductions in arrest rates for acts of delinquency since the 1990's, self-reported data indicates that criminal activity among youth have remained elevated and fairly constant. Acts of theft, aggression/assault, and property damage are characteristics of antisocial behaviors and conduct disorders, suggesting elevated prevalence of these behavioral problems. Based upon this information, there has not been a decline in acts associated with conduct problems and delinquency, despite arrest records indicating otherwise. The elevated prevalence of these behaviors can have consequences for continued criminal activity into adulthood.

CHAPTER 2: POLYUNSATURATED FATTY ACIDS - SIGNIFICANCE & DIETARY TRENDS

2.1 Introduction

Of the different fatty acids, docosahexaenoic acid (DHA) has been the only omega-3 polyunsaturated fatty acid (ω-3 PUFA) used as a main structural component of neurons throughout millions of years of evolution. The high concentration of DHA in brain tissues in humans and other mammals lends weight to the importance of this fatty acid for brain development. In many countries, higher omega-3 fatty acid tissue levels are associated with lower risks of major and postpartum depression, bipolar disorder, and homicide mortality (61). Epidemiological studies have shown associations between aggression, hostility, and antisocial behaviors and poor essential fatty acid status in various populations (62). Over the last century, the altered PUFA composition of our modern diet could be a contributing factor to the high prevalence of conduct problems, deviant activity, and other behavioral issues associated with criminal and violent acts described in the previous chapter.

2.2 Defining polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFAs) are fats that are liquid at room temperature, unlike saturated fats, which are solid at room temperature. The two most commonly known PUFAs are omega-3 (ω-3) PUFAs and omega-6 (ω-6) PUFAs. Certain ω-3 and ω-6 PUFAs are considered essential fatty acids (EFAs) because they cannot be synthesized by the body. Instead, these essential polyunsaturated fatty acids have to be obtained from dietary sources. The two essential PUFAs are linoleic acid (LA), an ω-6 PUFA, and alpha-linolenic acid (ALA), an ω-3 PUFA (63).

LA and ALA are obtained mainly from plant sources like vegetable oils, nuts, and seeds, but can also be obtained from animal source foods. Subsequent longer-chain ω-6 and ω-3 PUFAs come from the biochemical conversion of LA and ALA into new fatty acids, or from animal source foods such as eggs, meat, fish, dairy, and poultry (**figure 2.1**) (63-65). The metabolites, or products, that can be formed from LA and ALA, are non-essential fatty acids. Non-essential PUFAs include ω-3 eicosapentaenoic acid (EPA), ω-3 docosahexaenoic acid (DHA), ω-3 and ω-6 forms of docosapentaenoic acid (DPA), and ω-6 arachidonic acid (AA) (63-65). It is important to obtain sufficient amounts of PUFAs from the diet because they have critical roles in cell membrane structure, cell signaling, epithelial cell function, regulation of gene expression, and neural formation and function (64).

In order to convert ALA and LA precursors into their respective ω-3 and ω-6 products, specific desaturase enzymes are needed to complete these processes. The Δ6-desaturate enzyme is used in the first step for both ω-6 and ω-3 fatty acid metabolism (**figure 2.1**). ALA and LA compete for Δ6-desaturase activity to convert into their immediate products (64). Other ω-3 and ω-6 PUFAs also compete for specific enzymes in order to form new fatty acids (65).

The current recommended adequate intake of LA is 17g/day for men, and 12g/day for women, with no upper limits set (64). When LA intake in healthy men is increased from 15g/day to 30g/day, which raises the LA:ALA ratio from 8:1 to 30:1, there is a 40 to 50 percent reduction in the conversion of ALA and LA into their metabolites (64). Healthy individuals in Western countries have limited synthesis of ALA into EPA. Because the magnitude of the conversions of ALA and EPA into DHA is negligible (66), it is important to obtain sufficient ω-3 PUFAs from dietary sources (67).

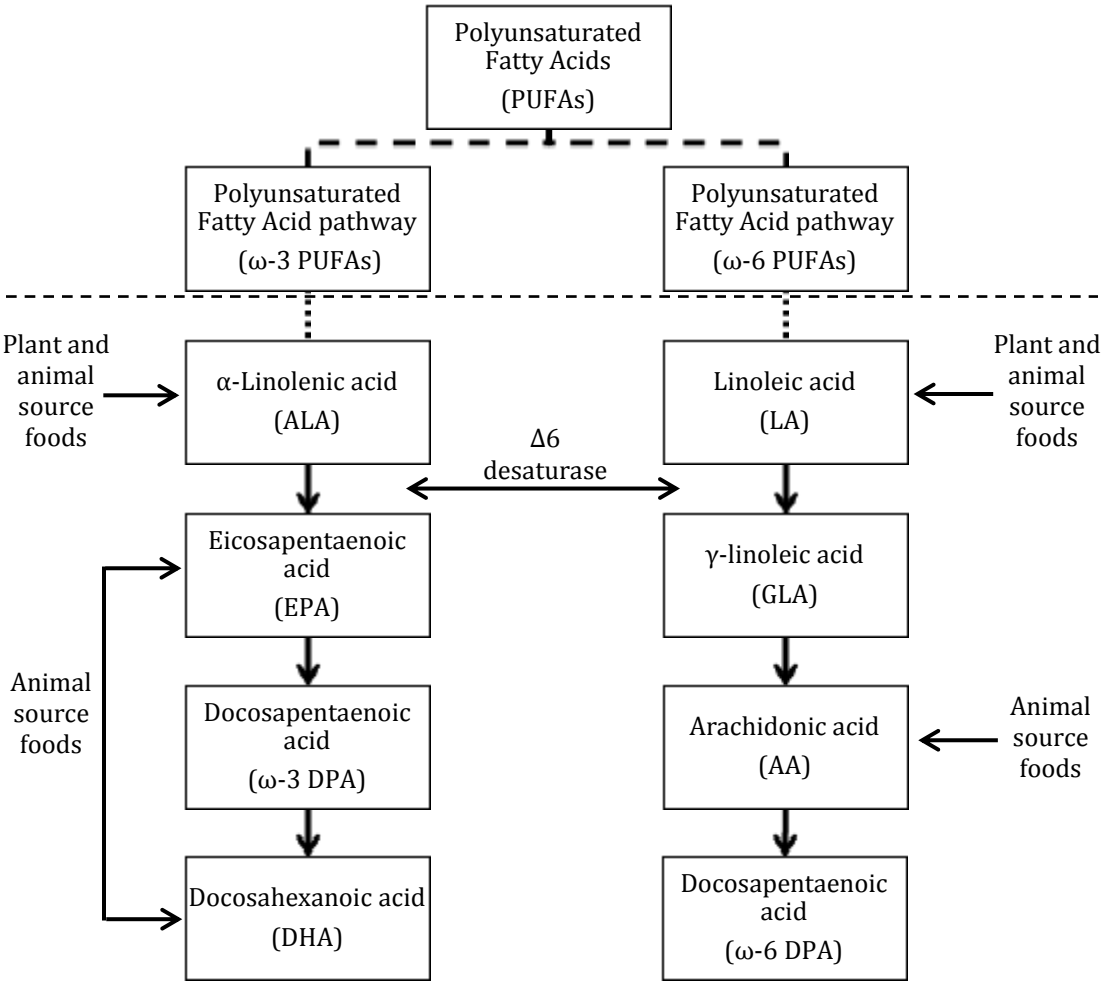

Figure 2.1 Polyunsaturated fatty acid metabolism. Main dietary sources of ALA and LA are plant and seed oils. Other fatty acids in the conversion pathway can also be obtained from animal source foods. Δ6 desaturase is an enzyme responsible for both ω-3 and ω-6 metabolic pathways. It is unknown whether or not the same Δ6 desaturase enzymes used to convert ALA and LA into their subsequent metabolites are the same enzymes used to convert other fatty acids into DHA and ω-6 DPA.

2.3 Dietary sources and importance of omega-3 and omega-6 polyunsaturated fatty acids

Mammals require sufficient dietary sources of ω-3 fatty acids to maintain adequate tissue concentrations. ALA, the precursor for making EPA and DHA, can be obtained from plant sources like linseed, perilla, canola, and flaxseed oils (64, 65, 67). In the absence of ALA, DHA and EPA must be obtained from the dietary sources. Fatty cold water fish (salmon, tuna, and trout) and fish oil supplements are the most abundant sources of pre-

formed DHA and EPA, with lesser amounts also present in the milk and meat of ruminant animals. Neither DHA nor EPA can be found in plant-based foods (64, 67, 68).

Linoleic acid (LA) is an essential ω-6 fatty acid and a precursor for arachidonic acid (AA). LA is used for eicosanoid production (inflammatory molecules), is part of cell membrane structure, and important for cell signaling pathways. AA is involved in decreasing gene expression of proteins responsible for regulating the enzymes involved in fatty acid synthesis. In healthy adults, LA makes up approximately ten percent of total fatty acids content (64). Unlike ω-3 PUFAs, which are mostly found in animal sources and few plant sources, the ω-6 precursor linoleic acid can be readily found in the modern-day food supply. These are abundant in plant sources such as soybean, sunflower, and corn oils, with LA making up over half of the total fatty acid content in these oils (65).

During pregnancy, approximately 600g of essential fatty acids are transferred from mother to fetus (69). The transfer of fatty acids through the placenta for fetal growth is dependent on the maternal plasma levels of EFAs. However, this transfer is not regulated to protect against high ω-6 or low ω-3 fatty acids from maternal stores. The fetus will obtain most of its ω-3 fatty acids from the mother even she has low concentrations of these PUFAs (65, 69, 70).

ω-3 PUFAs like EPA and DHA are important for maintaining normal central nervous system function and structure (**table 2.1**), including the regulation of phospholipid membrane formation of neural tissues (63). Much of the DHA transferred to the fetus is devoted to the brain, which is composed of gray matter (cell bodies of neurons) and white matter (glial cells and myelin sheaths on the axonal projections from neurons). DHA is the main ω-3 fatty acid found in gray matter, making up 15% of total fatty acids composition

(67, 71). DHA and EPA are also components of myelin (72) - fatty acid structures that surround the axons of neurons and help to conduct electrical signals in the brain (63).

DHA and AA are the main components of phospholipid bilayers of neuronal membranes in gray matter (73). These fatty acids, and to some extent LA, influence the fluidity, permeability, and structure of the phospholipid membranes (74). DHA increases fluidity and permeability of membranes, which can impact ion channel function needed for proper neurotransmission (73, 75), the transport of molecules through membranes for intercellular communication (74, 76), and activity of membrane-bound enzymes (73). By modulating membrane fluidity and the function of many neurotransmitters (serotonin, dopamine, acetylcholine, and norepinephrine), DHA can also regulate mood and behavior (73, 76, 77).

Table 2.1 Summary of neurobiological roles for select ω-3 and ω-6 polyunsaturated fatty acids

Polyunsaturated Fatty Acid Types	Roles of Fatty Acids
Omega-3 (ω-3) PUFAs	**Development and maintenance of CNS structure and function**
ALA (α-linolenic acid)	Precursor for subsequent omega-3 PUFAs
EPA (eicosapentaenoic acid)	precursor for DHA Anti-inflammatory actions Component of myelin (white matter)
DHA (docosahexaenoic acid)	Component of myelin (white matter) Main component of gray matter phospholipid membranes Neurotransmitter function and signal transmission Regulation of membrane-bound enzymes Inhibit production of pro-inflammatory factors in brain Protect neural cells from apoptotic death Stimulate neural growth, size, and synaptic development
Omega-6 (ω-6) PUFAs	**Development and maintenance of CNS structure and function**
LA (linoleic acid)	Precursor for subsequent omega-6 PUFAs Neural (gray matter) phospholipid membrane structure Component of myelin (white matter)
AA (arachidonic acid)	Main component of gray matter phospholipid membranes Formation of cell membrane signal transduction messengers Precursor for pro-inflammatory factors

2.4 Polyunsaturated fatty acids in breast feeding and formula-feeding

Once born, the fetus's only sources of ω-3 and ω-6 fatty acids are human breast milk or formula until foods can be slowly introduced months later. The fatty acid profile of human milk is heavily influenced by maternal fat consumption. DHA, which is found in human milk (78), varies in concentration throughout different populations. The variation in breast milk DHA levels can be largely explained by maternal diet (65). DHA concentrations can range from 0.1% to 1.0% or more depending on the mother's intake of fatty fish and other seafood (79). Increasing maternal intake of DHA raises the DHA levels in breast milk (80).

In the last few decades, DHA concentrations in human milk have decreased to less than 0.2%; a 50% decline since the 1970's (81), while the LA content of breast milk has increased (80). If a mother does not have adequate dietary intake of DHA, her breast-fed infant can have low circulating levels of DHA that is akin to infants fed formula lacking DHA (79). ω-6 fatty acids are also found in human milk, and the LA content can range from 6-30% of total fatty acids depending on the amount of LA in the mother's diet (78). In the 1970's, LA made up approximately 7% of total fatty acids in breast milk. Today the LA content of human milk ranges from 12% to 16% of total fatty acids. This increase is attributed to rising consumption of LA-rich vegetable oils in recent years (80).

DHA accumulation still occurs in the first 40 weeks of life, regardless of if the infant was breast-fed or formula-fed. Formula-fed infants have much lower rates of DHA accumulation and lower brain DHA concentrations compared to breast-fed infants (82-87). Even though infant formulas have similar amounts of ALA as human milk, formulas that contain ALA as its only ω-3 source might be ineffectual in supplying adequate DHA to the

infant brain (87). It is still unknown whether or not the conversion of ALA can meet the infant's DHA and EPA requirements for rapid neural growth during this time (64). Astrocytes in infant brains have been shown to produce DHA and AA from their precursors ALA and LA, respectively (88), but dietary ALA has been shown to be ineffective in restoring cerebral DHA concentrations when deficient in ω-3 fatty acids (89). Adequate cerebral DHA concentrations could depend more on intake of dietary DHA than its precursor ALA in post-natal feeding.

2.5 Maintaining omega-6 and omega-3 balance

One's diet can alter the fatty acid composition of the brain (69). 50-60% of the brain is composed of lipids, and PUFAs make up about 30% of total lipid content. Both ω-6 and ω-3 PUFAs are incorporated into the plasma membranes of neurons during development (63). Maintaining a balance between LA and ALA is critical for determining how much AA, EPA, and DHA is inserted into different tissues, especially for people who have low intakes or are devoid of these fatty acids (64). Maternal deficiencies in dietary ω-3 PUFAs during pregnancy and lactation can cause reductions of DHA and increased synthesis and deposition of ω-6 PUFAs like AA in the brains of their offspring (90-94). Imbalances in the ω-6:ω-3 ratio could occur because intakes of either LA or ALA are too high, intakes of a particular fatty acid is too low, or some combination of these two situations. Optimal ω-6:ω-3 ratios could also vary at different life stages, depending on the physiological needs at the time (64).

In general, tissue levels of ω-6 fatty acids are usually low, with 1% of total energy coming from LA. This means that the tissue concentrations of ω-6:ω-3 rations (particularly

LA:ALA) are typically in a ratio of 2:1 or lower. This ratio is optimal for pregnant women because it supports higher levels of DHA deposition into the brain during fetal development. Since both ω-6 and ω-3 PUFAs are incorporated into neuronal phospholipid membranes, the ω-6:ω-3 ratio is thought to determine neuronal membrane fluidity and the function of membrane-bound proteins (63). If this ratio is suboptimal due to high intakes of ω-6 fatty acids - LA in particular - the conversion of ALA into DHA and EPA is inhibited. This can result in a reduction of DHA accumulation in the brain (65). The amount and types of ω-6 and ω-3 fatty acids obtained from the diet can determine how much DHA is obtained and utilized for fetal brain development.

2.6 ω-6:ω-3 imbalances and implications in neurological and psychological abnormalities

Consuming essential fatty acids can regulate learning, memory, and behavior. The central nervous system (CNS) is made of a variety of fatty acids. Of those fatty acids, the majority of the brain gray matter is composed of DHA, which accumulates most rapidly in the brain during gestation and post-natal development (65, 69). DHA accumulation occurs rapidly during the prenatal period and the first two years of life (63). All of the ω-3 fatty acids that are needed for fetal development are transported to the fetus from maternal circulation via the placenta. Varying dietary intakes of ω-3 and ω-6 fatty acids can alter the concentration of DHA in the brain. Plasma levels of DHA in the fetus are heavily influenced by maternal diet. Higher levels of circulating DHA in mothers and infants at the time of birth are associated with better neural development and long-term benefits for mental development in early childhood (69, 70, 95-98).

Because of the rapid periods of neural growth and DHA accumulation during prenatal development and into the first couple years of life, the infant brain is more susceptible to ω-3 deficiencies compared to a mature brain. Insufficient DHA in the brain can interfere with proper neurological function (99). To compensate for decreased concentrations in neural DHA during this time, more ω-6 DPA is incorporated into neural membrane to maintain total membrane PUFA content (64). Once this critical period passes, increasing dietary sources of PUFAs might not help with improving outcomes for neurological or psychological disorders (63, 65, 70, 100). Numerous studies have shown that decreased ω-3 intake or imbalances in ω-6:ω-3 ratios can lead to behavioral and cognitive deficits, neurological abnormalities, poor growth in infants and children (64), degenerative neurological diseases, and psychiatric disorders (63). Some studies (63), but not all (101), have demonstrated a positive relationship between maternal intake of dietary ω-3 PUFAs during pregnancy and later cognitive development of her child. Low levels of DHA in plasma and blood lipids have been linked to poor neural development in infants and children (65).

Cross-sectional and clinical studies have implicated the role of ω-3 and ω-6 PUFAs in the pathophysiology of many major psychiatric disorders (67, 102-104). Deficiencies in EPA and DHA are associated with psychological issues such as bipolar disorder (105-107), anxiety disorder (108), ADHD (109-112), schizophrenia (107, 113-115), depression (105, 116-120), and borderline personality disorder (121). Greater intake of fish high in ω-3 PUFAs is associated with a lower prevalence of depression and bipolar disorder (122-129). Diets high in ω-6 PUFAs also suppress DHA accretion, a process that is important for

regulating these behaviors (130). For example, high intakes of LA in men (19.32mg/day) was associated with 2.3 higher odds of suffering from severe depressed mood (131).

2.7 Changing dietary patterns and fatty acid composition of the U.S. diet in the United States in the 20th and 21st centuries

2.7.1 Fatty acid composition of the U.S. diet: 1909-1999

For millions of years, hominids consumed diets high in seafood and other ω-3 PUFA-rich foods, with only minute amounts of seed oils high in ω-6 PUFAs in the diet. Recently, the human diet has changed dramatically from what it was throughout much of human evolution (132-135). Not only has the total consumption of dietary fats increased, but the types of fats consumed have shifted away from saturated fats in favor of polyunsaturated oils (**figure 2.2**). Between 1909 and 2006, total fat availability in the U.S. diet increased from approximately 120 grams to 180 grams per person per day. The 4-fold rise in the availability of polyunsaturated fats (from 10 grams to 40 grams/person/day) was a major contributor to total rise in fat consumption. During the same time, saturated fat availability remained fairly constant, while moderate increases in monounsaturated fats contributed to the remainder of the total increase in fat consumption.

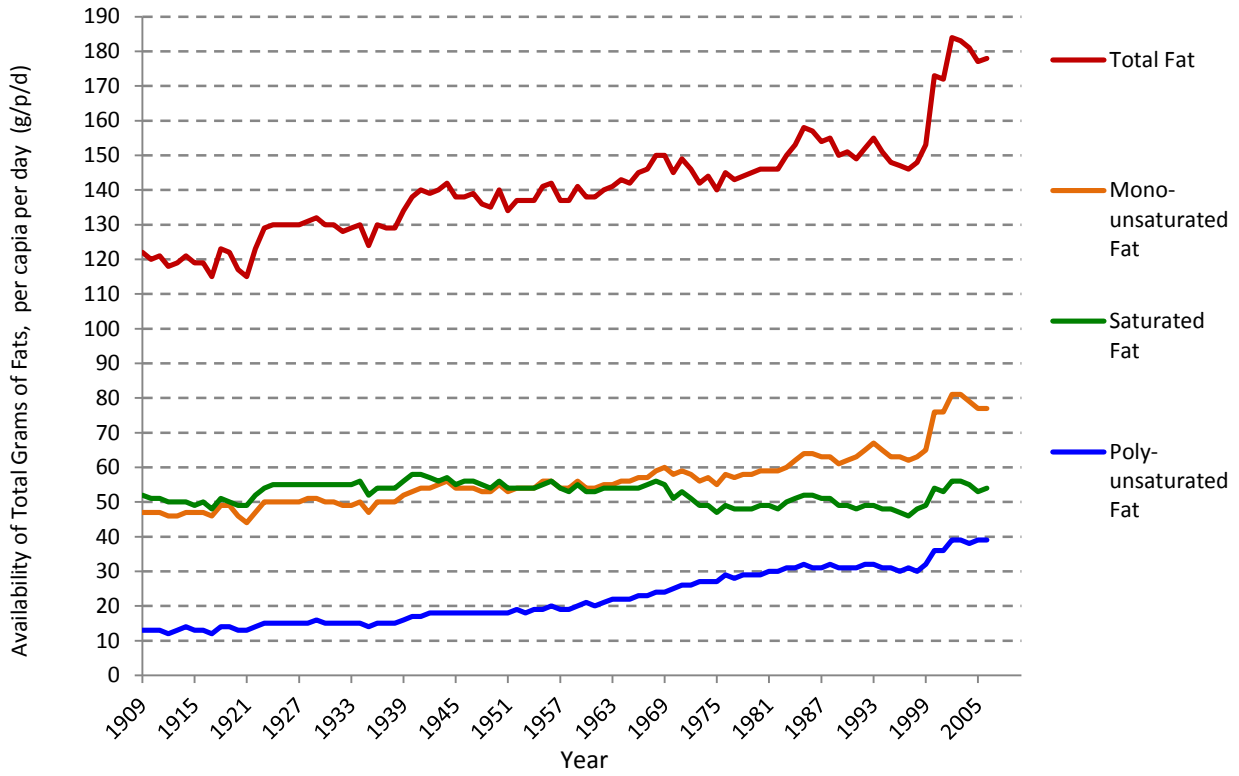

Figure 2.2 Total availability of dietary fats (grams) in the U.S. food supply, per capita per day (g/p/d), 1909-2006. Data calculated by USDA/Center for Nutrition Policy and Promotion. Calculations based on ERS estimates of per capita food available for consumption. Source: Economic Research Service (ERS), U.S. Department of Agriculture (USDA). Food Availability (Per Capita) Data System. http://ers.usda.gov/data-products/food-availability-(per-capita)-data-system.aspx. Last updated Feb. 1, 2013.

Despite Americans decreasing total fat consumption between 1965 and 1995 from 45% to 35% (136), consumption of polyunsaturated fats in favor of other fats has increased. The rising consumption of polyunsaturated fats can be attributed to vegetable oils - namely soybean oil. From 1975 to 2007, worldwide rapeseed and soybean oil production increased significantly (137). Over 80% of worldwide vegetable oil production is due to the food market demands, and not biofuel or industrial needs, as is commonly thought. Not only is the U.S. one of the top producers of soybean oil in the world, it is also one of the top consumers. Compared to other major producers of soybean oil, the U.S.

exports very little of its total soybean oil production, the majority of it being used in the food market. Between 2004 and 2008, soybean oil production in the U.S. represented approximately 88.4-90.0% of total vegetable oil production, ranging from 8.78-9.33 million tons per year, exporting only about 7-12% (1.7 million tons) per year (137).

Due to the rise in vegetable oil consumption over the past century, the modern food supply has lower levels of ω-3 fatty acids EPA, DPA, and DHA, and higher levels of LA, compared to the food supply of the early 1900's (138, 139). The optimal diet should have an ω-6:ω-3 PUFA ratio between 2:1 and 1:1, but current ratios have increased, reaching as high as 30:1 (135, 140). In the early 2000's, soybean oil contributed approximately 20% of all calories in the median US diet. Moreover, almost 9% of total daily calories were attributed to LA intake alone. This amount is three times higher than it was a century earlier, skewing the ω-6:ω-3 ratio towards ω-6 (141, 142). The advice to replace other dietary fats with polyunsaturated fats like vegetable oils, which are high in ω-6 PUFAs, was done in an effort to lower cholesterol levels among patients at risk for heart disease. This recommendation was made without considering how it might affect ω-3 metabolism since there was little information on the importance of DHA until recently (65).

Blasbalg et al. examined the changes in fatty acid composition and availability of foods and oils between 1909 and 1999. During this time, the fat sources of commonly eaten foods changed drastically. Whole milk, eggs, beef, butter, chicken, turkey, and pork produced through traditional methods in 1909 had higher levels of ω-3 fatty acids DHA, DPA, EPA, and ALA, and lower levels of ω-6 fatty acids AA and LA, compared to the same foods produced using current 1999 methods. Additionally, during this 90-year span, beef tallow, margarine, lard, and shortening had large increases in LA content (138). While

there was a decrease in butter and lard consumption during this time, margarine saw a 1038% increase in per capita consumption, while shortening and beef tallow had 170% and 371% increases, respectively. An increase in oil consumption also occurred during this time period. Many vegetable and seed oils are high in ω-6 fatty acids, especially soybean, cottonseed, safflower, sunflower seed, and corn oils (**figure 2.3**). Soybean oil consumption increased 1163-fold between 1909 and 1999. Soybean oil also had a 1238-fold increase in its total contribution to the US diet, increasing from 0.006% to 7.38% of total calories during this time (138).

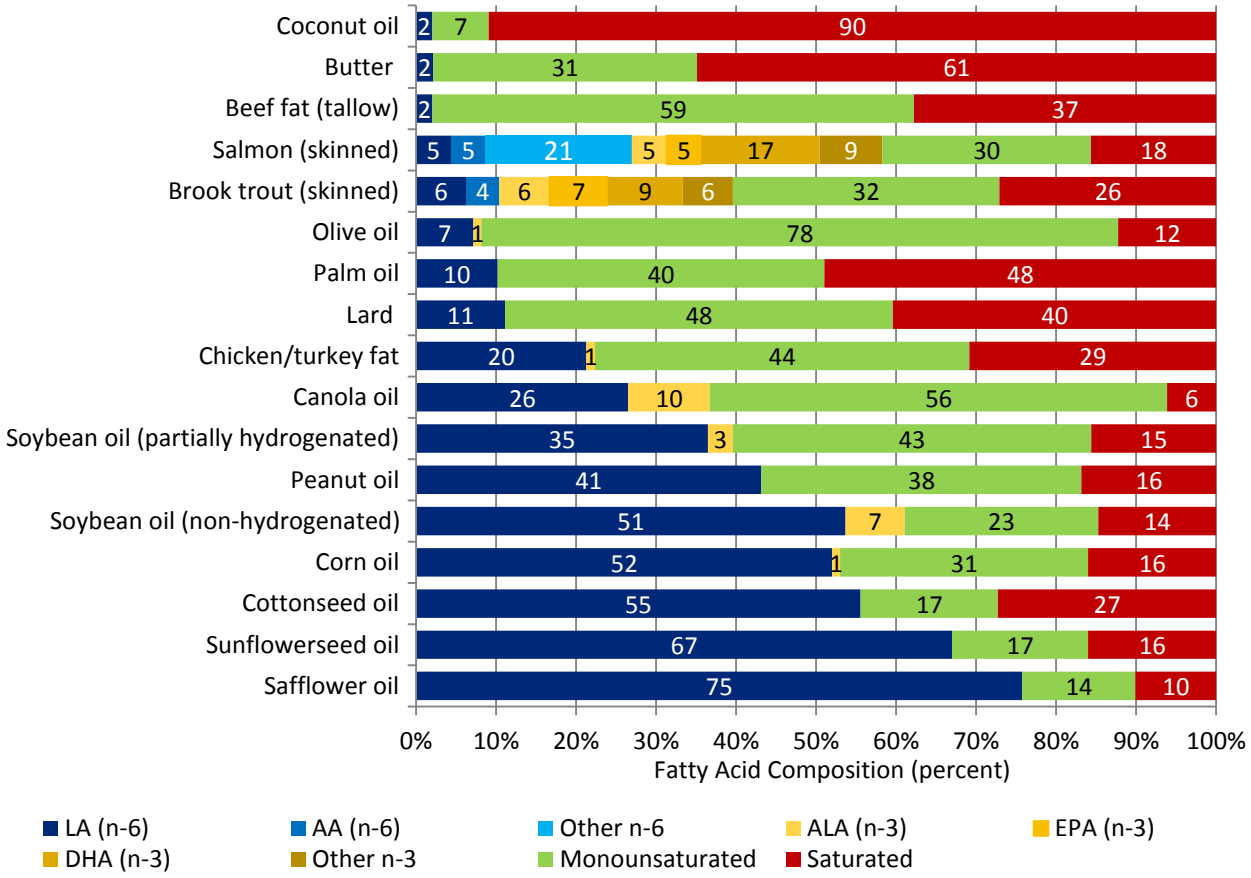

Figure 2.3 Fatty acid compositions of commonly used fats and oils, by percentage of total weight. 'Other fatty acids' includes those not listed (unsaturated and both naturally occurring and manufactured trans-fatty acids). Data source: http://web.pdx.edu/~wamserc/C336S06/fat.pdf

In the same time period, the availability of dietary LA and ALA from various foods increased, but AA, EPA, DPA, and DHA availability either decreased or stayed the same. Due to the increase in dietary ω-6 fatty acid content - mainly from LA - the total ω-6:ω-3 ratio increased from 5.4:1-6.7:1 in 1909 to 9.6:1-10.0:1 in 1999 (138, 139), with the LA:ALA ratio increasing from 6.5:1 to 10.0:1 in the same timeframe (138). In 1985, the ratio was as high as 12.4:1, but this ratio decreased to approximately 10.6:1 in 1994, which coincides with a 5-fold increase in canola oil use since the 1990's (139). The biggest dietary change from 1909 to 1999 was the use of soybean oil as a significant dietary fat and major contributor of LA and ALA to the US diet. In 1909, soybean oil was an insignificant part of the U.S. diet, contributing less than 0.1% of total dietary LA (ω-6) and ALA (ω-3). By 1999, it became a primary source of both dietary LA (43% of total LA consumption) and ALA (45% of total ALA consumption). The increased use of soybean oil amplified the total intake of LA 568-fold, replacing all other dietary sources of LA. It also increased ALA availability by more than 1000-fold, displacing diary, other fats, and pork as the primary source of ALA (138).

Since there were little changes in the consumption other dietary fatty acids, less ω-3 PUFAs in relation to ω-6 PUFAs were being incorporated into cells throughout the body. ω-3 fatty acids were being displaced by high intakes of LA, even with increased in ALA intake as well. The estimated percentage of ω-3 fatty acids in human tissue decreased from 31.28-36.81% in 1909 to 22.95% in 1999, a total decrease in tissue ω-3 of 27-38% (138). Similar changes in tissue fatty acid composition were reflected in studies on human breast milk and tissues. In U.S. women, the amount of LA in breast milk increased from 6-7% of total fatty acids in 1945, to 15-16% of total fatty acids in 1995 (143). The LA content of adipose

tissue in U.S. men and women also increased from approximately 6% to 18% between 1960 and 1986 (144-146). Infants who used formulas with high LA levels (6.7% of total calories) had decreased tissue levels of ω-3 PUFAs compared to infants who were fed formulas with low LA levels (1.7% total calories). Infants fed low-LA formulas also had higher membrane erythrocyte concentrations of EPA and DHA (228% and 29%, respectively) (147).

2.7.2 Fatty acid composition of the U.S. diet: 1980-2012

The rise in soybean oil in the second half of the 20th century greatly contributed to the changes in fatty acid composition of human tissues by increasing the availability of dietary LA. Dietary ω-3 content of many foods did not decrease enough in comparison to the increase in ω-6 content to account for the changing ω-6:ω-3 ratio (138). Most likely, large increases in dietary LA displaced ω-3 fatty acids like EPA, DPA, and DHA, decreasing the ω-3 composition of human tissues and breast milk (138). A possible explanation for these changes is that high levels of LA in the body impair the conversion of ALA to subsequent ω-3 products by competing for the active sites of delta-6-destaruate enzymes. ALA and LA both require this enzyme to become subsequent products in fatty acid metabolism. This competition impairs the conversion of ALA into EPA, DHA, and other ω-3 fatty acids. The incorporation of these ω-3 PUFAs into tissue membranes might also be impaired due to competing against LA for the same positions in cell phospholipid bilayers of cells throughout the body (138).

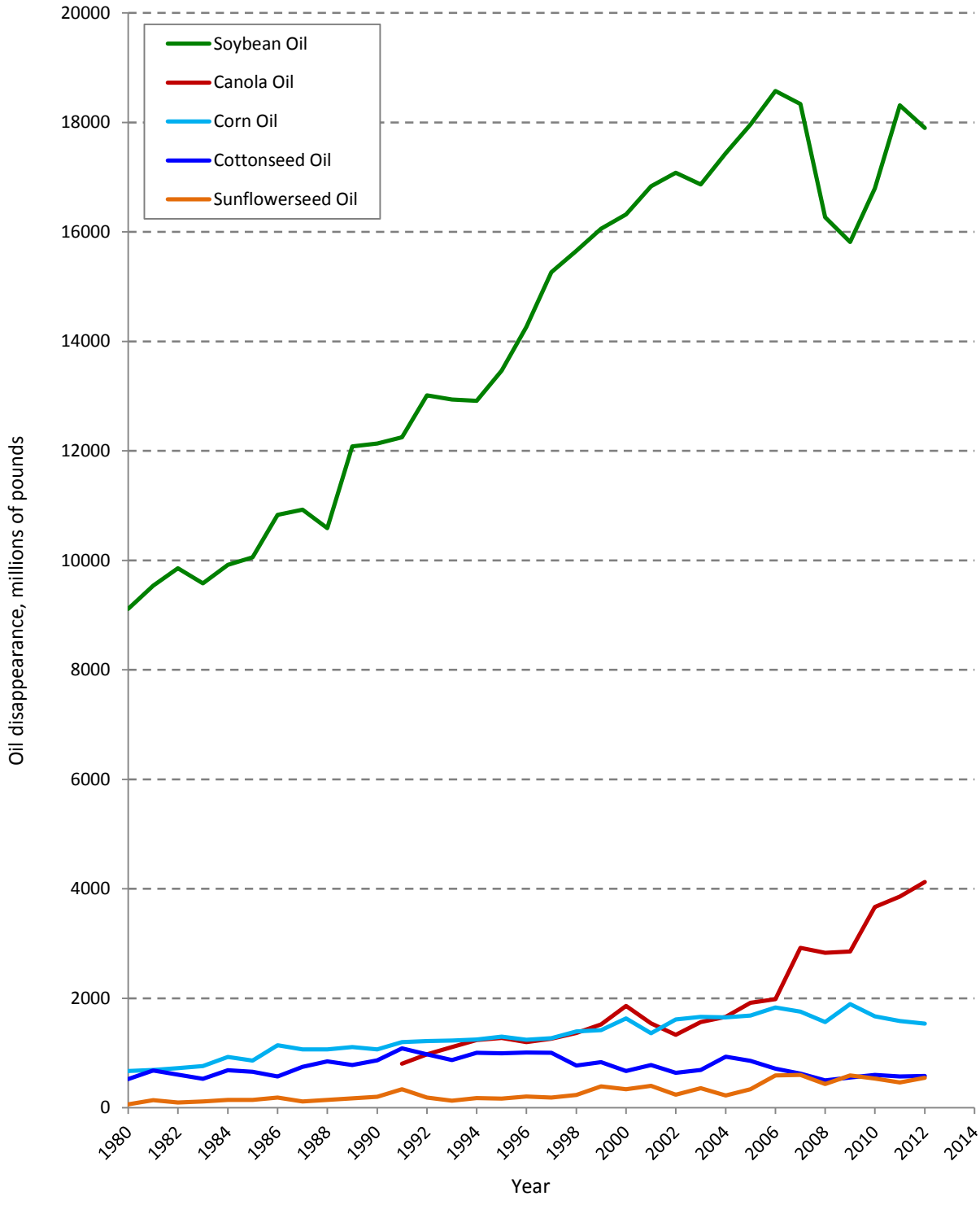

Figure 2.4 Annual disappearance data for plant-based oils (million pounds) in the U.S., 1980-2012. Tallow was measured as a direct via ERS calculations; factory use of lard and other fats were measured a proxy for domestic consumption in other food products; data for 2000-2002 are ERS estimates. Values are not adjusted for waste. Data source: U.S. Census Bureau, Fats and Oils: Production, Consumption and Stocks. Available at: http://www.ers.usda.gov/data-products/oil-crops-yearbook.aspx#.UxtlqYVnjFB

The use of food disappearance data shows that between 1980 and 2010, there was a rapid increase in the use of plant-based fats in food manufacturing and at the individual level. The vast majority of the increase in plant-based fats can be attributed to the rise in soybean oil usage. Between1980 and 2012, the total annual use of soybean oil increased almost 2-fold compared to other commonly used oils (**figure 2.4**). When comparing annual per capita disappearances (in pounds) for fats and oils, the disappearance for most other fats and oils has stayed at or less than five pounds per year (**figure 2.5**). In contrast, the annual per capita soybean oil disappearance was 8-fold higher in 1980 compared to other commonly used fat sources. By the 21st century, the disappearance of soybean oil was 10- to 12-fold higher than other fats and oils.

The use of soybean oil in food manufacturing also rose between 1980 and 2010. Disappearance data for these categories reveals that soybean oil was the primary source of fat for salad and cooking oils (**figure 2.6**). The use of soybean oil in salad and cooking oils has steadily increased over time, while most other fats remained fairly stable at much lower amounts. By 2010, the use of soybean oil was four-times higher than corn oil, the second most commonly used salad/cooking oil. Soybean oil was also the main source of fat for baking and frying oils during the same time period (**Figure 2.7**). In 1980, the use of soybean oil was about three times greater than beef tallow, and by 2010, the use of soybean oil increased, while all other common fats decreased. The large spike in 2000, and the subsequent decline in 2006, is also attributed to the use of soybean oil in this food manufacturing process. However the net use of soybean oil for baking and frying was still four-fold higher compared to other oils and fats used in food manufacturing.

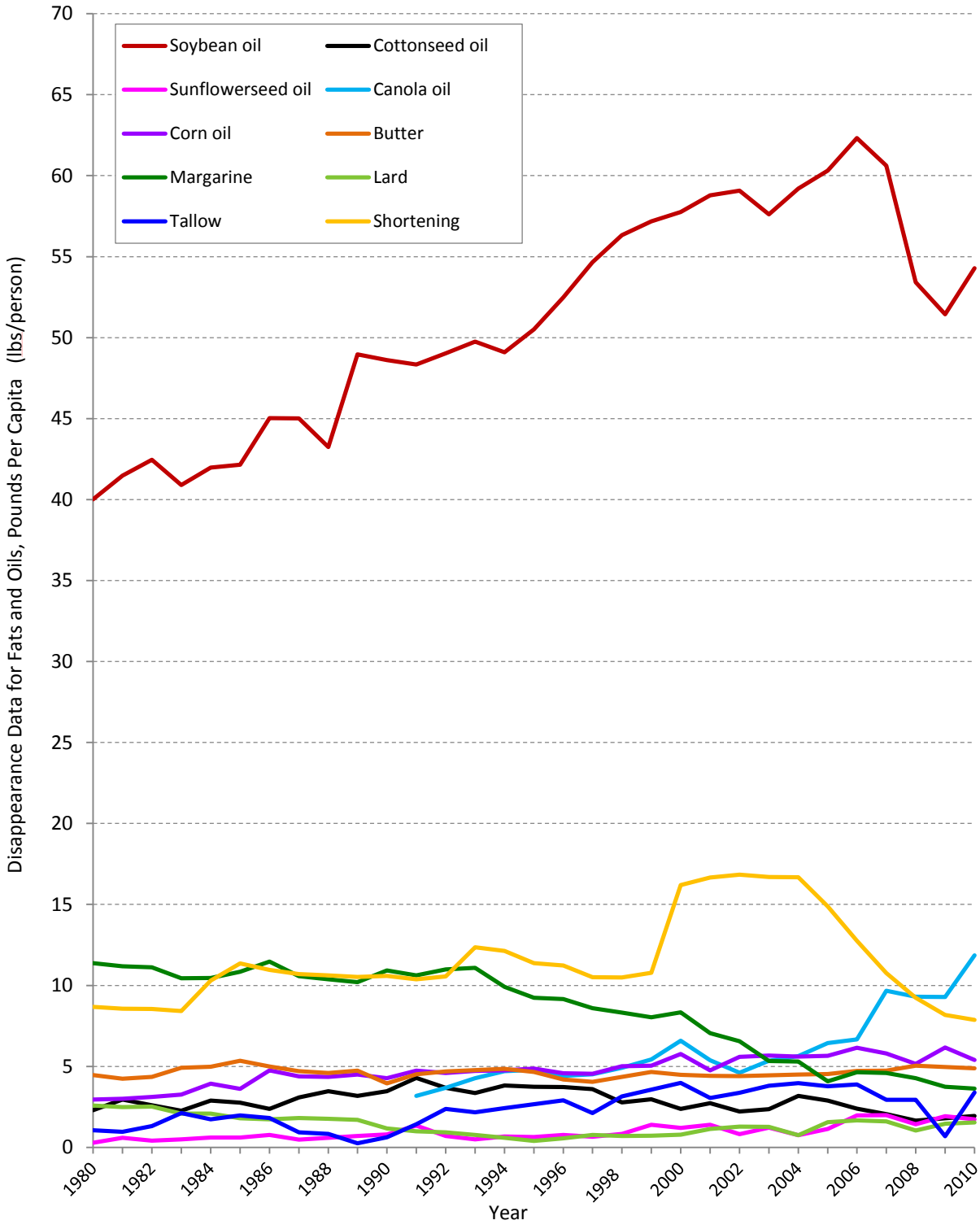

Figure 2.5 Annual per capita disappearance data for fats and oils (pounds) in the U.S., 1980-2010. Per capita calculations are based on U.S. Census data for all residents in the U.S. on July 1st of every year. Shortening and margarine consist of various plant-based oils. Values are not adjusted for waste. Data source: U.S. Census Bureau, Fats and Oils: Production, Consumption and Stocks. Available at: http://www.ers.usda.gov/data-products/oil-crops-yearbook.aspx#.UxtlqYVnjFB

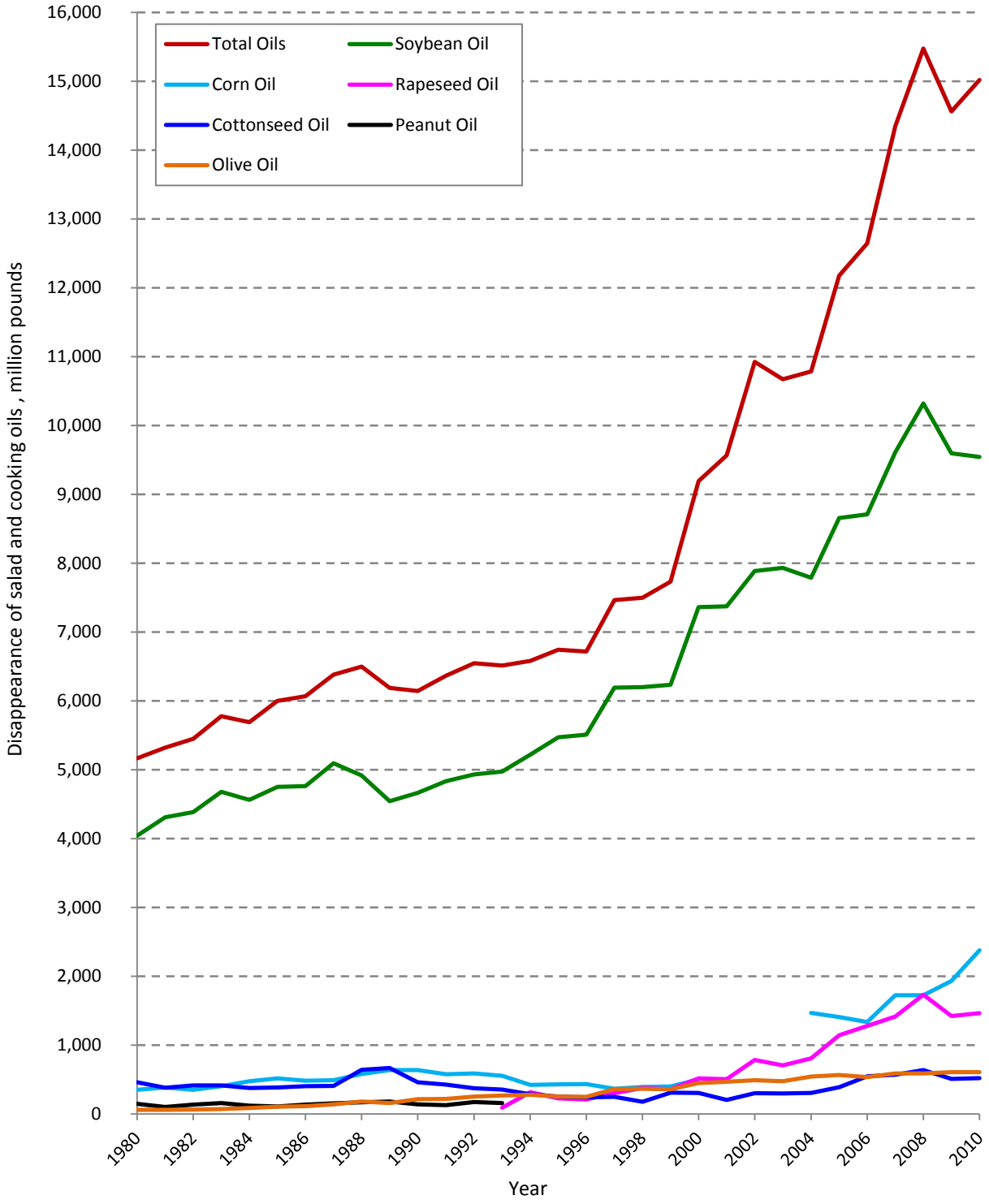

Figure 2.6 Annual disappearance data for salad and cooking oils used in food manufacturing (millions of pounds per year) in the U.S., 1980-2010. Total fats include small amounts of other fats and oils not listed. Missing values indicate withheld data to avoid disclosure of information by manufacturers.
Data source: U.S. Census Bureau, Fats and Oils: Production, Consumption and Stocks. Available at: http://www.ers.usda.gov/data-products/oil-crops-yearbook.aspx#.UxtlqYVnjFB

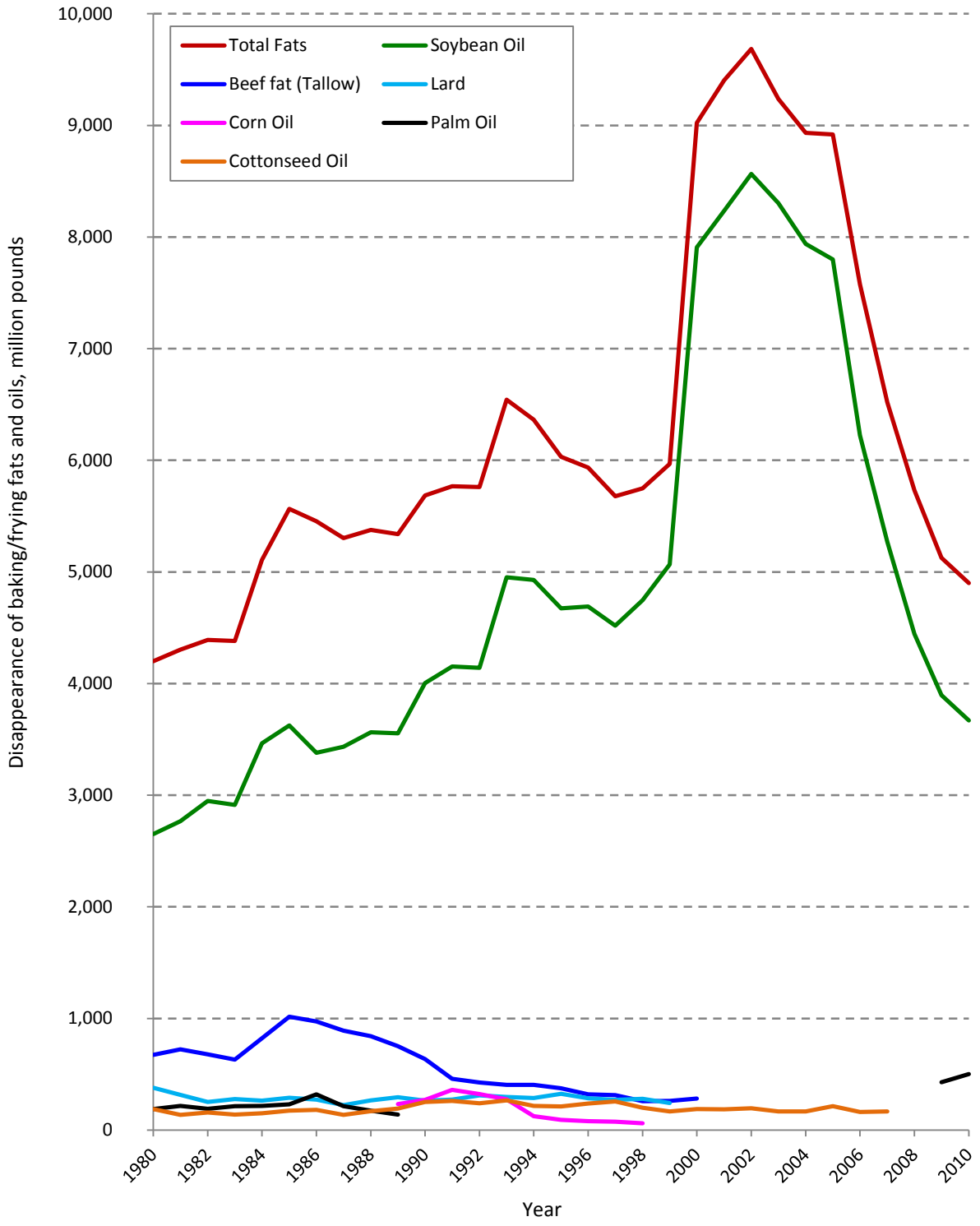

Figure 2.7 Annual disappearance data for baking and frying fats and oils used in food manufacturing (millions of pounds per year) in the U.S., 1980-2010. Total fats include small amounts of other fats and oils not listed. Missing values indicate withheld data to avoid disclosure of information by manufacturers. Data source: U.S. Census Bureau, Fats and Oils: Production, Consumption and Stocks. Available at: http://www.ers.usda.gov/data-products/oil-crops-yearbook.aspx#.UxtlqYVnjFB

Not only is soybean oil the overwhelming primary source of salad and cooking oils, but the annual per capita use of salad and cooking oils has more than doubled between 1980 and 2010, while the use of baking/frying fats and solid fats have either declined or remained stable at much lower levels (**figure 2.8**). Taken together, these trends reveal how on average, Americans have been using disproportionately increasing amounts of soybean oil as their main dietary source of fat. This is concerting because soybean oil, compared to animal source fats and some other plant-based oils, is high in linoleic acid (**figure 2.3**), which can affect tissue ω-6:ω-3 ratios as previously suggested.

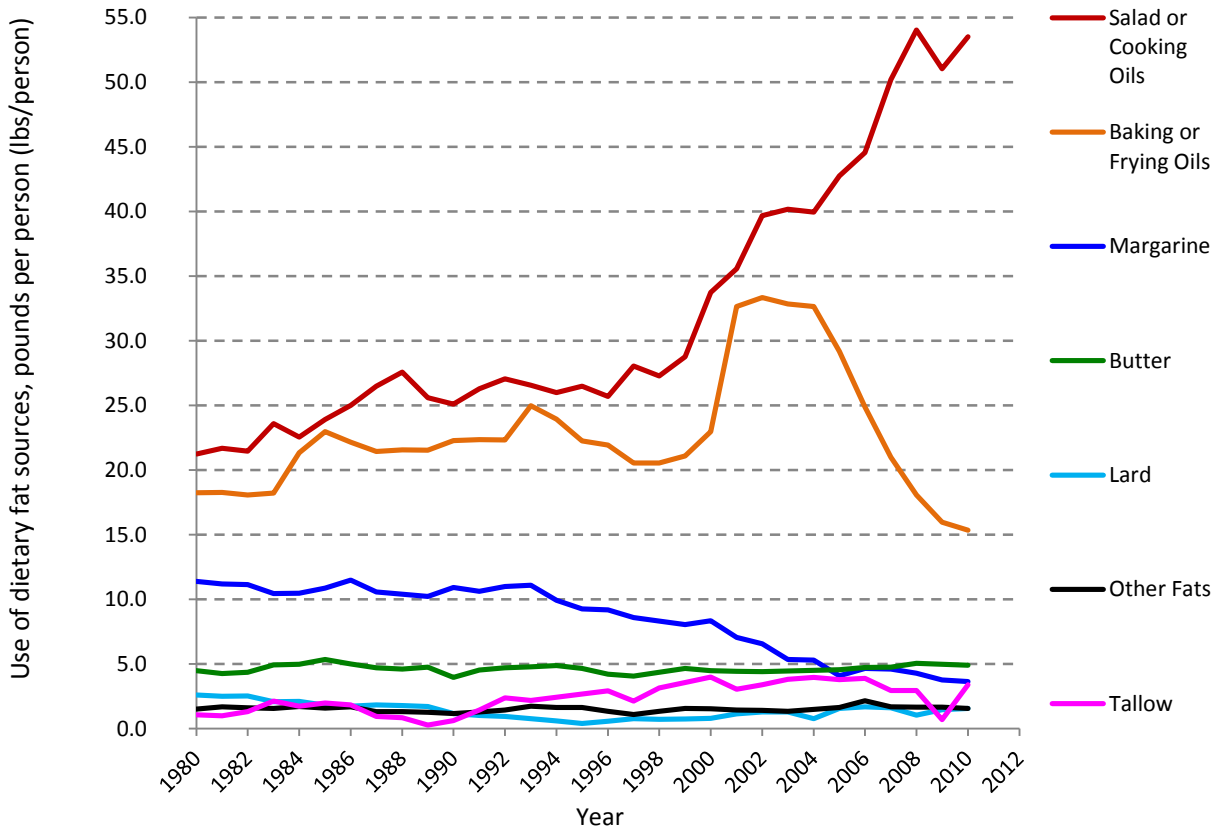

Figure 2.8 Per capita consumption of dietary sources of fats (pounds) in the U.S., 1980-2010 (lbs/p/y). Tallow was measured directly via ERS calculations; factory use of lard and other fats were used as a proxy for domestic consumption in other food products; data for 2000-2002 are ERS estimates. Values are not adjusted for waste. Data source: U.S. Census Bureau, Fats and Oils: Production, Consumption and Stocks. Available at: http://www.ers.usda.gov/data-products/oil-crops-yearbook.aspx#.UxtlqYVnjFB

2.8 Summary

Based on the data presented here, the increased use of soybean oil in the U.S. diet over the past century has contributed to drastic shifts in the fatty acid composition of our diet. The rising use of soybean oil as a primary fat source since the beginning of the 20th century has introduced higher levels of linoleic acid into the average American diet, influencing the PUFA composition of cell membranes throughout the body and central nervous system. Higher linoleic acid competes with ω-3 PUFAs for integration into cell membranes, impacting cellular function. Such changes can have implications for altered neuronal function, and consequently, abnormal behavioral or psychological outcomes in childhood and adulthood.

CHAPTER 3: BIOLOGICAL PLAUSIBILITY FOR THE LINK BETWEEN NUTRITION AND CONDUCT DISORDERS, JUVENILE DELINQUENCY, AND ANTISOCIAL BEHAVIORS

3.1 Overview

There has been a long-standing debate over the etiology of aggressive behaviors and conduct problems in childhood and adolescents, but only recently have biological mechanisms been implicated as a contributing factor (50). Specific genetic mutations, brain functioning patterns, and childhood neuropsychological or cognitive deficits have already been implicated in escalating the risk of criminal activity in later life (148-152). While genetics are thought to contribute to about half of the variance in antisocial behaviors - more so for life-course persistent offenders than for adolescent-limited offenders - environmental factors also play a large role (45, 151, 153-155). Some of these cognitive and psychological deficits are thought to be caused by several complications during fetal or child development (149, 151, 156).

3.2 Biological plausibility of ω-3 PUFAs in neurological development and behavior outcomes

Abnormal aggressive behaviors can be attributed in part to psychological, neurological, and neurochemical dysfunctions (20, 21). Many youth who display aggressive behaviors or conduct problems frequently have deficits or distortions in cognitive abilities (1). Individuals who have both APD and anxiety disorders have a greater number of serious criminal convictions (homicide, attempted homicide, and physical aggression) compared to those who only have APD, even though the average number of total offenses remains similar (157). Impulsivity, a characteristic of aggression, antisocial personality disorder, psychopathy, delinquency, and a comorbidity of conduct disorder, is argued to be the most

important behavior for predicting the development of criminality (158-160). Male violent offenders who meet the diagnostic criteria for both APD and psychopathy have significantly reduced volumes of gray matter in brain regions associated with the processing of morality, empathy, and guilt, when compared to APD-only violent offenders and non-offenders without APD or psychopathy (161). Because essential fatty acids are pertinent for neural formation and cognitive development (162), omega-3 fatty acid deficiencies can represent a risk factor for psychopathologies (67) in addition to having a major role in aggression, impulsivity, and criminal outcomes.

Stressors, such as poor diet quality in the early stages of life, can lead to organizational changes in brain formation and maturation. Perinatal nutritional status can influence the severity of psychiatric disorders in subsequent generations (163). Neurological changes that can arise from nutritional inadequacies during this critical period include dopaminergic and serotonergic abnormalities, reduced glucose metabolism in the brain, and deficits in structural components of the brain (**figure 3.1**). Fatty acids, specifically omega-3 PUFAs, are implied in the functional maintenance of these neurological processes that have been linked to many of the behavioral outcomes discussed so far. Gender differences in fatty acid metabolism might also contribute to the varying psychiatric outcomes seen in people with conduct disorders or behavioral problems.

3.2.1 ω-3 PUFA deficiencies and neurological mechanisms: dopamine

Changes in dopaminergic enzyme and receptor function can increase the risk for abnormal behavioral outcomes. Infants with a copy of the 7-repeat allele for dopamine D4 receptor (DRD4) showed higher risks of aggression (164), CD and ODD (165) in adulthood.

In boys, lower levels of peripheral dopamine-beta-hydroxylase (166), an enzyme necessary for the conversion of dopamine into norepinephrine and the control of anxiety, is associated with overt aggression.

Animal models have been useful for investigating dopaminergic changes that occur in the absence of sufficient ω-3 fatty acid intake. Deficiencies in ω-3 intake can lead to reduced dopamine release, transportation, and receptor expression (93, 167, 168). Rodent offspring from dams who suffered from perinatal ω-3 deficiencies have impaired dopamine synthesis and neurotransmission in the hippocampus, cortex, amygdala, and striatum, in addition to impaired microglial activation in the striatum (168). When the ω-3 deficiency is due to a lack of dietary ALA, there are reductions in dopamine synthesis and dopamine D2 receptor formation in the frontal cortex of rats at all ages (90, 93). ALA deficiencies during pre- and post-natal development also lead to higher dopamine availability in dorsal striatal regions in the brains of adolescent rats, but not adult rats. Higher dopamine synthesis in the striatum corresponds to increases in hyperactivity and impulsive behavior in these rats (90).

Re-introducing ω-3 fatty acids during different developmental stages has varying effects on restoring proper brain function. Rats fed salmon oil have 40% more dopamine and greater dopamine-receptor binding in the frontal cortex compared to control rats fed peanut and rapeseed oils (92). When offspring of dams that experienced ω-3 deficiencies during prenatal development were given sufficient ω-3 during lactation, dopamine synthesis and transmission were restored. When dietary ω-3 PUFAs are reintroduced during the weaning period, membrane fatty acid composition was only partially restored, and dopamine neurotransmission processes were not restored (91). The different

outcomes based on the various timings of dietary interventions in restoring dopaminergic function suggests that irreversible neural changes can occur during lactation in absence of ω-3 of dietary PUFAs (91).

3.2.2 ω-3 PUFA deficiencies and neurological mechanisms: serotonin

Low serotonin activity or abnormal serotonergic function has been implicated in many behavioral outcomes. Reduced concentrations of serotonin can result from periods of poor diet quality, leading to increased impulsivity and aggression (169, 170). Men with pedophilia have depletion of total ω-3 and DHA fatty acids, and increases in total ω-6:ω-3 and AA/EPA ratios. Lower DHA levels in these men correlated to higher impulsiveness (171). First-degree relatives of persons with serotonin system abnormalities have a higher risk of experiencing impulsive aggression (172). Boys who scored high on measures of covert hostile and aggressive behavior had lower measures of peripheral serotonin metabolism compared to boys who were covertly aggressive or who displayed no signs of aggression (173).

Deficiencies in DHA and total ω-3 PUFA reductions can alter the serotonergic activity that is linked to hostility, aggression, and impulsive behaviors (93, 171, 174). Animal studies have suggested the role of ω-3 PUFAs in proper serotonergic function. ω -3 deficiencies can increase serotonin turnover (breakdown and reuptake) in all brain regions, especially in the frontal cortex, hypothalamus, and ventral striatum (94). Administration of sufficient ω-3 PUFAs can re-regulate normal serotonin turnover (94, 175) and reverses poor serotonin neurotransmission in the hippocampus and frontal cortex (174, 176) brought about by dietary ω-3 PUFA deficiencies. The addition of dietary

ω-3 PUFAs can also ameliorate anxiety-related behaviors in mice without serotonergic function due to the lack of serotonin receptors (177).

3.2.3 ω-3 PUFA deficiencies and neurological mechanisms: glucose metabolism

Reduced glucose metabolism in the prefrontal cortex is associated with impulsivity (58, 158, 178) and under-arousal of the autonomic nervous system. These issues are potential underlying factors in developing CD (25). Young rats fed diets deficient in ω-3 PUFAs have decreased GLUT1 gene expression in the cerebral cortex, a gene that is important for glucose transport in cells (179). Supplementing DHA-depleted rat brain endothelial cells with EPA or DHA, but not AA, increases glucose transport in these cells by 50% and 35%, respectively, by increasing GLUT1 expression (180).

3.2.4 Structural changes in brain and abnormal behavioral development

Abnormalities in a wide range of gray and white matter structures in various brain regions are also implicated in antisocial behaviors, social problems, and conduct disorders, (25, 181-185). Adolescents with conduct disorders can have white matter abnormalities (myelination, axon density, axon diameter, axon bundling, or membrane permeability) in many regions: frontal and temporal lobes, parietal-orbital and cortical-thalamic connections (186), and sagittal striatal tracts (187). Youth at high risk for psychotic behavior can have decreased axon bundling in brain regions associated with social development (188). Both gray matter and white matter contain a significant amount of DHA under normal conditions. Since ω-3 fatty acids are required for proper myelin and cell

membrane formation in gray matter and white matter, the aforementioned structural alterations may be partly attributed to ω-3 PUFA deficiencies or ω-6:ω-3imbalances.

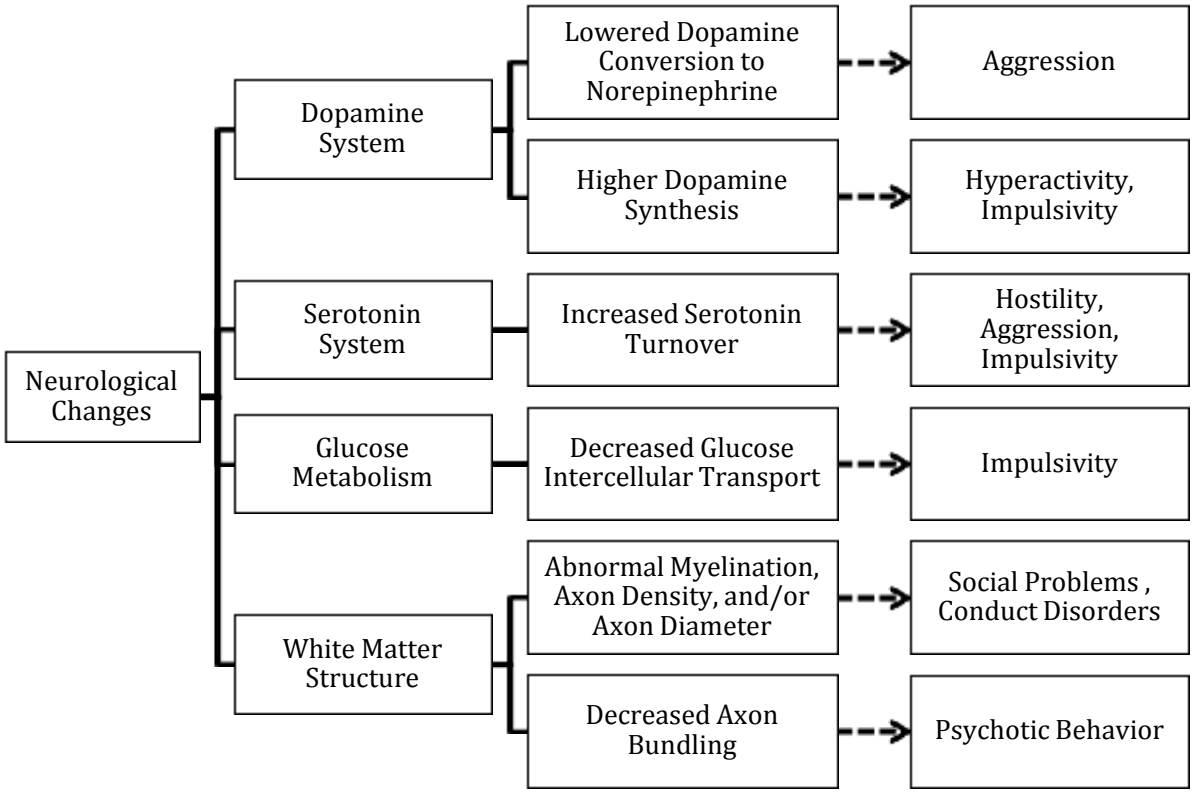

Figure 3.1 Flow chart summarizing neurological impairments that can occur from ω-3 PUFA deficiencies and the possible behavioral outcomes.

3.3 Gender differences in ω-3 PUFA status and metabolism

Women synthesize DHA more efficiently than men. In populations where there is low dietary PUFA intake, women have higher blood levels of DHA and lower levels of ALA compared to men, independent of diet (189-195). Meta-analyses have shown that men have DHA concentrations that are 37-47% lower in erythrocytes, plasma, and adipose tissue compared to women. Along with higher circulating levels of DHA and ALA, women also have lower levels of DPA and EPA (196-198). This disparity can be attributed to a

greater rate of conversion of ALA into DHA (190, 192, 199), which leads to higher circulating levels of DHA in women than in men (136). Min et al. found that platelet levels of DHA, EPA, and DHA:ω-3 DPA ratios were higher in women, while platelet AA and total n-6 PUFAs levels were higher in men. In addition to this observation, dietary intake of EPA and DHA was correlated with platelet DHA status in men, but not women. This data suggests that maintaining adequate DHA tissue concentrations is more dependent upon dietary intake in men than in women because women have a greater capacity for endogenous synthesis of DHA (200).

The reason behind these differences could be due to the effects of sex hormones mediating the synthesis of ALA to DHA. Post-menopausal women treated with progesterone and estrogen (201) and male transsexuals treated with synthetic estrogens (194) had increased blood levels of DHA compared to untreated women and men, while women transsexuals treated with testosterone had reductions in DHA (194). These studies suggest that estrogen and progesterone act as agonists for ω-3 PUFA synthesis, while testosterone acts as an antagonist. These observations are consistent with an n vitro study by Sibbons et al. (2014). Cells treated with progesterone had a two-fold increase FADS2 gene expression, while estrogen and testosterone had no effect (202). This response was dose-dependent, as more progesterone lead to greater gene expression. Progesterone also reduced the methylation of DNA regions upstream of the FADS2 gene, which codes for the delta-6 desaturase enzyme, allowing for greater transcription of this enzymatic gene. Additionally, progesterone induced a 38% decrease in ALA, a 5-fold increase in EPA, a 7-fold increase in DPA (ω-3), and a 36-fold increase in DHA, suggesting greater conversion of ALA into other ω-3 PUFAs with progesterone, but not estrogen or testosterone (202).

3.4 Summary of biological plausibility

The brain contains a significant amount of DHA, a fatty acid that is important for appropriate brain maturation. The dramatic shift in the fatty acid profiles of the modern diet since the 1900's may impact the prevalence of mental and psychiatric illnesses in current and future generations (203). Women seem to be more immune to these dietary fatty acid shifts and DHA deficiencies than men. The higher levels of progesterone and/or estrogen in females are thought to increase the rate of metabolism of ALA into DHA though genetic mechanisms that increase enzyme activity. In males, decreases rates of synthesis of ω-3 PUFA metabolites into DHA may be due to lower levels of these sex hormones, making men more susceptible to dietary fatty acid imbalances or deficiencies compared to women. Such findings can have additional implications on the gender differences in the prevalence of aggression, antisocial behaviors, and conduct disorders.

Inadequacies or deficiencies in ω-3 fatty acids can lead to altered function of the dopamine and serotonin neurotransmitter systems, abnormal brain metabolic function, and axonal structural deficits in similar brain regions - frontal cortex, striatum, and hippocampus. All of these neurological impairments are associated with impulsive, aggressive, and antisocial behaviors, which are all characteristics of juvenile delinquency and conduct disorders. Overall, insufficiencies in ω-3 PUFAs during fetal, infant, and childhood development may have the potential to cause irreversible neurological changes that are implicated in behavioral problems related to delinquency, violence, and criminal activity.

CHAPTER 4: STUDIES ON FATTY ACID INTAKE AND BEHAVIORAL OUTCOMES

4.1 Overview of behavioral studies with PUFA supplementation

Only recently have researchers begun to investigate the associations between omega-3 and omega-6 fatty acid tissue levels or supplementation, and behavioral outcomes related to aggression, conduct and antisocial problems, and criminal activity. Several studies so far have investigated the role of DHA and EPA consumption on hostility and anger outcomes (204-211) and antisocial behaviors (211-216). Seafood ingestion during pregnancy has been associated with higher cognitive function and reduced antisocial behavior in children (217). Fish oil supplementation has also been shown to reduced antisocial acts in adults (216). EPA supplements have reduced levels of aggression and depression in women with borderline personality disorder (211), while patients given DHA and EPA had reduced levels of aggression (212) and anger (218).

The studies that will be reviewed have shown some behavioral improvements with ω-3 PUFA supplementation, though they are limited in number and findings vary across sample populations. Despite small sample sizes, PUFA treatment compositions, and heterogeneity of the populations used, there appears to be a trend for ω-3 PUFA supplements in reducing behavioral outcomes associated with delinquency and criminality.

4.2 Methodology: study selection

Scientific databases (Web of Science and PubMed) were searched using key terms for behavioral or delinquent problems, then restricted to studies that included specific fatty acid terms (**table 4.1**). Studies were then limited to those that included juveniles (<18

years) or young adults (18-30 years). Because of the focus on criminal activity in youth, studies that focused solely on adult populations (30+ years) were excluded. Both U.S. and international trials were included due to the limited number of studies in U.S. sub-populations of interest. To ensure the evaluation of all possible PUFA-behavior studies related to delinquency or criminality, studies on populations with cognitive or psychological impairment (e.g. ADHD, schizophrenia, suicidal tendencies, depression), were also included in the review. In the end, a total of 27 studies were reviewed: 20 randomized control trials and 7 observational studies (6 longitudinal and 1 ecological).

Table 4.1 List of search terms used while searching for publications in selected databases

Category	List of search terms used
Fatty acid terms	fatty acid, FA, essential fatty acid, EFA, polyunsaturated fatty acid, PUFA, n-3, omega-3, n-6, omega-6, DHA, EPA, LA, ALA
Behavioral terms	conduct disorder, CD, oppositional defiant disorder, ODD, psychosis, psychopathy, antisocial behavior, antisocial personality disorder, APD, aggression, aggressive
Delinquency terms	violence, violent behavior, aggression, aggressive, criminal behavior, criminality, delinquency, delinquent behavior, homicide

4.3 Assessment of observational studies

A few observational studies investigated the association between fatty acid intake and behavioral outcomes related to delinquency or conduct problems (**table 4.2**). Hibbeln et al. found a linear relationship between the consumption of linoleic acid (LA) and homicide mortality rates in 5 countries between 1961 to 2000 ($r=0.94$, $p<0.001$) (2004). Within-country analyses showed varying magnitudes of this association, but findings

within each country were still significant (United States: r=0.65, p<0.001; United Kingdom: r=0.65, p<0.001; Australia r=0.74, p<0.001, Canada r=0.53, p<0.0004; and Argentina (1961-85): r=0.75, p<0.001) were still significant. Even with the exclusion of the United States, which had the most variation due to the implementation of gun control laws during the time frame observed, the correlation between LA intake and homicide mortality rates still remained significant (r=0.51) (219).

Table 4.2 Summary table of observational studies that look at the relationship between ω-3 PUFA and behavioral outcomes (hostility, impulsivity, aggression, anxiety, ODD/CD, and psychopathy) typically associated with delinquency and violence.

Study	Sample size and characteristics	Duration	Fatty acid of interest	Observations
Iribarren et al., 2004	Young adults aged 18-30 years (CARDIA study) N=5115	Measures at baseline, year 2, 5, 7, 10, and 15	total ω-3 PUFA, DHA	Consumption of fish high in ω-3 fatty acids was associated with a 0.82 times lower odds of having high hostility (OR=0.82, p=0.02) A 1-standard deviation increase in DHA was associated with a 0.90 times lower odds of having high levels of hostility (OR=0.90, p=0.02)
Watari et al., 2010	People with severe schizophrenia, 18-59 years N=75	Serum blood samples measured after admission	DHA, EPA, AA	Psychopathology ratings (using PANSS score) were positively correlated with serum levels of EPA (p=0.047) and DHA (p=0.02) Serum EPA (p=0.007), EPA/AA (p=0.008), and DHA (p=0.04) levels were negatively correlated with hostility scores; serum AA was positively associated with hostility scores (p=0.03)
Huss et al., 2010	Children with ADHD symptoms, 4-15 years N=810	12 weeks	2-8 capsules/ day: (per 4 capsules: 40mg DHA, 400mg EPA, 60mg γ-LA, 80mg Mg, 5mg Zn)	Children taking supplements saw a 33.6% relative improvement in attention deficit scores, 28.2% improvement in hyperactivity/ impulsivity scores, 28.1% decrease in emotional problem scores compared to baseline
Kohlboeck et al., 2011	Infants at birth, and 10 years of age LISAplus study N=416	N/A	DHA, EPA, AA	At birth, higher cord blood serum levels of DHA and AA were associated with lower levels of hyperactivity/ inattention and emotional difficulties at 10y Higher levels of EPA and LA at birth were associated with increased conduct problem and behavioral difficulty scores at 10y
Gow et al., 2013	Male children with and without ADHD, 12-16 years N=72	N/A	DHA, EPA, total ω-3 PUFA, total ω-6 PUFA	No significant relationships between ω-3 PUFA plasma levels and aggression, anxiety, impulsivity comparing ADHD to control group.

				Within the ADHD group, callous-unemotional traits were negatively associated with plasma EPA (r= -0.597, p=0.009) and total ω-3 PUFA (r= -0.498, p=0.027); near-significantly correlated with lower DHA (r= -0.436, p=0.054) and higher ω-6 PUFA levels (r=0.375, p=0.081)
Hibbeln et al., 2004	N/A (ecological study)	1961-2000	LA	Linear relationship between homicide rates (per 100,000) and LA levels from apparent consumption from 12 seed oils (r=0.94; 0<0.001). Linear relationships were significant for each country alone and when grouped without the United States.
Waylen et al., 2009	Children aged 7.9 years from ALSPAC N=364	32 weeks gestation, 3 yrs, 7.9 yrs	Total ω-3 PUFA	Low maternal intake of ω-3 PUFAs at 32 weeks gestation and exclusive use of infant formula were significantly associated with ODD/CD at 7.9yrs in unadjusted analyses (p=0.04 and p<0.001 respectively), but not in adjusted analyses (p>0.60) There was a near-significant trend for the association between low intakes of ω-3 PUFAs (<280mg/wk) at 3yrs and ODD/CD at 7.9yrs in adjusted analyses (p=0.06)

PANSS = Positive and Negative Syndrome Scale
γ-LA = γ-linoleic acid (n-6); Mg = magnesium; Zn = Zinc

Studies of infants and children revealed associations between ω-3 and ω-6 PUFA serum levels, emotional problems, and behavioral difficulties (220, 221). Higher DHA cord serum concentrations at birth were associated with reduced hyperactivity/inattention at 10 years of age, while DHA+AA and AA cord serum levels (which are influenced by maternal ω-3 PUFA status) was correlated with reduced emotional difficulty scores at 10 years of age (220). In contrast, higher cord serum levels of EPA and LA were associated with greater conduct problem and behavioral difficulty scores at 10 years, respectively (220). Waylen et al. showed that children with ODD/CD were less likely to have been breastfed (p<0.001), less likely to have been born to mothers with adequate maternal intake of ω-3 PUFAs during pregnancy (p<0.01), and more likely to have been male (p<0.001) (2009). These findings seem to support the general consensus that maternal sources of ω-3 PUFAs are important for later child development (65, 69, 70, 80). Children

that were never breast-fed had a 1.83 times higher odds of having ODD/CD at 7.9 years old ($p<0.001$) compared to children who had some breast-feeding. Those born to mothers with low intakes of ω-3 PUFAs (<340 mg/wk) during pregnancy had a 1.73 times higher risk of being diagnosed with ODD/CD at 7.9 years ($p=0.04$) compared to mothers with ω-3 PUFA intakes greater than 340 mg per week. These associations were not significant when adjusted for confounding factors (221). Taken together, these two studies suggest that maternal status of ω-3 PUFAs, either during pregnancy or lactation, are associated with fewer behavioral problems in their children when older.

Child status of ω-3 PUFAs is also thought to be important for behavioral outcomes (221-223). One study suggested that children who had low intakes of ω-3 PUFAs (<280mg/wk) at 3 years of age had a 1.62 times higher odds of meeting ODD/CD diagnostic criteria at 7.9 years of age ($p=0.06$) (221). However, Gow et al. found no significant relationships between ω-3 PUFA plasma concentrations in children with ADHD and behavioral outcomes (depression, anxiety, or aggression) when compared to controls (2013), which conflicts with other studies that showed ω-3 PUFA supplements improved emotional and behavioral outcomes (**table 4.3**). However, within-group analyses of ADHD children revealed negative associations between antisocial, callous-unemotional traits, and plasma levels of EPA and total ω-3 PUFAs (222). Trends also suggested positive and negative associations between callous-unemotional traits and plasma levels of total ω-6 PUFA and DHA, respectively (2013). Other observational studies noted that children with ADHD who used ω-3/ω-6PUFA supplements in conjunction with zinc and magnesium saw a 28% reduction in hyperactivity/impulsivity, and a 28% reduction in emotional problems

(223). The decrease in hyperactivity/impulsivity was greater among boys than girls, which also supports previous findings that boys are more likely to have ODD/CD than girls (221).

Adult studies have suggested that lower levels of hostility and behavioral issues are related to higher intakes of fish, higher serum levels of various ω-3 fatty acids, and lower levels of ω-6 fatty acids (224, 225). Among schizophrenics, hostility scores were negatively associated with higher plasma concentrations of EPA, DHA, and EPA:AA ratios, and positively associated with higher plasma AA levels. Furthermore, psychopathology ratings were positively correlated with serum levels of EPA and DHA. Schizophrenic patients also had significantly lower blood concentrations of EPA, DHA, and EPA:AA ratios and higher concentrations of AA compared to control patients (224). These results are consistent with other studies that showed consumption of fish high in ω-3 fatty acids and higher intakes of DHA were associated with lower levels of hostility in young adults (225). In contrast, Iribarren et al. found that greater intake of EPA was associated with a higher odds of experiencing hostility (225). This observation conflicts with Gow et al.'s data, which revealed that higher serum levels of EPA were associated with lower levels of antisocial and callous-unemotional traits in ADHD children (222). However, Iribarren et al.'s findings on EPA levels were consistent with previous evidence that found higher serum levels of EPA at birth correlated to greater risk for conduct problems and behavioral difficulties in childhood (220). Iribarren et al. noted high collinearity for EPA with other fatty acids (2013), therefore, the relationship between high EPA and hostility could be due to a secondary correlation of EPA with another fatty acid that is unaccounted for.

From the few observational studies that investigate the relationship between fatty acids and behavioral problems, the general consensus seems to be that greater serum

levels or higher intake of ω-3 fatty acids (DHA and/or EPA) decrease hostility, impulsivity, and ODD/CD. Additionally, higher serum levels of, or intake of, ω-6 fatty acids (LA and/or AA) increase the likelihood for these behavioral problems. These associations can be observed despite inconsistencies in the sample groups and the specific types of PUFAs used.

4.4 Assessment of randomized control trials

The impact of PUFA supplementation on aggressive behaviors and antisocial behaviors has been observed in a few placebo-controlled, randomized clinical trials. Subjects included children (**table 4.3**) and adults (**table 4.4**) with behavioral disorders, as well as incarcerated persons. Reductions in aggressive, antisocial, impulsive, or hostile behaviors occurred when given ω-3 PUFA supplements (205, 207, 211, 226, 227) in many of these trials.

4.4.1 Randomized control trials in children less than 18 years of age

Most clinical trials that investigated the effects of ω-3 PUFA supplements were in children with ADHD (226-232) or other behavioral disorders (233, 234). Only a few trials investigated behavioral changes in healthy children (208, 214). The following studies discuss the effects of ω-3 PUFA-only or ω-3 and ω-6 PUFA supplements on behavior improvements in children with and without clinical disorders (**table 4.3**).

Table 4.2 Summary table of randomized control trials that investigate the relationship between ω-3 PUFA and behavioral outcomes associated with delinquency and violence among children (<18 years)

Study	Subjects and sample size	Duration	Supplementation (dose per day)	Outcome
Itomura et al., 2005	Elementary school children aged 9-12 years N=166	12 weeks	Fish oil fortified foods (avg of 514mg DHA, 120mg EPA/day) (rapeseed/soybean oil control)	No significant changes in physical or verbal aggression, anger, or hostility among fortified group (HAQ-C); increased physical aggression among female children in control group (p=0.0008).
Stevens et al., 2003	Children with ADHD, aged 6-13 years N=50	16 weeks	480mg DHA, 80mg EPA, 40mg AA, 96mg γ-LA, 24mg α-tocopherol (olive oil placebo)	Supplements improved oppositional and defiant disorders compared to control group (p=0.02). Disruptive behavior (ASQ-P) was negatively correlated with EPA levels and positively correlated with AA levels (p<0.05)
Hamazaki & Hirayama, 2004; Hirayama et al., 2004	Children with ADHD, aged 6-12 years N=40	8 weeks	514mg DHA, 100mg EPA (olive oil placebo)	Children given DHA supplements had significant intragroup (p=0.001) and intergroup (p=0.01) reductions in aggression
Richardson and Puri, 2002	Children with ADHD 8-12 years N=41	12 weeks	864mg LA, 96mg ALA, 42mg AA, 186mg EPA, 480mg DHA, 60 IU Vitamin E (olive oil placebo)	Treatment group saw near-significant improvements in restless/impulsiveness (CRPS, p=0.09) but not hyperactivity/impulsiveness or oppositional behavior
Richardson and Montgomery, 2005	Children with developmental coordination disorder, 5-12 years N=117	12 weeks + 12-week crossover	174mg DHA, 60mg AA, 558mg EPA, 10mg γ-LA, 9.6mg Vitamin E (olive oil placebo)	In both initial RCT and crossover periods, supplementation group resulted in reduced opposition scores compared to control group (p<0.02)
Hamazaki et al., 2008	Children, 8-14 years N=233	12 weeks	0.65 g DHA, 0.1g EPA (placebo: 656mg LA)	No significant changes in overall aggression, anger, hostility (HAQ-C), or impulsivity (BIS-11)
Sinn et al., 2007, 2008	Children with ADHD symptoms, 7-12 years N=129 (initial) N=104 (crossover)	30 weeks (15 weeks + 15-week crossover)	2.4g fish oil (with 558mg EPA, 174mg DHA, 60mg γ-LA, 10.8mg vitamin E) (palm oil placebo)	In the initial and crossover periods, fish oil supplements improved impulsive (p<0.01) and oppositional (p<0.05) behaviors compared to placebo group. Multivitamins had no significant effect.
Sorgi et al., 2007 (Pilot study)	Children with ADHD, aged 8-16 years N=9	8 weeks	First 4 wks (full dose): 10.8g EPA, 5.4g DHA Last 4 wks (if needed): If AA:EPA < 1.0, took 1/2 dose; If <1.0 AA:EPA <1.5, took 2/3 dose	Supplementation resulted in significant decreases (p<0.01) in median plasma ratios of ω-6:ω-3 and AA:EPA ratios, and increases (p<0.01) in median plasma EPA, DHA, and total ω-3 levels. Supplementation resulted in decreases in oppositional/defiant behavior (ADHD SC-4, p<0.05; CPRS, p<0.01) and conduct disorder (ADHD SC-4, p<0.05)

Amminger et al., 2013	Adolescents and young adults with borderline personality disorder, 13-25 years N=81	12 weeks	Fish oil supplements (700mg EPA, 480mg DHA, 7.6mg vitamin E) (coconut oil placebo)	PUFA treatment significantly increased serum ω-3 PUFA levels (p=0.003), and significantly decreased PANSS symptoms of impulsivity (p=0.03), and anxiety (p=0.03) compared to control group
Voigt et al., 2001	Children with ADHD, 6-12 years N=54	16 weeks	345mg DHA (undefined placebo)	Treatment group had significant increases in plasma DHA content (p<0.001), but no significant improvements in impulsivity

HAQ-C = Hostility-Aggression Questionnaire for Children of the Buss-Perry Aggression Questionnaire
γ-LA = γ-Linoleic acid (ω-6 PUFA); ASQ-P = Abbreviated Symptoms Questionnaire - Parents;
CRPS = Connor's Parents Rating Scale; BIS-11 = Barratt Impulsiveness Scale, version 11
ADHD SC-4 = Attention Deficit Hyperactivity Disorder Symptom Checklist 4

ADHD is the most commonly investigated behavioral disorder for studying the effectiveness of ω-3 PUFA supplementation in children (226-232, 235). A 2-month study of ADHD children given ω-3 supplements showed that declines in the AA:EPA ratio was positively correlated with decreasing severity of ADHD (p=0.027). In addition, supplementation led to significant decreases in oppositional/defiant behavior and conduct disorder (p<0.05) (231). This is consistent with other trials that demonstrated the effectiveness of fish oil supplementation (primarily ω-3 PUFAs) in improving hyperactive-impulsive behaviors, oppositional behaviors, and social problems after 15 weeks (p<0.05), with continued improvements after 30 -weeks (229, 230). Additional studies showed significant reductions in aggression within the DHA and EPA supplementation group (p=0.001) and when compared to the control group (p=0.01) (226, 235).

Other studies of ADHD children given a combination of ω-3 and ω-6 PUFAs yield varying results on improving behavioral outcomes. One study found significant improvements in ODD (p=0.02), as well as the percent change of disruptive behaviors being positively correlated with plasma AA levels and negatively correlated with plasma EPA levels (p<0.05) (227). Improvements in restless/ impulsiveness was also suggested

(p=0.09) when ADHD children were given ω-3 and ω-6 PUFAs supplements for 3 months (228).

Not all supplementation trials in ADHD children are successful, and the lack of significant findings conflict with results of positive studies. Supplementation with ω-3 and ω-6 PUFAs for 12 weeks did not improve hyperactivity/impulsiveness (p=0.61) or oppositional behavior (p=0.93) in ADHD children (228). The lack of significant findings conflict with the trial by Stevens et al., which saw that ω-3 and ω-6 PUFA supplementation improved oppositional and defiant behavior in children with ADHD (2003). Administration of lower DHA doses for 16 weeks had no significant improvements in impulsiveness, despite a 260% increase in plasma DHA levels (p<0.001) (232).

Adolescents and young adults with borderline personality disorder (BPD) (234) and developmental disorders (233) had improvements in behavioral issues after taking ω-3 PUFA supplements. At the start of the study, BPD patients had higher scores for psychosis, the severity of which was negatively associated with erythrocyte concentrations of ω-3 PUFAs (p<0.05) compared to controls. After 3 months of taking EPA and DHA supplements, BPD patients had significantly increased erythrocyte ω-3 PUFA levels (p=0.003), and significantly lower scores for impulsivity and anxiety (234). Among children with developmental coordination disorders, ω-3 and ω-6 PUFA supplementation led to improvements in oppositional scores (p<0.02), impulsiveness (p<0.001), and some improvement in social problems (p=0.09) after 3 months. These improvements were maintained or increased with an additional 3 months of treatment (233). These results reflect other findings that show how changing fatty acid compositions correlated with improvement in behavioral disorders (231).

In contrast to the potential benefits of ω-3 PUFAs described above, ω-3 supplements do not appear to improve aggression or hostility among healthy children (208, 214). Children who took ω-3 PUFA fish oil capsules for 3 months had significantly increased blood concentrations of DHA, EPA, and the EPA:AA ratio ($p<0.0001$)(214). Blood concentrations of LA, AA, and the total ω-6:ω-3 ratio also decreased in the treatment group ($p<0.0001$). Despite improvements in plasma concentrations of these fatty acids, supplementation did not have any significant effect on reducing verbal aggression, physical aggression, anger, hostility, or impulsivity (214). These occurrences were similar to the results from Hamazaki et al., who also found that foods fortified with fish oil did not improve aggressive or hostile behavior (2008). In this trial, fortified foods increased blood concentrations of EPA ($p=0.0009$), DHA ($p=0.06$), and EPA:AA ratios ($p=0.0001$), and decreased ω-6:ω-3 ratios ($p=0.004$), compared to the control group (208). The improvements in PUFA blood levels did not have a significant impact on lowering verbal aggression, hostility, or anger among children given the fortified foods. While physical aggression remained stable among female children in the supplement group, there was a significant increase in physical aggression in the control group ($p=0.0004$). The increase in physical aggression among the control group was significant compared to the unchanged aggression levels in the food fortification group ($p=0.004$) (208).

Overall, ω-3 PUFA supplements seem to improve outcomes for conduct disorders, oppositional behavior, social problems, impulsivity, anxiety and aggression for children and adolescents with ADHD or other behavioral disorders. Combined ω-3 and ω-6 PUFA supplements appear to have conflicting results in improving aggression, hostility, impulsivity, and oppositional behaviors in these children. Supplementation with ω-3 or ω-

3/ω-6 PUFAs did not improve outcomes in aggression, hostility, impulsivity, or anger (208, 214, 232) in children lacking behavioral impairments, even with improvements in plasma ω-3 and ω-6 PUFA concentrations.

4.4.2 Randomized control trials in adults 18 years of age or older

The remaining clinical trials that investigate the effects of ω-3 and ω-6 PUFA supplements on behavioral outcomes are in adults with a history of psychological disorders (121, 211, 212, 218, 236), incarcerated persons (216, 237), and young adults with no emotional problems (205, 206, 238). The following studies discuss the effects of ω-3 PUFA only or ω-3 and ω-6 PUFA supplements on improving behaviors in these different adult populations (**table 4.4**).

Table 4.4 Summary table of randomized control trials that investigate the relationship between ω-3 PUFA and behavioral outcomes associated with delinquency and violence among adults (≥18 years)

Study	Subjects and sample size	Duration	Supplementation (dose per day)	Outcome
Hamazaki et al., 1996	University students aged 21-30 years N=41	90 days	1.5-1.8g DHA, 100-125mg EPA (97% soybean oil and 3% fish oil placebo)	Extra-aggression[a] was significantly increased in placebo group compared to treatment group (P-F, p=0.002)
Hamazaki et al., 1998	University students aged 21-30 years N=46	91 days	1.5g DHA, 0.1g EPA (placebo 97% soybean oil and 3% fish oil)	Extra-aggression[a] was significantly increased in treatment group compared to placebo (P-F, p<0.05), but not significant based on Cook-Medley
Long and Benton, 2013	Young adult males, average age 20.9 years N=173	12 weeks	672mg DHA, 4.2mg ALA, 10.6mg LA; DHA, multivitamins: Centrum Advance 50+, fatty acids above Multivitamins only: Centrum Advance 50+	DHA supplementation decreased extra-aggressive behavior (p<0.05) with picture-frustration task, but not BPAS. Multivitamins had no added effect DHA supplements decreased impulsivity among males with higher baseline levels (p<0.04) Near significant trends for decreases in intra-aggression[b] (BPAS, p<0.07)

Gesch et al., 2002	Young adult prisoners (18+ years of age) N=231	142 days (average)	44mg DHA, 80mg EPA, ω-6 PUFA (1.26g LA and 160mg γ-LA), vitamins/minerals (vegetable oil placebo)	Antisocial behavior (number of total offenses in prison) decreased by 35.1% ($p<0.001$), with a 33.3% reduction in minor offenses ($p<0.025$) and a 37% reduction in serious (including violent) incidents ($p<0.005$)
Zaalberg et al., 2010	Incarcerated male offenders, age 18-25 years N=221	4-12 weeks	0..4g DHA, 0.4g EPA, 0.1mg γ-LA, 25 vitamins and minerals (placebo reflected fatty acid composition of W. European diet)	Supplementation resulted in 34% reduction in reported incidents of aggression and rule-breaking ($p=0.017$) compared to placebo. There were no significant reductions in aggressive behaviors as measured by AQ ($p=0.09$) and SDAS ($p=0.23$)
Legare et al., 2007 (pilot study)	Violent male inpatients with schizophrenia N=12	12 weeks	0.6g DHA, 1.2g EPA, 1200n IU vitamin E (placebo n/a)	Decrease in anxiolytic medication administration (proxy for agitation) ($p=0.015$)
Hallahan et al., 2007	Patients who commit self-harm, age 16-64 years N=49	12 weeks	1.22g EPA, 0.91g DHA (corn oil placebo)	No differences between treatment and control groups with expression of impulsivity (IMT/DMT) or overt aggression (MOAS)
Zanarini and Frankenburg, 2003	Females with borderline personality disorder, 18-40 years N=30	8 weeks	1g EPA-ethyl ester (mineral oil placebo)	Significant reductions in aggression (MOAS, $p<0.0001$)
Buydens-Branchey et al., 2008	Male patients admitted for substance abuse with or without history of aggression N=24	12-weeks +(12-week follow-up for subset of 14 patients)	2.25g EPA, 0.5g DHA, 250mg ALA, DPA (ω-3) (soybean oil placebo)	Ω-3 PUFA supplementation for 3 months resulted in a significant decrease in anger scores ($p=0.024$) compared to placebo group. Among patients followed for 6 months, PUFA supplementation resulted in a near-significant decrease in anger scores ($p=0.06$)
Bellino et al., 2013	Patients with borderline personality disorder, age 18-50 years (avg 25 yrs) N=34	12 weeks	1.2g EPA, 0.8g DHA, valproic acid (control is valproic acid, a BPD drug)	Treatment with ω-3 PUFA supplements was associated with decreased impulsivity (BIS-11, $p=0.031$), impulsive (BDPSI, $p=0.031$) and anger outbursts (BDPSI, $p=0.001$). No significant decrease in overt aggression (MOAS, $p=0.376$)

[a]Extra-aggression = aggression towards others; P-F = Picture Frustration task;
Cook-Medley - Cook-Medley Hostility Scale; [b]Intra-aggression = aggression directed at self;
BPAS = Buss-Perry Aggression Scale; γ-LA = γ -linoleic acid; AQ = Aggression Questionnaire;
SDAS = Social Dysfunction and Aggression Scale; IMT/DMT = Immediate and Delayed Memory Task;
MOAS = Modified Overt Aggression Scale; BIS-11 = Barrett Impulsiveness Scale;
BPDSI = Borderline Personality Disorder Severity Index

Patients with a history of psychological problems (212, 218, 236) had varied results regarding the success of ω-3 PUFA supplements for reducing impulsivity or aggression. A three-month study investigated the effects of ω-3 supplements in reducing anger among substance abusers (218). At baseline, substance abusers with history of assaultive behavior had significantly lower average daily intakes of fish (22.7g vs 42.7g, $p=0.013$) and ω-3 PUFAs (89.6mg vs 179.4mg, $p=0.011$), compared to those without a history of assault. Patients who reported consuming more than 42g of fish per day reported no incidences of violence, whereas 60% of those who reported eating less than 42g day of fish reported acts of violence (218). After three months of ω-3 PUFA supplementation, substance abusers saw a significant reduction in anger scores ($p=0.024$). A subset of subjects who were followed for an additional twelve weeks had anger scores that decreased ($p=0.06$) beyond the three-month anger scores (218). Supplementation with EPA and DHA for three months was also shown to improve agitation levels (based on reductions of anxiolytic medications administered to inpatients) of violent schizophrenic male inpatients ($p=0.015$) in a pilot study (236). In comparison, supplementation with only EPA and DHA for three months was not effective for reducing impulsivity or aggression in patients with a history of self-harm (212).

Treatment with ω-3 PUFAs was fairly successful in reducing aggression and impulsivity among adults with bipolar personality disorder, another psychological disorder. A two-month pilot study on women with BPD used EPA as the only ω-3 supplement, and found significant reductions in overt aggression among females treated with EPA ($p=0.007$). The reductions in aggression at the end of the study were also significant among the treated women ($p<0.0001$) compared to the control group (211).

These results mirror improvements found in a three-month trial of ω-3 supplements given to male and female patients with BPD (121). Use of ω-3 PUFA supplements (EPA and DHA) was associated with decreased impulsivity as measured by the Barrett Impulsiveness Scale (BIS-11; $p=0.031$). When behaviors were measured based on a different index (BDPSI), impulsiveness ($p=0.031$) and anger outbursts ($p=0.001$) still showed significant declines after three months of supplementation with EPA and DHA (121). These results by Bellino et al. do not agree with Hallahan et al.'s conclusions that there is no change in impulsiveness among patients who self-harm, as measured by IMT/DMT tests (2007). When Bellino et al. assessed aggression based on the MOAS scores instead of the BDPSI, they saw no decreases in aggressive behavior among BPD patients ($p=0.376$) (2013). These results conflict with Zanarini and Frankenburg, who found that EPA-only treatment reduced aggression in females with BPD, when measured by the MOAS scale (211). However, Bellino et al.'s results on aggression are consistent with Hallahan et al., who found no reductions in aggression (based on the MOAS test) among self-harm patients given EPA and DHA (212).

Another two studies looked at the effectiveness of ω-3 and ω-6 PUFA supplements on improving delinquent or criminal behavior when given in conjunction with multivitamins (216, 238). In general, these studies showed some declines in aggression and antisocial behaviors (as indicated by the number of offenses or rule-breaking) with the administration of these supplements. Gesch et al. found that giving PUFA and micronutrient supplements to young adult prisoners reduced the number of total infringements by 26.3% (from 16 to 11.8 infringements per 1,000 person days) compared to the placebo group ($p<0.03$), based on intent to treat analyses (2002). With a more strict assessment, the number of total infringements was found to have decreased by 35.1%, dropping from 16 to

10.4 infringements per 1,000 person days ($p<0.001$). When analyzed by type of infringements, there were significant reductions in the number of minor incidences (33.0%, $p<0.025$), and serious (including violent) incidences (37.0%, $p<0.005$). Zaalberg et al. also found that PUFA and micronutrient supplements reduced the number of reported incidents of aggression and rule-breaking by 34% ($p=0.017$) among male incarcerated youth (2010). The total number of total incidents, and the number of incidents sans drug and alcohol reports, dropped from approximately 11.0 to 7.0 and 9.0 to 5.0 incidents per 1,000 person days, respectively. Inmates who were given placebos that similar in composition to a western diet had an increased number of incident reports. The decline in incident reports among the supplement group compared to placebo group was significant ($p=0.017$) (237), which is consistent with the results from Gesch et al (216). However, Zaalberg et al. found no significant reductions in aggressive behaviors among male incarcerated youth when this behavior was measured by an aggression questionnaire ($p=0.09$) or by social dysfunction and aggression scale ($p=0.23$) (237).

The three remaining clinical trials (205, 206, 238) investigated the effects of PUFA supplements in reducing levels of interpersonal aggression and impulsivity in adults. The two studies by Hamazaki et al. (1996, 1998), which investigated interpersonal aggression among young adult university students, had results that conflict with the aforementioned findings that showed how ω-3 PUFAs reduced aggression. One study by Hamazaki et al. saw a significant increase in interpersonal aggression in the placebo group, while the EPA/DHA treatment group saw no changes in aggression ($p=0.02$) (206). The second study by Hamazaki et al. found that interpersonal aggression actually increased with EPA and DHA supplementation compared to the placebo group ($p<0.05$) (206). The remaining study

by Long and Benton was of young adult males given ω-3 and ω-6 PUFA supplements and multivitamins (238). The results from this study conflicted with the studies by Hamazaki et al (1996, 1998). Long and Benton found that ω-3 and ω-6 PUFA supplements decreased interpersonal aggression ($p<0.05$) when measured by the picture frustration task (238) used by Hamazaki et al. (1996, 1998). However, the decreases in aggression found by Long and Benton were not significant when measured with the Buss-Perry Aggression scale (238). They also found a near-significant reduction in intrapersonal aggression ($p=0.07$), and significant reductions in impulsivity ($p=0.04$) compared to the multivitamin placebo group. Multivitamin supplements did not have any added effect on the results that occurred from ω-3 and ω-6 PUFA supplementation (238).

4.5 Summary of findings from observational studies and randomized control trials

Based on the observational and randomized control trials discussed, there is some evidence that ω-3 PUFA supplements improve outcomes for aggression, anxiety, impulsivity, hostility, oppositional/conduct disorders, and antisocial behaviors. ω-3 PUFA supplementation seems to be more effective in children and young adults who have existing behavioral (substance abuse, criminal offenders) or psychological (ADHD, schizophrenia, bipolar disorder) complications as opposed to people without any disorder. These results have implications for the role of ω-3 PUFAs in maintaining normal behavior. ω-3 PUFAs deficiencies may be a risk factor for these disorders, and supplementation appears to relieve some of the behavioral issues associated with these psychological disorders and improve conduct of incarcerated persons.

CHAPTER 5: SUMMARY OF FINDINGS, LIMITATIONS, AND FUTURE DIRECTIONS

5.1 Summary of findings

Over the past century, major dietary shifts have occurred. The largest change in the U.S. diet has been the drastic increase in ω-6 fatty acid content of the American diet, greatly attributed to the increased production and consumption of soybean oil. ω-3 fatty acids are important for optimal brain development and behavioral outcomes, and greater intakes of fats high in ω-6 can interfere with proper neural growth and function. Cerebral ω-3 deficiencies during fetal development and childhood have been implicated in many neurological disorders and cognitive impairments in later childhood and adulthood.

This dietary shift has been implicated in the prevalence of conduct disorders, delinquency, and violence, due to the increasing crime rates in the last few decades. While crime statistics imply that criminal activity is decreasing, official arrest records only capture a small minority of total criminal or delinquent occurrences. Self-reports have shown that the prevalence of aggression and antisocial behaviors have not declined, but have remained the same since the 1990's. Children and adolescents who develop oppositional defiant disorder, conduct disorder, antisocial personality disorder, or psychopathy early in life have a higher risk for continued criminal activity into their adult years. Observational studies and clinical trials have shown that ω-3 PUFAs can be effective in reducing aggression, anxiety, impulsiveness, and oppositional/defiant behaviors - all of which are defining characteristics of juvenile criminality and delinquency. Despite these findings, the numbers of studies performed are minimal, the populations assessed are varied, and the effectiveness of PUFA treatments is inconsistent and conflicting at times.

5.2 Limitations in assessing antisocial behaviors, delinquency, and criminality

Variations in assessing the prevalence of antisocial, aggressive, and delinquent behaviors can be attributed to the methodologies for disease diagnosis and data collection (2). In the United States, nationally representative data on these behavioral disorders are still not available. Efforts are being made by the National Institute of Mental Health (239) and the Surgeon General's Report on Mental Health (240) to develop cross-sectional and longitudinal surveys to track the prevalence and projections of many mental and behavioral disorders in children and adolescents. While national behavioral data might not be readily available, violence-based information is available from various sources, but they can vary widely in content and accuracy.

Mortality data is the most widely collected statistic, but determining the homicide rates from this information might not be dependable due to an unreliable population count in a given area of the country. Additionally, data on non-fatal outcomes from violent crimes are not always available (241). Violence data typically comes from many independent organizations, such as police stations, hospitals, and medical examiners. Lack of uniformity in data collection procedures means it can be near-impossible to compare these statistics across communities within a country, making it difficult to use for research purposes (241). Even if data pertaining to homicide and non-fatal crimes are obtainable, the quality of the data might not be conducive for research. Data might be incomplete, or there could be a lack the information needed to determine the type of violent act that lead to a non-fatal outcome. For example, medical records contain information on injuries, but not the violent act that led to the injuries. While surveys may inquire about a person's background and involvement in violent acts, they are limited by recall bias or omission of information by

the participant and how well an interview was conducted. Ethical considerations also need to be accounted for when collecting data regarding acts of violence. Because of these limitations, data collected through surveys might not be as thorough as desired for analytical purposes (241).

5.3 Limitations in assessing dietary trends in PUFA consumption

National data on dietary trends are subject to biases, and can either over- or under-estimate true consumption of foods at the individual level. Domestic food disappearance data is an estimate of national intake, not a direct measure of actual consumption at the individual level. While it is valuable for observing annual trends over time at a national level, it is becoming a less reliable indicator for fat and oil consumption because it only reflects the total amount of various fats that were sold each year. Disappearance data is not adjusted for food losses (food waste or spoilage, plate loss), and therefore is not the most accurate measure for food intake at the individual level. Adjusting for food losses is important for assessing individual and national intake since food losses are especially high in recent decades. The rising trends in eating out at restaurants or fast-food places, which discard large amount of oil as waste, can inflate the amounts of fats consumed based on unadjusted disappearance data (242).

The uses of dietary history records in studies by Iribarren et al. (2004) and Buydens-Branchey et al. (2008), and food frequency questionnaires in Waylen et al. (2009), are subject to biases in determining subject's average food consumption. Food frequency questionnaires can be inaccurate in determining intakes of different foods or food groups, especially for underestimating fats and oils (243). Additionally, food lists for these

questionnaires are not always comprehensive, and personal characteristics like gender can lead to varying degrees of recall bias for the foods that are listed (243, 244). Dietary histories are generally more thorough, but are still subject to recall bias, most notably during the weekend (245). The estimation of nutrient intakes from these food questionnaires are also subject to biases due to the food surveys used, duration of the survey, and lack of accounting for the use of supplement (246, 247).

5.4 Limitations of current studies assessing the link between PUFA consumption and behaviors related to delinquency and violence

The ecological study by Hibbeln et al. was limited by various factors when investigating the association between LA and homicide. Murder is the most extreme form of overt aggression and antisocial behavior, and is only a subset of criminal acts exhibited among youth with conduct disorders. Though the trends are significant in all countries observed, the relationship between linoleic acid and homicide might be due to secondary covariates not controlled for, such as socioeconomic or cultural factors. Other confounders include an increase in media exposure during the 40-year period studied, drug and alcohol use, and gang violence. Additionally, seed oils are not the only source of LA in the diet, and other food sources of LA were not taken into account as part of the total consumption of LA. Moreover, the estimates of LA consumption did not account for hydrogenation, waste, spoilage, and calorie disappearance in these models (219).

For many of the randomized control trials and observational studies, the inconsistency of patient demographics (age, gender, mental or emotional health status, incarceration status, country of origin), types of PUFA supplementation given to subjects (ω-3 only, ω-3 and ω-6, or specific types of ω-3), and behavioral tests used to assess

outcomes can increase the likelihood for conflicting results. These factors, combined with the inconsistency in time frames used for observational studies (from immediately upon enrollment to years later) and randomized control trials (ranging from 8-30 weeks), can impact the external validity of these findings for the general population. Additionally, the external validity of these results might lower when applying to people who might not be diagnosed with a clinical disorder but still experience delinquent or antisocial behaviors, or to those who might have higher lifetime risks for dietary fatty acid deficiencies due to environmental factors.

The types of placebos used for control groups in the randomized control trials can also impact the validity of findings regarding the effectiveness of ω-3 PUFAS for improving behavioral outcomes. The types of placebos used included soybean oil, corn oil, palm oil, olive oil, mineral oil, vegetable oil, and rapeseed oil. These oils have very different fatty acid compositions (**figure 2.3**) that could potentially interfere with the effectiveness of the ω-3 PUFA supplements in the treatment groups. Soybean oil was used as a control in four studies (205, 206, 208, 218), corn oil was used in one study (212), linoleic acid was used in another study (214), and vegetable oil acted as a control in the final study (216). These oils are very high in ω-6 PUFAs; ω-6 PUFAs make up approximately 35-51% of total fatty acid content in soybean oil, approximately 52% of the total fatty acid content of corn oil, while vegetable oil is generally a combination of the two. The high levels of ω-6 PUFAs may have contributed to conflicting results in ω-3 PUFA treatment effectiveness in these various randomized control trials, since ω-6 PUFAs are known to interfere with ω-3 PUFA metabolism (65, 138). For the same reason, the use of PUFA supplements that contained ω-6 fatty acids alongside ω-3 fatty acids may have reduced the overall effectiveness of the

PUFA supplements in ameliorating behavioral problems. Amminger et al. cited the importance of using coconut oil as a control because it does not contain ω-3 PUFAs, contains inconsequential amounts of ω-6 PUFAs, and it does not impact ω-3 PUFA metabolism (2013). Palm oil and olive oil are also very low in ω-6 PUFAs, accounting for 10% or less of total fatty acid content. Palm oil and oil were used in 1 study (229, 230) and 4 studies (226-228, 233, 235), respectively, which may have improved the significance of the findings in these trials compared to studies that used soybean or rapeseed oils.

5.5 Conclusions and future directions

Despite the small number of studies investigated in this review, the general consensus is that ω-3 PUFAs are important for alleviating aggression, impulsivity, anxiety, oppositional and defiant behaviors, acts of delinquency, and conduct disorders in people of different ages, genders, and psychological status. Due to the consequences of high ω-6 PUFAs and low ω-3 PUFAs on neural formation and function, it is plausible that the changing nutritive environment in the last century is associated with the sustained prevalence of behavioral and emotional problems associated with criminal activity. To date, many studies look promising, but more are needed to fully comprehend the relationship between dietary insufficiencies and behavioral outcomes. More consistent and long-term studies are needed to determine the true impact of ω-3 fatty acids on modulating criminal-related behaviors. Understanding the extent to which fatty acid deficiencies or imbalances can increase the risk for these disorders can help with intervention programs for currently afflicted youth and help prevent future children and adolescents from developing these abnormal personalities in the first place.

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