The effect of the Roots of Empathy program on the use of psychotropic medications among youth in Manitoba

by

Lindsey Dahl

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Department of Community Health Sciences,

Rady Faculty of Health Sciences, Max Rady College of Medicine

University of Manitoba

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Abstract

Background: Psychotropic medications prescriptions to youth have increased. Roots of Empathy (ROE) is a social and emotional learning program that may influence the use of psychotropic medication.

Methods: Administrative data was analyzed in a matched sample of children who received ROE during 2002/03 to 2012/13. Kaplan-Meier survival curves and Cox proportional hazard models were used to estimate the association between ROE and psychotropic medication dispensations.

Results: Few significant differences were observed. Children who received ROE in kindergarten to grade 3 had a lower adjusted hazard for an anxiolytic dispensation. Children who received ROE in grade 7 to 8 had a higher hazard for an antipsychotic dispensation. Males who received the program had an increased hazard for an antipsychotic dispensation.

Conclusion: There was no consistent differences in the likelihood of being dispensed a psychotropic medication between children who received ROE and children who did not in Manitoba.

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Introduction

The use of psychotropic medications among children and adolescents has increased in recent decades in Manitoba (Brownell et al., 2008). Even though many of these medications are not licensed for use among pediatric populations in Canada, they are often the first line of treatment, as other forms of treatment (i.e. psychotherapy) are difficult to access (Henry, Kisicki, & Varley, 2012). The safety and efficacy concerns with using these medications, as well as high costs associated, justify the preference for effective programs that promote mental health and prevent mental illness in children at an early age over the current approach of waiting and dealing with symptoms as they arise (O'Connell, Boat, & Warner, 2009). Positive mental health outcomes have been associated with high social and emotional function in children. Therefore, this study evaluated whether Roots of Empathy, a school-based program that has demonstrated an ability to improve important social and emotional skills in children, reduced the use of psychotropic medications among children who participated in the program in Manitoba.

Chapter 1. Literature Review

Social and Emotional Learning (SEL)

Research indicates that exposure to SEL programs is associated with greater well-being, social and emotional skills, attitudes, behaviours and academic performance of children compared with their peers not exposed to SEL programs (Devaney, Utne O'Brien, Tavegia, & Resnik, 2005; Durlak, Weissberg, Dymnicki, Taylor, & Schellinger, 2011; Elias, 2006; Guerra & Bradshaw, 2008; Masten & Coatsworth, 1998; Schonert-Reichl & Hymel, 2007; Zins, 2004). Furthermore, these programs have demonstrated a protective and long-lasting effect against the development of negative mental health outcomes related to emotional distress, depression, anxiety, and stress (Hawkins, Kosterman, Catalano, Hill, & Abbott, 2008; R. D. Taylor, Oberle, Durlak, &

Weissberg, 2017). Conversely, children who lack social skills have been shown to experience a variety of personal, social, and academic difficulties (Blum, Libbey, Bishop, & Bishop, 2004; Guerra & Bradshaw, 2008). Therefore, educational approaches that incorporate SEL strategies stand to benefit the social and mental well-being of those exposed without compromising academic performance; while approaches that focus solely on academic performance may not allow for optimal social and emotional skill develop and may hinder their chance of greatest success in life. In addition, these programs have demonstrated a benefit of approximately $2 - $14 for each $1 spent on these programs (Belfield et al., 2015).

The "Roots of Empathy" Program

Description

Roots of Empathy (ROE) is a classroom-based program designed to foster caring, peaceful, and civil societies through the development of empathy in children (Gordon, 2003). The program is based on SEL principles and the concept that developing empathy in children will improve their social and emotional functioning, providing them with the best opportunity for success in life. In doing so, a societal foundation of citizens who appreciate the commonalities between themselves and others, rather than the differences, is established (Gordon, 2005).

Empathy is defined as a multidimensional construct involving affective and cognitive components (Soenens, Duriez, Vansteenkiste, & Goossens, 2007), where individuals are able to express concern and sympathy based on the emotional state of another person, in addition to being able to take the perspective of that person (Davis, 1983). The ability to be empathetic is born within everyone and thought to "transcend race, culture, nationality, social class and age" (Gordon, 2005). However, the level of empathy and emotional development that an individual demonstrates is largely influenced by the strength of the relationship and connection between a

parent and child. Indeed, research has shown an association between children and adolescents who express low levels of empathy and parents who exhibit negative, neglectful, abusive behaviours or poor parenting styles (Schaffer, Clark, & Jeglic, 2009; Zhou et al., 2002). Unfortunately, non-empathetic responses learned in the early years may persist into adulthood and eventually be passed down to future generations, creating an intergenerational cycle (or 'transference') of inappropriate behaviours (Serbin & Karp, 2004). The ROE program attempts to disrupt this cycle by putting relationships at the centre of what makes a civil society, and aims to equip children with a set of skills that will help develop meaningful relationships in all aspects of their lives. As such, present and future generations stand to increase their likelihood of success in a variety of areas in their lives.

The program is typically delivered "universally" to all children in an elementary school classroom, but may also be offered to specific populations who may be targeted for their greater risk of violence and bullying behaviours (Gordon & Green, 2008). The ROE team includes a trained instructor, a classroom teacher, and a parent and baby (2-4 months of age in September), who follow a curriculum aimed at providing students with an opportunity to learn the concepts of infant development, behaviour and care (Gordon, 1999). The parent and baby are considered the cornerstone of the program and visit the classroom once a month throughout the school year for a total of nine visits (Gordon, 1999). During each of these visits, the students are encouraged to take the baby's perspective to understand the baby's needs and feelings. The ROE instructor visits the classroom twice a month without the parent or baby. The first visit prepares the class for the upcoming parent and baby visit, while the second visit involves discussions related to their observations from the parent and baby visit, and engages the students in activities that support the themes and learning concepts set out by the program (Gordon, 1999). During these

visits, the students explore the connection between the baby's development and their own development, as well as the connection between the baby's feelings and their own feelings (Gordon, 2005). Having the baby in the classroom facilitates the learning process by providing real experiences that bring awareness to the physical, cognitive, social and emotional aspects of child development. It is through these experiences that students are exposed to the elements that make strong human connections as they begin to understand the emotions and feelings of themselves, one another, and society (Gordon, 2005). These connections are critical to the development of empathy and become solidified as each student progresses through the program (Gordon & Green, 2008). Six strands of human connection guide the themes for the ROE program: neuroscience, temperament, attachment, emotional literacy, authentic communication, and social inclusion (Gordon, 2005).

History

ROE was developed by Canadian educator Mary Gordon, based upon her experiences as an elementary school teacher, and a family literacy program developer. Her experiences gave her a first-hand look at the importance of providing children with the best start possible, and eliminating the transference of addiction, violence, low literacy and poor parenting (Gordon, 2009). She believed the best way to address these issues was through the development of empathy in a person's early years. The first ROE program was funded by the Maytree Foundation and appeared in inner-city schools in the Toronto District School Board in 1996 (Gordon, 1999). Since then, it has been implemented in thousands of schools worldwide.

As of 2011, every Canadian province has schools offering the ROE program, which has now reached over 645,000 Canadian children (Rootsofempathy.org, n.d. Where we are.). The program and related materials are available in English or French, and was endorsed and

supported by the Assembly of First Nations in 2008 citing that it was compatible with traditional First Nations teachings (Government of Manitoba, n.d.). In Manitoba, ROE is supported by the Healthy Child Manitoba Office (HCMO), a governmental cross-department strategy, and was first launched as a pilot project during the 2001/02 school year. Each year, all public and private schools in Manitoba are invited by HCMO to participate in the program. To date, all schools in Manitoba who have expressed interest have been accommodated, and the program has reached approximately 35,000 children in the province (Government of Manitoba, n.d.). In 2015, the Manitoba government announced an investment of $2 million towards a multi-year strategy to enhance supports for mental health for children, which includes an expansion of the ROE program to more classrooms across Manitoba (Government of Manitoba, 2015).

Effectiveness

There has not been a large number of evaluation studies on the ROE program; however, the studies that have been conducted consistently show the program to be effective at improving certain social skills and behaviours consistent with empathy, such as emotional knowledge and pro-social behaviour, while reducing most forms of aggression associated with bullying (Schonert-Reichl & Hymel, 2007).

Evaluations have typically examined outcome measures attained from self-reports, teacher-reports, and peer-reports using a variety of methodologies. For example, teachers and students reported ratings on three mental health outcomes in a cluster randomized controlled field trial in Manitoba (Santos, Chartier, Whalen, Chateau, & Boyd, 2011). Individual-level instruments were used to measure indirect aggression, physical aggression and pro-social behaviour in grade 4 and grade 8 children prior to the start of the program, at the end of the school year, and annually for three years after that. Immediately following the program, all teacher-rated outcomes showed

improvement, while student-rated effects were less pronounced. Similar outcomes were reported in the wait-listed control group who received the program the following year. Importantly, most of the effects as rated by the teachers were either maintained or showed further improvement during the three years after the program completed.

Another study evaluated the ROE programs' effect on social behaviour and social understanding outcomes among children in grade 4 to grade 7 from 28 public elementary schools in two large Canadian cities (Schonert-Reichl, Smith, Zaidman-Zait, & Hertzman, 2012). Outcomes were measured in children who received the program and compared to matched controls from schools that did not have ROE in any classrooms. Student-, teacher- and peer-reports were collected two to four weeks prior to receiving the program and two to four weeks following the end of the program. Children who received the ROE program had a significantly decreased number of incidents of proactive and relational aggression according to teacher-rated responses, and displayed greater pro-social behaviours as reported by their peers. The students also reported an improved understanding of infant crying despite no significant change in self-reported measures of empathy and perspective-taking.

A qualitative assessment of the effect the ROE program has on teachers, children, the classroom environment and the broader community was conducted following a trial of the program in Western Australia in 2004 (Cain & Carnellor, 2008). There were 15 trial program sites and each teacher was sent an initial questionnaire. Eight teachers from seven different schools participated in a follow-up interview. The program was delivered to grade 1 and grade 2 classes. The themes that emerged from the interviews showed significant improvements in the attitudes, knowledge and social-emotional competencies among the participating teachers and children. Specifically, teachers found that their knowledge and understanding of teaching social emotional learning had

improved, regardless of whether they had received previous SEL training. Teacher behaviour was also positively influenced by the program, as all participants reported a change in their ability to see another side of children and be more empathetic towards children, colleagues and parents. Furthermore, positive relationships between teachers, children, parents and the school community were promoted. Teachers also noted beneficial effects on the children in the program with reductions in bullying, and improvements in pro-social behaviours and positive behaviours related to anxiety, self-confidence and empathy.

Mental Health/Mental Illness

Definition

Individuals of all ages may experience good or poor mental health regardless of whether they have been diagnosed with a mental illness (Government of Canada, 2006, p. 2). In other words, mental health and mental illness are two distinct concepts in which some individuals may have good mental health while concurrently living with a mental illness, while others who have not met the diagnostic criteria of having a mental illness may also be affected by poor mental health (Keyes, 2002).

The World Health Organization defines mental health as a "state of well-being in which an individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and is able to make a contribution to his or her community" (World Health Organization, 2014). On the other hand, mental illness has been defined as the "alterations in thinking, mood or behaviour associated with significant distress and impaired functioning" (Government of Canada, 2006, p. 2), and often associated with a clinical diagnosis. Mental illness symptoms range in length and severity, giving rise to more than 400 types of mental illnesses identified in the International Classification of Diseases (ICD), 10th revision (Public

Health Agency of Canada [PHAC], 2015, p. 3). Building upon this definition, the National Research Council and the Institute of Medicine refer to mental disorders among children and adolescents as mental, emotional, and behavioural (MEB) disorders, which includes both clinically diagnosed disorders and the problem behaviours associated with them, such as violence, aggression, and anti-social behaviour (O'Connell, Boat, & Warner, 2009).

Epidemiology of Mental Illness Among Youth

Given the substantial number of conditions and the variation in symptoms and duration among individuals, it is difficult to estimate the incidence of mental illnesses (PHAC, p. 4 and 5). As such, reporting on the status of mental illness within populations has generally been accomplished with prevalence estimates of specific conditions, or a composite of more common conditions. It should also be noted that there are various methodological approaches that should be considered while comparing studies that report on the prevalence of mental illness, which include differences in measurement, changes in diagnostic criteria, and changing methods of diagnosing and treating childhood mental illness over time (McMartin, Kingsbury, Dykxhoorn, & Colman, 2014).

Among Canadian children and adolescents between 0 and 19 years old, approximately 15% have been estimated to have a mental illness at any given point in time, with the most common diagnoses being anxiety disorders, conduct disorders, attention deficit disorder, depression, and substance abuse (Canada. Parliament. Senate. Standing Committee on Social Affairs, Science and Technology, Kirby, & Keon, 2004a). In 2012, 8.2% of Canadians between 15 and 24 years old indicated that they had a mood disorder during the 12-months prior to being surveyed, which was higher than the estimates for any of the older age groups (Statistics Canada, 2015). The 2002/03 cycle of the National Longitudinal Survey for Children and Youth estimated that 17% of

children between 2 and 5 years old in Manitoba had emotional and anxiety problems, and 17% had physical aggression and conduct problems (Healthy Child Manitoba Office, 2005, p.46).

It is uncertain whether the prevalence of mental illness among children has increased over time given the number of diagnosable illnesses, the increased awareness of mental illness, and the methodological considerations regarding the measurement of mental illness. Using administrative data, 14% of children and adolescents 0 to 19 years in Manitoba were diagnosed with a mental illness over a 4-year period (2009/10 – 2012/13), which was up from the 12.5% that was estimated during the previous 4-year period (Chartier et al., 2016). However, national data on self-reported symptoms related to mental and behavioural problems remained relatively stable between 1994 and 2008 in Canadian children (McMartin et al., 2014). The McMartin et al. (2014) study also reported stable mean scores over time for depression and anxiety symptoms for children 10-11 years and 12-13 years, although symptoms decreased among the 14-15-year old youth. Mean scores for the conduct disorder and indirect aggression scales significantly decreased over time for all age groups, and the proportion of 12-13 and 14-15-year-old children who considered attempting suicide also decreased. The only increase that was reported was for symptoms of hyperactivity among the 10-11 and 12-13-year-old children.

The proportion of children and adolescents living with a mental illness remains significant. Furthermore, mental illnesses carry a substantial social, emotional and economic burden, which have negative impacts at the individual, family, community, and societal levels. Individually, youth who suffer from mental illness have a difficult time establishing healthy relationships, succeeding in school, and transitioning to the workforce, which in turn can be disruptive to the families that are caring for them (O'Connell et al., 2009). From a societal perspective, the costs of mental illnesses among young people extend well beyond the health sector to impact various

other service systems that support young people and their families such as the education, child welfare, and justice systems (Chartier et al., 2016; O'Connell, Boat, & Warner, 2009). In terms of economic impacts, the total cost of diagnosed and undiagnosed mental illnesses in Canada was estimated to be approximately $51 billion in 2003 (Lim, Jacobs, Ohinmaa, Schopflocher, & Dewa, 2008). This estimate was calculated from direct medical costs, short and long-term costs of lost work, and the loss in health utility that is associated with mental illness. Additionally, at least 7.2% of all governmental health service spending in Canada was directed to mental health services in 2007/08, with the greatest share being spent on pharmaceuticals (Jacobs et al., 2010). In Manitoba, expenditures on mental health spending in 2007/08 was estimated at $471 million (Jacobs et al., 2010).

Mental Health Services

The Kirby Report in 2004 provides a comprehensive history of mental health services in Canada highlighted by a shift in the provision of mental health care from psychiatric institutions to general hospitals and communities (Canada. Parliament. Senate. Standing Committee on Social Affairs, Science and Technology, Kirby, & Keon, 2004b). This current model of care is meant to enable individuals with mental illness to receive services while continuing to live meaningful lives within their communities (Canada. Parliament. Senate. Standing Committee on Social Affairs, Science and Technology, Kirby, & Keon, 2004). Mental health services are delivered through a variety of sectors and providers such as general hospitals, specialized services, outpatient community clinics, community-based services providing psychosocial supports and private counselling, and through the education, justice, and child welfare systems (Canada. Parliament. Senate. Standing Committee on Social Affairs, Science and Technology, Kirby, & Keon, 2004). However, a common problem in many provinces is that the system is fragmented,

posing a real challenge to individuals and families to access and navigate appropriate services (Davidson, 2011). In fact, only 25% of Canadian children and young adults between 15 and 24 years who reported having a mental illness or who had a substance dependency used a mental health service in the previous 12 months, while 24% felt that they needed but were not able to receive help (Statistics Canada, 2003). Indeed, the pathways to seeking help are complicated and many barriers impact the ability of children to access mental health services. Broadly, barriers have been classified as structural, mental health problem perception, and mental health service perception barriers (Owens et al., 2002), or as either sociopolitical or cultural/familial factors (Power, Eiraldi, Clarke, Mazzuca, & Krain, 2005). Examples of specific barriers include the ability of parents to recognize mental health problems, professionals failing to identify troubles, family-based stigma, and wait times (Davidson, 2011).

The various barriers and factors that a child may experience can also be described as a progression through the help-seeking behaviour stages, which include (1) the recognition that a problem exists, (2) deciding to seek help, and (3) selecting a service or treatment (Power et al., 2005). During each stage, the various factors comprising that stage influence what type of action, if any, is taken towards pursuing help (Srebnik, Cauce, & Baydar, 1996). In this help-seeking model, the stages are separated by the factors which relate to the child's illness profile, their predisposing demographic and sociocultural characteristics, and the barriers and facilitators to treatment (Srebnik, Cauce, & Baydar, 1996). If a child does reach the stage of selecting a service or treatment, the options most often used include psychological and pharmacological strategies, which may be used separately or in combination (Salum, DeSousa, Rosario, Pine, & Manfro, 2013). While psychological treatments have been shown to be efficacious in the treatment of some mental illnesses in youth, such as depression (Klein, Jacobs, & Reinecke, 2007) and have

significantly fewer serious adverse side effects, their accessibility may be hindered by a lack of psychotherapy resources, and the time and effort commitment required to participate in the structured nature of the treatment may influence patient compliance (Henry, Kisicki, & Varley, 2012). On the other hand, pharmacological treatments for children and adolescents may be more accessible; however, their safety, efficacy, and the long-term impacts from their use remains controversial (Henry et al., 2012; Rapoport, 2013).

Psychotropic Medications

Psychotropic medications are drugs that affect a person's mental state by acting on the central nervous system to produce either a calming or a stimulating effect. These medications are used to treat a wide range of clinical conditions, illnesses, and behavioural problems. According to The World Health Organization's (WHO) Anatomical Therapeutic Classification (ATC) System, psychotropic medications are found in the nervous system group, which has seven second-level subgroups: (1) anesthetics, (2) analgesics, (3) antiepileptics, (4) anti-Parkinson drugs, (5) psycholeptics, (6) psychoanaleptics, and (7) other nervous system drugs (WHO Collaborating Centre for Drug Statistics Methodology, 2000). The medications of interest within this study primarily fall under the psycholeptic or psychoanaleptic subgroups, which are further categorized as antidepressant, psychostimulant, anxiolytic, antipsychotic, and hypnotic and sedative medications.

Epidemiology of Psychotropic Medication Use Among Youth

The use of psychotropic medications gained acceptance in child psychiatry in the early 1980's following evidence of efficacy for disorders that were resistant to psychological treatments, such as ADHD and enuresis (Rapoport, 2013). Canadian research into the therapeutic management and treatment of mental illnesses in the 1970s and 1980s has also contributed significantly to the

development of new psychotropic medications (Canada. Parliament. Senate. Standing Committee on Social Affairs, Science and Technology et al., 2004b). Over time, a wider range of psychotropic medications have been prescribed to treat a variety of mental illness symptoms and conditions in children and adolescents, and while considerable variation exists, the use of these medications has increased over time in many countries (Steinhausen, 2015a).

Antidepressants represent a collection of medications identified in the ATC system as non-selective monoamine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), non-selective monoamine oxidase inhibitors, monoamine oxidase A inhibitors, and other antidepressants. The most common antidepressants prescribed to children under 18 years of age are SSRIs (Abi Khaled et al., 2003). Initially, antidepressants were used in children with enuresis, and then later to treat symptoms of depression disorders, anxiety, obsessive compulsive disorder, panic disorder, ADHD, autism, eating disorders, and chronic pain (Abi Khaled et al., 2003; Elia, Ambrosini, & Rapoport, 1999; Kodish, Rockhill, Ryan, & Varley, 2011; Oswald & Sonenklar, 2007; Rapoport, 2013).

In Saskatchewan, 15.4 /1000 children under 20 years of age were dispensed at least one antidepressant in 2007 (Meng, D'Arcy, & Tempier, 2014). Considering that many children receive more than one prescription per year, the total number of antidepressant dispensations during 2007 was 19,715, or 79.29 prescriptions filled per 1000 population (Meng et al., 2014). In Manitoba, the prevalence of children under the age of 20 who received at least one antidepressant prescription during the 2005/06 year was 10.9/1000 (Brownell et al., 2008). The prevalence in Manitoba appeared to have been increasing steadily between 1995 to 2004 before decreasing significantly in 2005/06 (Katz et al., 2008). This decrease occurred at a time when public health authorities in many countries were issuing regulatory warnings following concerns

of an increased risk of suicidality among children and adolescents using SSRIs (Hammad, 2004; Sparks & Duncan, 2013; Whittington et al., 2004). A similar effect was also experienced in other countries and jurisdictions following the warnings (Isacsson & Rich, 2014; Meng et al., 2014; Wijlaars, Nazareth, & Petersen, 2012). However, longer-term studies reveal that the initial effect of the warnings has dissipated, as concerns over suicidality decreased, and therefore rates of antidepressant use started to rise again, reaching pre-warning period levels in 2009 (Lam et al., 2013; Wijlaars et al., 2012). Lam et al. (2013) reported that prescriptions by pediatricians for SSRIs to Canadian children under 20 years of age had increased by 39% from 5.34/1000 children in 2005 to 7.45/1000 children in 2009.

Age and sex differences in the use of antidepressants among children and adolescents have also been reported. The prevalence of antidepressant use increases with age, and they are more frequently prescribed to females (Abi Khaled et al., 2003; Karanges, Stephenson, & McGregor, 2014; Meng et al., 2014; Vitiello, Zuvekas, & Norquist, 2006; Wijlaars et al., 2012). These differences are largely driven by the relatively high proportion of females between 12 and 20 who are prescribed these medications (Karanges et al., 2014; Wijlaars et al., 2012). These observations support findings regarding mental health service use, which is greatest among children between 15 and 19 years of age (PHAC, 2015, p. 8). Similarly, the incidence of depressive symptoms and diagnoses were higher for females than males in the 12-18-year-old group, but lower in the 3-11-year-old group (Wijlaars et al., 2012). Similarly, females between 15 and 24 in Canada have been shown to be 1.5 times more likely to report fair or poor mental health compared to males in the same age group (Government of Canada, 2006, p. 3).

Psychostimulants are most frequently used in the treatment of ADHD (Elia et al., 1999), and evidence has shown them to be effective at improving on-task behaviour among children

diagnosed with ADHD to become comparable to that of children without the condition (Rapoport, 2013). Psychostimulants are the most common of all psychotropic medications prescribed to youth in many countries, with the highest prevalence occurring in the United States (Abi Khaled et al., 2003; Olfson, Blanco, Wang, Laje, & Correll, 2014; Steinhausen, 2015b). Approximately 3.5% of all children under 19 years of age in the U.S. were prescribed a psychostimulant in 2008 according to a nationally representative annual survey of households (Zuvekas & Vitiello, 2012). Administrative data from an insurance program in a single state reported that 4.29% of individuals were prescribed a psychostimulant in 2000, with the highest proportion (7.4%) occurring in children between the ages of 10 and 14 years (Zito, Safer, & deJong-van den Berg, 2008). Furthermore, population-based prevalence in U.S. youth under the age of 21 visiting physicians in an office-based practice increased from 3% during the period of 1995 to 1998 to 9% during the period of 2007 to 2010 (Olfson et al., 2014). Similarly, psychostimulant prescribing to children between 5 and 19 years of age in Manitoba increased from 1.9% in 2000/01 to 2.7% in 2005/06 (Brownell et al., 2008). The studies by Olfson et al. (2014) and Brownell et al. (2008) also consistently demonstrate that children between 6 and 12 years, and males, are the most likely to be prescribed psychostimulant medications among child and adolescent populations.

Anxiolytic medications are typically used to treat anxiety disorders and their symptoms, but have also been used among children with autism (Oswald & Sonenklar, 2007). Although an antidepressant, SSRIs are the most common psychotropic medications used to treat symptoms of anxiety among children. The most common anxiolytic medication used for anxiety disorders are benzodiazepines, but are only used when symptoms are severe and other treatments have not been effective (Kodish et al., 2011). There are few published estimates of the prevalence of

anxiolytic medication use in the literature, but they indicate that the proportion of children and adolescents prescribed these medications are relatively low. The highest estimates have been found in the Netherlands, where 6.9 per 1000 children in 1999 and 7.3 per 1000 adolescents in 2000 have been reported (Schirm, Tobi, Zito, & de Jong-van den Berg, 2001; Zito et al., 2008). Slightly lower estimates were found in Manitoba, with a prevalence of 5.0 per 1000 children under the age of 20 in 2000/01 and 6.1 per 1000 in 2005/06 who received at least one anxiolytic prescription (Brownell et al., 2008).

Antipsychotics were initially used to treat schizophrenia, states of psychomotor excitation and sleep disorders among adults, but are now also used in children to treat a variety of conditions such as hyperkinetic disorders, ADHD, autism, anxiety, and conduct disorders (Bachmann, Lempp, Glaeske, & Hoffmann, 2014). The prevalence of antipsychotic use among children and adolescents is relatively low but has increased in recent years. In Germany, 0.23% of children under 19 years of age were prescribed an antipsychotic in 2005 compared to 0.32% in 2012 (Bachmann et al., 2014). In Canada, the proportion of youth between 15 and 24 years of age who were dispensed an antipsychotic increased from 0.9% in 2007/08 to 1.6% in 2013/2014 (CIHI, 2015, p. 17). In Manitoba, estimates from two studies reveal a steady increase from 0.19% in 1999 to 0.74% in 2008 (Brownell et al., 2008). The proportion of children prescribed antipsychotics increases with age, and they are more likely to be prescribed to males than females (Bachmann et al., 2014; Brownell et al., 2008).

Hypnotics and sedatives are very uncommonly prescribed to children and adolescents. A study examining the prescribing of these medications by community-based pediatricians showed that these medications were used most often for children with neurological impairment,

developmental delays, psychiatric conditions, ADHD, and in some cases, healthy children with difficulty falling or staying asleep (Owens et al., 2002).

Study Rationale

Compared to children without mental disorders, those with disorders use more health care services, more social services, have more interactions with the justice system, are more likely to be taken into care, to live in social housing, and to be in families receiving income assistance (Chartier et al., 2016). As such, improving mental health remains a priority for individuals and societies. Indeed, the overall vision in Manitoba's 2011 mental health strategic plan, titled *Rising to the Challenge*, is that "all Manitobans experience their optimal level of mental health and well-being" (Government of Manitoba, 2011, p.7). To achieve the best population mental health outcomes, an approach that incorporates prevention and promotion efforts is likely to produce the best results and be most cost-effective. Prevention has been defined as effectively avoiding risk factors for a disorder prior to onset, while promotion is the development of protective factors and certain skills that enhance the well-being of individuals and avoid adverse emotions and behaviours (O'Connell et al., 2009). Given that mental illness and mental health are two distinct concepts, it is evident that prevention and promotion are equally important in the context of achieving an optimal mental state. However, the predominant approach of most modern healthcare systems in addressing mental health is that of treating the symptoms of mental illness rather than preventing illness and promoting positive mental health.

The rate of psychotropic medications prescriptions has risen among children and adolescents, despite safety and efficacy concerns regarding their use. This trend that is reflected in each of the psychotropic medication classifications (Karanges et al., 2014; Meng et al., 2014; Murray, de Vries, & Wong, 2004; Olfson et al., 2014). Furthermore, many of the medications prescribed to

children and adolescents are being prescribed to treat conditions for which they are not indicated, which has led to the suggestion that these medications may be over-prescribed to children and adolescents (Rapoport, 2013), even though many children and adolescents go undertreated (E. Taylor, 2013). Furthermore, medications are a significant contributor to the overall cost of mental health care (Frank, Conti, & Goldman, 2005) experienced by individuals, families, and society (O'Connell et al., 2009). Clearly, effective mental health promotion and prevention programs are needed.

Many individuals living with mental illness in adulthood trace their first symptoms to a much younger age (O'Connell et al., 2009). Therefore, there is an increasing recognition that helping children early in their lives is important to their development and provides the best chance of preventing, or at least delaying, mental disorders, and promoting mental health (O'Connell et al., 2009). Interventions that develop characteristics of healthy social-emotional functioning in children, such as behaviour and emotion regulation, and positive social skills, present an opportunity to prevent mental illness and promote mental health (Jones, Greenberg, & Crowley, 2015). Previous evaluations of the Roots of Empathy program clearly demonstrate that it effectively facilitates the development of essential social and emotional skills, which may reduce the prescribing of psychotropic medications and avoid any side effects or unknown effects from their long-time use.

Study Objective and Hypothesis

The objective of this study is to determine whether participation in the ROE program is associated with psychotropic medication dispensations. It is hypothesized that the skills and associated positive mental health outcomes acquired from participating in the ROE program

prevent mental illness in children and adolescents such that it reduces their use of psychotropic medications.

Chapter 2. Methods

Research Design

A retrospective cohort research design was used to estimate the association between the ROE program and the use of psychotropic medications in a matched sample of children who received the program between 2002/03 and 2012/13 and children who did not. Children were stratified into three school grade groupings and then matched on key variables and propensity scores. The grade groupings were selected based on the grades that three ROE curricula are intended for and defined as:

(1) Grade grouping 1. Kindergarten to Grade 3 (inclusive)

(2) Grade grouping 2. Grade 4 to Grade 6 (inclusive)

(3) Grade grouping 3. Grade 7 and Grade 8

The outcomes were then analyzed in each grade grouping separately to determine if any impacts of the program could be attributed to participation in the program.

Data Sources

Several sources of data were used that provided information for the variables used in the matching, as well as in the calculation of the propensity score. The databases were originally created and are maintained by the various organizations which provide the services described in their files. De-identified copies of these data are housed in the Population Research Data Repository at the Manitoba Centre for Health Policy (MCHP), which facilitated secure, confidential data linkage and analysis capabilities. The databases included:

(1) Drug Program Information Network (DPIN) database (April 1st, 1995 – March 31, 2015)

The DPIN database is an electronic prescription drug database maintained by Manitoba Health, which provides information about pharmaceutical dispensations for all Manitoba residents, regardless of age, insurance coverage or final payer. The database collects information on the drug, dosage and prescription date for all prescriptions issued to Manitobans from retail pharmacies (i.e. excluding drugs provided in hospital).

(2) Enrollment, Marks, and Assessment database (April 1st, 1994 – March 31st, 2014)

The Enrollment, Marks, and Assessment database is maintained by Manitoba Education and Advanced Learning (now called Education and Training), and contains enrollment and demographic information on all children in kindergarten to grade 12 in Manitoba since the 1994/95 school year.

(3) Roots of Empathy program class lists (September 1st, 2002 – June 30th, 2013)

Class lists of the students who received the Roots of Empathy program were collected and maintained by provincial government's Healthy Child Manitoba Office (HCMO) in their data system for the Roots of Empathy program. Class lists were collected for the first year that each trained instructor implemented the program. The school and grade(s) that the program was administered to, along with demographic information of the children in those classrooms, are collected and stored in the database.

(4) Manitoba Health Insurance Registry (April 1st, 1984 – March 31st, 2015)

The Manitoba Health Insurance Registry is a population-based registry maintained by Manitoba Health and contains individual-level demographic information, family composition information, residential postal codes, and data fields for registration, birth,

entry into province, and migration in and out of province for all Manitobans covered under the universal provincial insurance plan.

(5) *Medical Services database (April 1st, 1988 – March 31st, 2014)*

Administrative health data for physician claims are collected in the Medical Services database, which is maintained by Manitoba Health. Fee-for-service physicians and nurse practitioners submit claims to Manitoba Health for payments corresponding to the services provided; salaried providers are instructed to file similar "shadow billing" claims for services provided, though these data are known to be somewhat incomplete.

(6) *Hospital Abstracts (April 1st, 1988 – March 31st, 2014)*

Demographic and clinical information is included in the abstract forms that are completed at the point of discharge from hospitals in Manitoba. Diagnosis codes from ICD-9-CM are used prior to April 1, 2004 and ICD-10-CM thereafter. All information in this database is maintained by Manitoba Health.

(7) *Canada Census (2006)*

Statistics Canada administers the Canada Census every 5 years, which collects basic socio-demographic information from all people living in Canada, and more extensive information from a randomly-selected sub-sample of the population. Information such as age, sex, marital status, employment, and income is collected and aggregated within small geographic areas called Dissemination areas, which contain between 400 and 700 people. MCHP uses the data from the Census to calculate, for each year, a composite measure of average socioeconomic status (i.e. SEFI-2) of the people living in each dissemination area.

(8) *Social Allowances Management Income Network database (April 1st, 1995 – March 31st, 2014)*

Records of all Manitobans who have ever received support from the provincial Employment and Income Assistance Program are kept in the Social Allowances Management Income Network database. Demographic and program information is collected in this database, which is maintained by Manitoba Jobs and the Economy.

(9) *Child and Family Services: Applications and Intake (April 1st, 1992– March 31st, 2014)*

Information on all children who have been taken into "out of home" care (aka foster care), and those receiving voluntary support and protective services from the Manitoba Department of Families (formerly called the Department of Family Services).

(10) *Fetal Alcohol Spectrum Disorder (April 1st, 1999 – March 31st, 2014)*

Clinical health information is collected and maintained by the Manitoba Fetal Alcohol Spectrum Disorder (FASD) clinic for all Manitobans assessed by the clinic, whether they receive a formal diagnosis of FASD or not.

Study Period

The study period began immediately after the end of the school year during which the ROE child received the program, and served as the "index date" for the start of follow-up. There were eleven index dates used in this study (July 1st each year from 2003 to 2013), corresponding to the eleven consecutive school years for which ROE participation data was available (2002/03 – 2012/13). All children in the study were followed forward from their index date until they were dispensed a psychotropic medication or were censored. Children were censored if they met any one of three criteria: (1) discontinued Manitoba Health Insurance coverage, (2) reached 18 years of age, or (3) reached the study termination date of March 31, 2015.

The reasons for choosing these censoring conditions are that health insurance coverage, under Manitoba's publicly-funded health care system, is discontinued when an individual moves out of the province or dies. In these instances, follow-up data is not available for these individuals and it is unknown whether they were dispensed a psychotropic medication beyond their censoring date. The second condition was used because every person in Manitoba gets assigned their own health insurance registration number once they reach 18 years of age, and are no longer automatically part of their parent's public health insurance coverage. This change may alter their ability to access medications, which is the outcome of this study. The study termination date was chosen because this was the latest date that medication dispensation data were available when the analysis began.

Study Sample

All school divisions in Manitoba received written invitations to have their schools become involved in the ROE program, and any schools that expressed interest were accommodated. Therefore, participation in the program was not randomly assigned, and the ROE group may not accurately represent the entire population of Kindergarten to Grade 8 children in Manitoba. However, the aim of this study was to determine the association of the ROE program on the group of children who received the program by making a comparison to a larger similar group of children who did not. Significant effort was used to ensure a fair comparison between the groups using matching and multivariate propensity scores, as described in detail below.

The ROE group was identified through class lists collected by the Healthy Child Manitoba Office (HCMO), which were collected when an ROE instructor implemented the program for the

first time.[1] The control group was selected from the population of Manitoba-born children who were enrolled in any kindergarten to grade 8 classrooms between the 2002/03 and 2012/13 school years. To minimize the potential contamination bias related to children who received the program but were not identified on the HCMO class lists, only children attending schools that never implemented the ROE program were eligible for the control group. For computational efficiency, random samples of 10,000 children from each grade level (kindergarten through grade 8) in the control group were selected to proceed to subsequent stages.

Any child who had been dispensed any of the medications that were also considered in the study outcomes for this study during a one-year period prior to the start of follow-up were excluded because they would be considered existing users. This period, called a washout period, was used to ensure that only children who were dispensed any of the medications under investigation for the first time after the start of follow-up index date were considered new users. Further exclusions were made for children with missing information on any of the baseline variables used in the calculation of the propensity scores, or health insurance coverage dates that did not include their start of follow-up index date. The remaining children are referred to as the original sample and were used in the creation of the matched sample (described below).

Variables

Variables used in this study are defined below and categorized as either hard-matching, propensity score matching, control, or analysis variables.

[1] Instructors could choose to continue providing the program in subsequent years, but class lists were not required to be recorded beyond the first year. Therefore, only a subset of all children who received ROE in Manitoba could be identified.

Hard-Matching Variables

Academic Year

A categorical variable that indicated the school year and specific grade that the child was in at the start of the ROE program. Children were hard matched on this variable to ensure that matches were concurrent (e.g. ROE and control group children who were in grade 4 in different years could not be matched with one another).

School Division

School division was assigned to each child based on the school they were attending at the start of the ROE program to provide a measure of where the child resided. This variable provided a smaller geographic area (better matching) than regional health authority area, and was used during the first step of matching.

Regional Health Authority (RHA)

A categorical variable used to indicate the residential location of the parent(s), or guardian(s) which whom the child was residing at the propensity score index date. Each family's postal code as recorded in the Health Registry file was used to determine the RHA that their residence belonged. RHAs are larger geographic areas than school divisions, and were used to find matches only for children who could not be matched by school division.

Sex

A dichotomous variable indicating the sex of the child at birth as indicated in the Manitoba Health Registry. This variable was used to create a similar composition of males and females in the ROE and control groups.

Propensity Score Variables

Propensity scores were calculated with a logistic regression model and separate scores were calculated for each of the three grade groups. The dependent variable was a dichotomous

variable indicating whether or not a child received ROE between the 2002/03 and 2012/13 school years. The independent variables are divided into three categories: (1) sociodemographic, (2) home, family and health, and (3) mental health and developmental disability.

Sociodemographic Variables

Birthdate

Each child's exact date of birth was taken from the Manitoba Health Registry file. This variable was used in conjunction with the academic year variable to ensure that matches not only required children to be in the same school grade in the same year, but were also as similar as possible in age (sometimes to the day).

SEFI-2 (at birth and at propensity score index date)

A continuous variable that may take negative or positive values indicating better or worse socioeconomic conditions, respectively. The Socioeconomic Factor Index 2 (SEFI-2) is a quantitative measure of average socioeconomic conditions of small geographic areas based on four variables recorded in Canadian census data (Chateau, Metge, Prior, & Soodeen, 2012). Annual SEFI-2 scores for census dissemination areas are available at MCHP and can be assigned to individuals using postal codes. Two dates were used to calculate separate SEFI-2 scores for each child based on their parent(s), or guardian(s) area of residence: (1) the child's birth date, and (2) the propensity score index date (defined in the Matching section below). The mother's postal codes were taken from the Manitoba Health Registry. This variable was used to account for the known association of socioeconomic status with many aspects of child health and well-being, including social and emotional development (Bradley & Corwyn, 2002).

Mother's Age at First Birth

A continuous variable indicating the age of the child's mother on the day she had her first child. This variable was used to account for the negative health, educational, and social outcomes observed for children of young mothers (Jutte et al., 2010).

Home, Family, and Health Variables

Residential Mobility

A discrete variable indicating the number of times that a child's family moved residences between birth and their propensity score index date. This was measured as the number of different postal codes assigned to the child's parent(s), or guardians(s) in the Manitoba Health Insurance Registry between birth and their propensity score index date. The postal codes are updated in the Registry every 6 months. Therefore, some moves may be missed if a child's family moves more than once between updates. This variable was used to account for the stress and disruption to children and families when moving residences. Stressors in the home have been shown to be associated with a variety of childhood health outcomes including depression as well as behavioural and emotional problems (Jelleyman & Spencer, 2008).

Family Size

A discrete variable defined as the number of children aged 0-19 years who live together in one household at the time of the child's propensity score index date. This information was collected from the Manitoba Health Insurance Registry.

Younger Sibling

A dichotomous variable that indicated if the child had a younger sibling at the time of the propensity score index date was used to control for exposure to a baby prior to the ROE program that provides a child with experience observing a baby and their development. Younger sibling was determined using the Manitoba Health Insurance Registry.

Income Assistance

A dichotomous variable indicating whether a child's family ever received income assistance between birth and their propensity score index date. This information was available from the Social Allowances Management Information Network database. Low income has consistently been shown to be associated with poor health and developmental outcomes for children, which result from the stressors and negative situations that are related to the home environment and relationships characteristic of families living in poverty (Duncan & Brooks-Gunn, 2000).

Child and Family Services

Two dichotomous variables were used to indicate a child's status regarding contact with the Child and Family Services system in Manitoba: (1) whether a child was ever placed in the care of Manitoba Child and Family (CFS) services, and (2) whether their family ever received voluntary protection or support services from CFS. These variables were measured during the period between birth and the study child's propensity score index date.

Major Illness

A dichotomous variable indicating whether a child experienced a major illness between birth and their propensity score index date. The John Hopkins Adjusted Clinical Group case-mix system was used to identify major illness, which categorizes ICD-9/ICD-10 diagnosis codes into aggregated diagnosis groups (ADGs). The ADGs suggested and adapted by Currie et al. (2010) for child populations were used in this study, as the default algorithms used by the ACG software exclude some important diagnoses relevant to child health outcomes, such as ADHD, conduct disorders, asthma, and major injuries.

Fetal Alcohol Spectrum Disorder (FASD)

A dichotomous variable indicating whether a child was referred to the Manitoba FASD centre program, regardless if they received a diagnosis for FASD, between birth and their propensity

score index date. Only the referral was used, because the circumstances that lead to referrals to the centre were thought to be adequate to possibly indicate that the child's family situation poses an elevated level of stress. This variable was also helpful to account for the greater risk of being prescribed psychotropic medications associated with children with FASD (Brownell et al., 2013).

Intellectual Disability

A dichotomous variable indicating whether a child was identified as having an intellectual disability between birth and their propensity score index date. Having an intellectual disability was determined using Enrollment, Marks, and Assessment database, and using ICD9/ICD-10 diagnosis codes in the hospital abstracts and medical claims databases (specific codes are included in Appendix A)

Special Needs Funding Level 2 or 3

A dichotomous variable indicating whether a child ever received special needs funding in school during the time between starting school and the child's propensity score index date.

Mental Health Variables

Attention Deficit/Hyperactivity Disorder (ADHD)

A dichotomous variable indicating whether a child had been diagnosed with ADHD. It is a neuro-behavioural developmental disorder with symptoms that may lead to difficulties learning and developing relationships. Psychostimulants are often prescribed for children with an ADHD diagnosis. This variable was measured between August 31 of the year 3 years before the child entered kindergarten (i.e. approximately 2 years of age) and their propensity score index date.

Autism Spectrum Disorder (ASD)

A dichotomous variable indicating whether a child had been diagnosed with ASD. Children with ASD are characterized by social, communicative and behavioural impairments. Children with ASD were identified using hospital and physician visit records. This variable was measured

between August 31 of the year 3 years before an individual entered kindergarten and August 31 of their propensity score index date.

Mental Illness

A dichotomous variable indicating whether a child had a diagnosis in mental health chapter of the ICD system, other than for ADHD or ASD. These were gathered from physician visit and hospital discharge abstract records. This variable was measured between August 31 of the year 3 years before an individual entered kindergarten and August 31 of their propensity score index date.

Psychotropic Medication Dispensation

A dichotomous variable indicating whether a child was dispensed any of the psychotropic medications under the N05 (psycholeptics) or N06 (psychoanaleptics) classes of the Anatomical Therapeutic Chemical (ATC) classification system. This variable was measured between August 31 of the year 3 years before an individual entered kindergarten and August 31 of their propensity score index date.

Control Variable

Given the matched nature of the study, many of the potential confounding variables were controlled for during the design stage by way of propensity score and hard-matching. There was one potential confounding variable that could not be included in the propensity score calculation, and therefore it was included as a control variable in the outcome models (described below). Therefore, the variables used in the final models consisted of only the outcome variable (psychotropic prescription dispensation), the independent variable (ROE receipt), and one control variable (annual physician visit rate).

Annual Physician Visit Rate

A discrete variable indicating the annual average number of visits with a physician at their office, walk-in clinic, the patient's home, outpatient departments, and some emergency room instances. The first annual visit rate was calculated for the one-year period before the start of follow-up, and subsequent visit rates were calculated for each year thereafter until medication dispensation or censoring occurs. This variable was treated as a time-dependent variable in the analysis, and was used to account for the fact that those with higher visits rates are more likely to receive prescriptions for any kind of medication.

Analysis Variables

Outcome variable: time to dispensation of a psychotropic medication

Explanatory variable: ROE program receipt

To estimate whether there was difference in the proportion of children who received a psychotropic medication the outcome variable was the time from the start of follow-up to the first dispensation of a psychotropic medication, measured in days. The specific medications under investigation were identified by their Anatomical Therapeutic Chemical (ATC) classification code, developed by the World Health Organization (WHO Collaborating Centre for Drug Statistics Methodology, 2000). This included most drugs in the N05 (psycholeptics) and N06 (psychoanaleptics) categories. The drug names and classification codes for the medications used in this study are listed in Appendix B.

The psychotropic medications that were analyzed primarily fall in the psycholeptic and psychoanaleptic subgroups for medications that act on the nervous system (one medication falls in the antiepileptic subgroup). The psycholeptic medications included antipsychotics, anxiolytics, and hypnotics and sedatives, while the psychoanaleptics were limited to antidepressants and

psychostimulants. The specific medications were selected based on a discussion and recommendations from a clinical pharmacist with extensive experience in clinical pharmacy and pharmaco-epidemiology, who identified any medications that might be prescribed to a child or adolescent.

The explanatory variable was a dichotomous variable indicating whether a child received ROE between the 2002/03 and 2012/13 school years.

Matching

Matching of control group children to ROE group children was accomplished by hard-matching on key variables, and then by propensity scores. The propensity scores expressed each child's probability of receiving the ROE program, based on baseline variables that were selected for their potential to be a predictor of being dispensed a psychotropic medication and to account for any systematic differences between the groups at the start of follow-up. The stratification of children into the three grade groupings made it possible to assess the same variables for varying lengths of time depending on the grade grouping they belonged. The time periods used for measuring most baseline variables were:

1) Grade grouping 1 (K-Gr 3): Birth until August 31 of the year they entered Kindergarten.
2) Grade grouping 2 (Gr 4-6): Birth until August 31 of the year they entered Grade 4.
3) Grade grouping 3 (Gr 7-8): Birth until August 31 of the year they entered Grade 7.

The end dates used are referred to as the "propensity score index date."

For baseline variables relating to a diagnosis of a mental illness or developmental disability, the period used for all three grade groupings started on August 31 of the year that was three years before the child entered kindergarten and ended on the propensity score index date. The start

dates used for these variables, rather than right from birth, was chosen because the likelihood of being confirmed 'cases' for these variables is very small at that age (approximately 2 years old).

Propensity scores were created using a logistic regression model where ROE receipt (0/1) was the outcome. Matches were made using the nearest neighbor matching method, with a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score, which has been recommended as an optimal caliper width under a variety of settings (Austin, 2011). This method matched a child from the control group whose logit of the propensity score was closest to that of the ROE group child, and within the caliper range.

Four matched samples were initially created from four propensity score models that were created using different combinations of predictor variables. Along with the propensity scores, two additional variables were used as hard-matching variables for each matched sample: (1) an indicator of the family's geographic area of residence (school division or regional health authority), and (2) academic year (grade and school year). In two of the four matched samples, sex was removed from the propensity score and used as a hard-matching variable. The matched sample chosen for the final analysis was determined through an assessment of the balance in baseline variables between the ROE and control groups in the matched sample. The four propensity score models were:

1. Model 1: Only main effects for all baseline variables
2. Model 2: Sex variable removed from Model 1 and used as a hard-matching variable.
3. Model 3: Model 1 but relaxing the assumption of a linear relationship between the continuous variables and the log-odds of receiving ROE by using restricted cubic splines.
4. Model 4: Sex variable removed from Model 3 and used as a hard-matching variable.

Given the substantially higher number of children who had not received ROE compared to those who had, a k:1 matching scheme was used to improve the power to detect real differences between the groups. Specifically, a two-step incomplete k:1 matching without replacement protocol was used. School divisions are smaller geographic areas than regional health authorities, so the first step identified matches using school division of residence, academic year, propensity score, and, depending on the model, sex. All children not matched in Step 1 had their propensity scores re-calculated, and the second round of matching used regional health authority of residence, academic year, (recalculated) propensity score, and, depending on the model, sex.

Analysis

Children's baseline characteristics in the ROE and control groups of the original sample were compared using standardized differences. ROE and control groups in each grade grouping were compared separately. A difference greater than 0.10 was used to indicate an imbalance in the baseline characteristics (Austin, 2014), and would act as the trigger for further analysis and revision to overcome the imbalance. The mean ages and proportion of males were also compared between children who were excluded from the starting sample and those who made up the original sample using a t-test and chi-square test, respectively.

Next, the balance of baseline characteristics was examined in each grade grouping of the matched sample using weighted standardized differences for all variables, as well as weighted variance ratios, side-by-side boxplots, and empirical cumulative distribution functions for the six continuous variables. The weight that was assigned to each child in the ROE groups was equal to one. The weight assigned to a child in the control group was equal to the reciprocal of the number of control group children in each given matched set (Austin, 2008). A comparison of baseline variables using standardized differences was done to identify any differences between

the ROE group children in the matched sample and those who went unmatched. This was done to get a sense of the characteristics of the children who did receive ROE but were not included in the study, and to avoid making any inferences regarding the programs impact on children who share those characteristics.

Lastly, separate analyses were conducted for each grade grouping in the matched sample, to model six outcomes:

(1) the first dispensation of any psychotropic medication (composite)

(2) the first dispensation of an antidepressant

(3) the first dispensation of an anxiolytic

(4) the first dispensation of an psychostimulant

(5) the first dispensation of an antipsychotic

(6) the first dispensation of an hypnotic or sedative

The number and proportion of children in the ROE and control groups who were dispensed at least one medication in each of the six outcomes are reported for the entire group and stratified by sex. Given the various start of follow-up dates and lengths of follow-up, the differences in medication dispensations were statistically tested using survival analysis methods on the time to event data, which allowed for the analysis to make use of all the available data. Kaplan-Meier survival curves and Cox proportional hazard models (unadjusted and adjusted modes) were constructed for each medication dispensation outcome, and compared for each grade grouping separately. Given that the Cox proportional hazard models included a time-dependent variable, Schoenfeld residuals were used to test for any violations of the proportionality assumption

(Allison, 2010). No violations of the assumption were observed for any hazard models that reached statistical significance.

The Kaplan-Meier survival curves illustrate the probability of not being dispensed a psychotropic medication at least to time *t*, and provide a measure of the absolute difference in the probabilities between groups. Differences were calculated for *t* values of 1, 3, 5, 7, 9, and 11 years of follow-up for Grade grouping 1; at 1, 3, 5, 7, and 9 years for Grade grouping 2; and at 1, 3, and 5 years for Grade grouping 3. To account for the lack of independence in matched samples, a stratified log-rank test that stratified on the matched sets was used to compare the equality of the survival curves (Austin, 2014).

Hazard functions quantify the instantaneous risk that an event will occur at time *t*, given that an individual has survived to time *t*, and were used to provide a measure of the relative change in the hazard of being dispensed a psychotropic medication between the groups. Unadjusted and adjusted hazards ratios that accounted for each child's annual physician visit rate were calculated for each outcome. In these models, the (larger) control group was the reference group, and the ROE group was compared to that. Hazard ratios, 95% confidence intervals, and p-values for the unadjusted and adjusted models were calculated. The partial likelihood method was used to estimate the β coefficients in the Cox models. To account for the matched nature of the sample, a robust variance estimator that accounts for the clustering with matched sets was used (Austin, 2014). Similar analyses were conducted on subgroups stratified by sex.

Statistical significance was set at the $p \leq 0.05$ level for all statistical tests. All data manipulation and statistical analyses were performed on the MCHP secure system, with SAS statistical software, version 9.3.

Ethics

The feasibility of the proposed research using repository data was approved through a process of writing and submitting a proposal to MCHP prior to gaining access to the data. MCHP also requires the completion of an accreditation session that provides an overview of MCHP, and the data access and use process. The accreditation also included the signing of a pledge of confidentiality and an agreement that the researcher understands and will follow the process for doing research at MCHP. Once the study was deemed feasible, ethical approvals from the University of Manitoba's Human Research Ethics Board (H2016:037) and the Manitoba Health's Health Information Privacy Committee (HIPC No. 2015/2016-62) were granted. Approvals were also granted from HCMO, Manitoba Education and Advanced Learning, Manitoba Jobs and the Economy, Manitoba Family Services, and the Winnipeg Health Authority (WRHA) for the use of the databases maintained by each of these organizations and housed at MCHP. Finally, a UM researcher agreement was signed upon receipt of all approval documentation.

Data Management

All information stored in the databases housed at MCHP are de-identified before being placed in the repository: identifying information is either removed or scrambled. Access to the repository data requires approval of the research proposal by MCHP, by the UM's Health Research Ethics Board, by the province's Health Information Privacy Committee, and by the organizations whose data are being used (e.g. Department of Education and Healthy Child Manitoba). Information between databases is linked through an encrypted unique personal identifier. All analyses were conducted in the tightly controlled environment at MCHP. The MCHP workplace, data spaces and computers storing the databases are restricted areas and access is granted only to those with authorization, using two-factor authentication.

Chapter 3. Results

Original Sample

There was a total of 6,876 children identified in the HCMO class lists who received ROE and 90,000 children randomly selected from 339,874 children who did not receive the program. The proportion of the total children in each group who were excluded during the process of creating the original sample was small (ROE = 7.1%; control = 13.1%; Table 1). There were 417 children in the ROE group (Grade grouping 1 = 99; Grade grouping 2 = 265; Grade grouping 3 = 53) and 3,876 control children (Grade grouping 1 = 1,410; Grade grouping p 2 = 1,457; Grade grouping 3 = 1,009) were excluded after being identified as being dispensed one of the psychotropic medications under investigation during one-year washout period (Table 1). Another 70 children in the ROE group (Grade grouping 1 = 17; Grade grouping 2 = 36; Grade grouping 3 = 17) and 7,887 children in the control group (Grade grouping 1 = 2,647; Grade grouping 2 = 2,917; Grade grouping 3 = 2,323) were excluded due to missing baseline information or possessing health insurance coverage that did not include their start of follow-up date. There were also 19 children in the control group for Grade grouping 3 who were excluded because they had been referred to the FASD clinic, whereas none of the children in the ROE groups had been referred. The decision to exclude these children was made to avoid any potential problem during matching.

Table 1. Number and percentage of children excluded following the 1-year washout period and those with missing information in each grade and grade grouping.

ROE Group				
Grade	Washout Period	Other Exclusions	Total Exclusions	% Excluded
K (n=274)	9	2	11	4.01%
1 (n=389)	17	4	21	5.40%
2 (n=630)	29	4	33	5.24%
3 (n=676)	44	7	51	7.54%
Grade grouping 1 Total (n=1,969)	99	17	116	5.89%
4 (n=1,910)	107	15	122	6.39%
5 (n=1,117)	72	5	77	6.89%
6 (n=983)	86	16	102	10.4%
Grade grouping 2 Total (n=4,010)	265	36	301	7.51%
7 (n=363)	22	4	26	7.16%
8 (n=534)	31	13	44	8.24%
Grade grouping 3 Total (n=897)	53	17	70	7.80%
Overall Total (n=6,876)	417	70	487	7.08%
Control Group				
Grade				
K (n=10,000)	213	268	481	4.81%
1 (n=10,000)	315	562	877	8.77%
2 (n=10,000)	422	809	1,231	12.3%
3 (n=10,000)	460	1,008	1,468	14.7%
Grade grouping 1 Total (n=40,000)	1,410	2,647	4,057	10.1%
4 (n=10,000)	488	460	948	9.48%
5 (n=10,000)	490	993	1,483	14.8%
6 (n=10,000)	479	1,464	1,943	19.4%
Grade grouping 2 Total (n=30,000)	1,457	2,917	4,374	14.6%
7 (n=10,000)	524	846	1,370	13.7%
8 (n=10,000)	485	1,458	1,943	19.4%
Grade grouping 3 Total (n=20,000)	1,009	2,304	3,313	16.6%
Overall Total (n=90,000)	3,876	7,868	11,744	13.1%

The mean ages of the children in the ROE group who were excluded were 8.21, 11.06, and 13.80 years in Grade groupings 1, 2, and 3, respectively (Table 2). Compared to the ROE children in the original sample, the excluded children were significantly older in Grade groupings 1 ($p = .0053$) and 2 ($p < .0001$), and similar in Grade grouping 3 ($p = 0.3863$). In all three grade groupings, the proportion of males who were excluded were significantly higher compared to the proportion of males in the original sample ($p < .05$). Among control children, those excluded were significantly older and made up of a higher proportion of males than the children in the original sample in all three Grade groupings ($p < .0001$; Table 3).

Table 2. Demographic comparisons between original sample and excluded children in the ROE group

	Original Sample	Excluded	p-value
Grade grouping 1			
N	1,853	116	
Age, years, mean (SD)	7.91 (1.10)	8.21 (1.06)	.0053
Male sex, n (%)	956 (51.6%)	72 (62.1%)	.0284
Grade grouping 2			
N	3,709	301	
Age, years, mean (SD)	10.8 (0.90)	11.1 (0.97)	<.0001
Male sex, n (%)	1,837 (49.5%)	215 (71.4%)	<.0001
Grade grouping 3			
N	827	70	
Age, years, mean (SD)	13.7 (0.72)	13.8 (0.66)	0.3863
Male sex, n (%)	388 (46.9%)	51 (72.9%)	<.0001

Table 3. Demographic comparisons between original sample and excluded children in the control group

	Original Sample	Excluded	p-value
Grade grouping 1			
N	35,943	4,057	
Age, years, mean (SD)	7.51 (1.19)	8.02 (1.15)	<.0001
Male sex, n (%)	18,304 (50.9%)	2,365 (58.3%)	<.0001
Grade grouping 2			
N	25,626	4,374	
Age, years, mean (SD)	11.1 (0.95)	11.4 (0.93)	<.0001
Male sex, n (%)	12,844 (50.1%)	2,556 (58.4%)	<.0001
Grade grouping 3			
N	16,687	3,313	
Age, years, mean (SD)	13.7 (0.75)	13.8 (0.75)	<.0001
Male sex, n (%)	8,436 (50.6%)	1,906 (57.5%)	<.0001

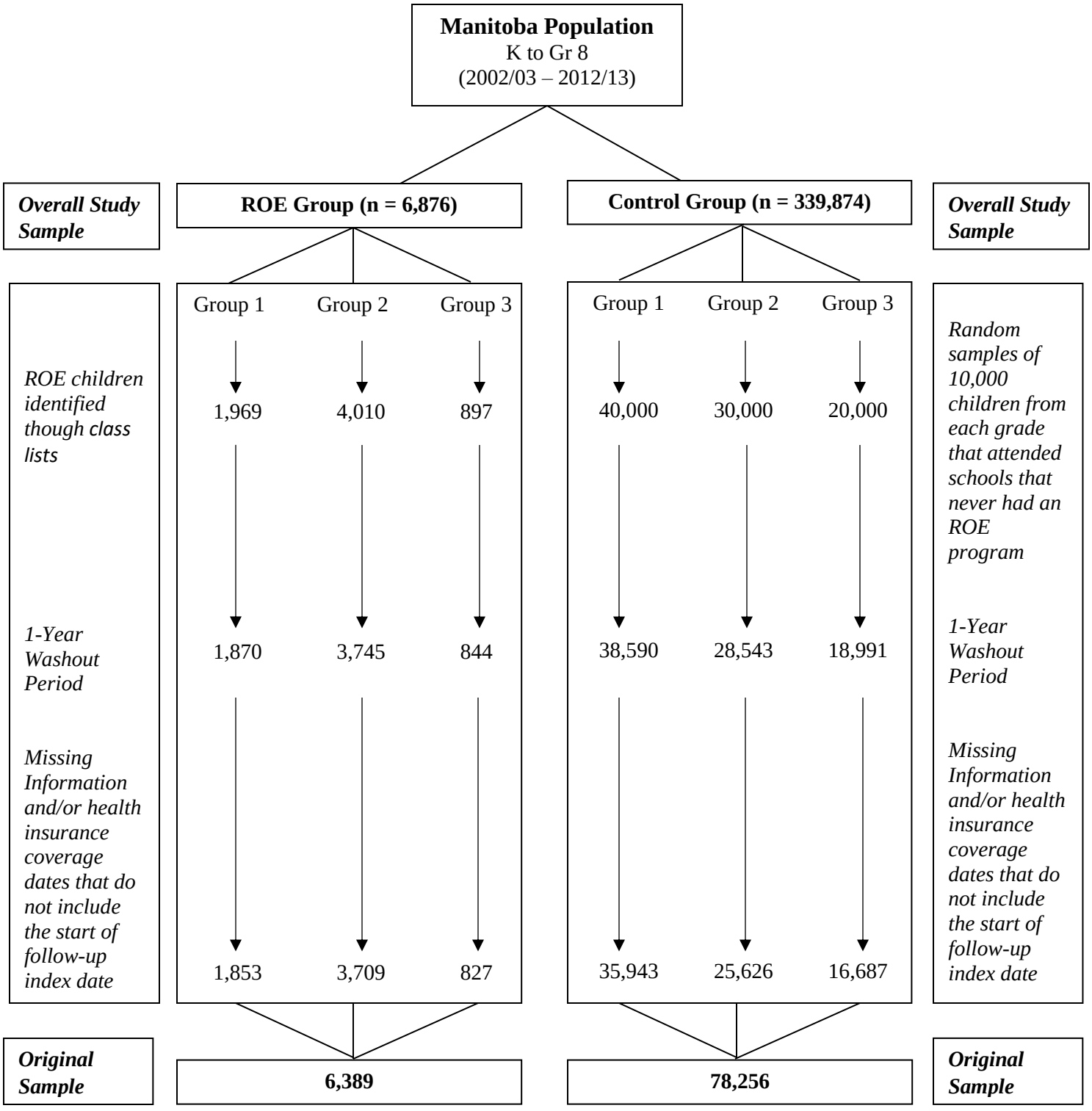

Figure 1. Sample sizes for the three grade groups following the 1-year washout period and exclusions that led to the original sample

The remaining children following the exclusions represented the original sample, which consisted of 6,389 children in the ROE group and 78,256 children in the control group (Figure 1). The proportion of children in the ROE group in each grade was highest in Grade 4 (20.8%) and lowest in kindergarten (4.1%; Table 4). At the grade grouping level, the highest proportion of children in the ROE group was in Grade grouping 2 (58.1%) and the lowest was in Grade grouping 3 (13.0%).

Table 4. Sample size breakdown by grade in the original sample

Grade	ROE n (%)	Control n (%)
Grade grouping 1		
K	263 (4.1)	9,519 (12.2)
1	368 (5.8)	9,123 (11.7)
2	597 (9.3)	8,769 (11.2)
3	625 (9.8)	8,532 (10.9)
Total	1,853 (29.0)	35,943 (45.9)
Grade grouping 2		
4	1,788 (28.0)	9,052 (11.6)
5	1,040 (16.3)	8,517 (10.9)
6	881 (13.8)	8,057 (10.3)
Total	3,709 (58.1)	25,626 (32.7)
Grade grouping 3		
7	337 (5.3)	8,630 (11.0)
8	490 (7.7)	8,057 (10.3)
Total	827 (13.0)	16,687 (21.3)
Overall Total	6,389	78,256

Matched Sample

Matching

The matched sample created from propensity score model 4 demonstrated the greatest balance between the ROE and control groups (results reported below in this section). The standard deviation of the logit of propensity score, caliper widths, and the number of matched sets during the two steps of matching are shown in Table 5. The first step in the matching process used caliper widths of 0.27, 0.48 and 0.22, and resulted in the formation of 2,180 matched pairs in Grade grouping 1; 2,534 in Grade grouping 2; and 739 in Grade grouping 3. The second step, using a broader geographic area for residence (RHA rather than school district), resulted in caliper widths of 0.26, 0.49, and 0.22 leading to another 5,267, 5,122, and 1,272 matched pairs in the three Grade groupings, respectively. Therefore, the final matched sample consisted of 7,447, 7,656, and 2,011 matched pairs in grade groupings 1, 2, and 3, respectively. The matched sample also consisted of a large proportion of ROE group children in the original sample who were able to be matched with at least one control group child (Grade grouping 1 = 92.0%; Grade grouping 2 = 88.3%; Grade grouping 3 = 79.1%; Table 6).

Table 5. Caliper widths and number of matched sets formed during the first and second attempts at matching.

First propensity scores			
Grade grouping	Std Dev*	Caliper Width†	Matched Pairs
1 (n = 37796)	1.33	0.27	2,180
2 (n = 29335)	2.42	0.48	2,534
3 (n = 17414)	1.08	0.22	739
Second propensity scores			
Grade grouping			
1 (n = 35425)	1.32	0.26	5,267
2 (n = 25950)	2.45	0.49	5,122
3 (n = 16562)	1.09	0.22	1,272
*of Logit of Propensity Score † Caliper Width = 0.2 x Standard deviation of logit of propensity score			

Table 6. Number of ROE group children who found at least one match.

	Step 1		Step 2		Overall	
Grade grouping	No.	Percent	No.	Percent	No.	Percent
1 (n = 1853)	733	39.6%	972	86.8%	1,705	92.0%
2 (n = 3709)	1,224	33.0%	2,051	82.5%	3,275	88.3%
3 (n = 827)	227	27.4%	427	71.2%	654	79.1%

The number of controls that were matched to a child in the ROE group in the three grade groupings are shown in Table 7. Of the 1,705 children in Grade grouping 1 who received ROE who also found at least one match, 254 were matched to the maximum of 10 control children. The ratio of ROE to control group children in Grade groupings 2 and 3 in the original sample made it possible for only a maximum of 6 control children per each ROE child. There were 408 of the 3,275 children in Grade grouping 2 and 167 of the 654 children in G Grade grouping 3 who received ROE and were also matched to the maximum 6 control children.

Table 7. Number of control group children matched per ROE group child

Control No.	Grade grouping 1	Grade grouping 2	Grade grouping 3
1	1,705	3,275	654
2	1,238	1,739	416
3	1,041	1,052	319
4	834	678	254
5	641	504	201
6	541	408	167
7	459	-	-
8	394	-	-
9	340	-	-
10	254	-	-
Total	7,447	7,656	2,011

The grade distributions of ROE group children were similar between the original and matched samples (Figure 2). The greatest difference between proportions of original and matched samples was 2.4% in grade 4. Therefore, the matching process was applied equally across for all grades where children from the ROE group who went unmatched came from each grade proportionately. The total number and proportions of ROE and control group children in each grade of the matched sample are shown in Table 8.

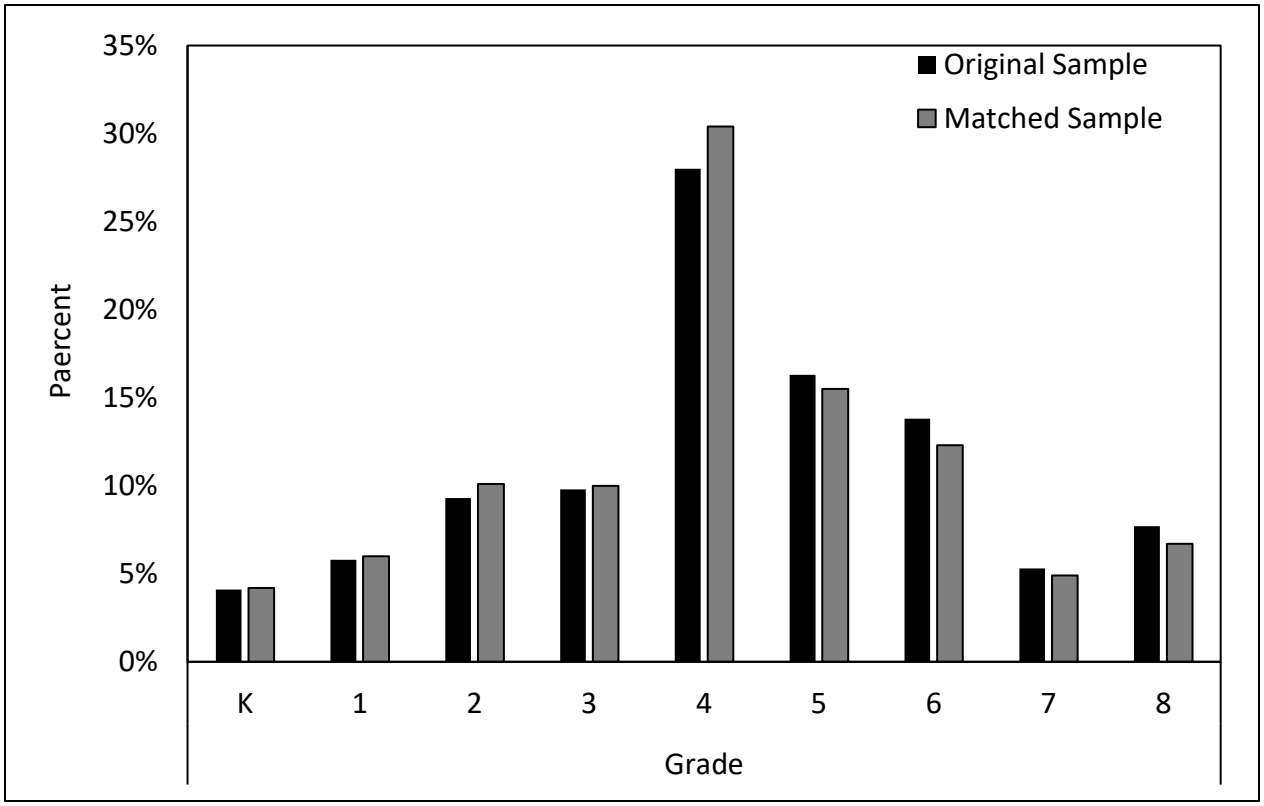

Figure 2. Grade distributions of original and matched samples

Table 8. Sample size breakdown by grade in the matched sample

Grade	ROE n (%)	Control n (%)
Grade		
K	237 (4.2)	902 (5.3)
1	337 (6.0)	1,666 (9.7)
2	567 (10.1)	2,478 (14.5)
3	564 (10.0)	2,401 (14.0)
Grade grouping 1 Total	1,705 (30.3)	7,447 (43.5)
4	1,710 (30.4)	3,917 (22.9)
5	873 (15.5)	2,457 (14.4)
6	692 (12.3)	1,282 (7.5)
Grade grouping 2 Total	3,275 (58.1)	7,656 (44.7)
7	274 (4.9)	893 (5.2)
8	380 (6.7)	1,118 (6.5)
Grade grouping 3 Total	654 (11.6)	2,011 (11.8)
Overall Total	5,634	17,114

Balance Diagnostics

Weighted Standardized Differences

Standardized differences in the original sample revealed that six of the 19 baseline covariates in Grade groupings 1 and 2, and seven covariates in Grade grouping 3 had differences above the 0.10 threshold (Tables 9,10, and 11). Matching reduced the differences for each of these variables, and all except the Residential Mobility variable in Grade grouping 1 (0.124) and Grade grouping 3 (0.126) were below the acceptable threshold. Matching reduced the differences in all but four covariates in Grade grouping 1 (Family Size, SEFI2 at birth, Intellectual Disability, and Special Needs Funding); two in Grade grouping 2 (Intellectual Disability, and Autism), and five in Grade grouping 3 (Family Size, SEFI2 at birth, Age at Follow-up, ADHD, and Psychotropic

Medications). However, the standardized differences for each of the covariates that were higher in the matched sample were still below 0.10, except for Family Size in Grade grouping 1 (0.109)

Table 9. Comparison of baseline characteristics between Grade grouping 1 ROE group and control group children in the original and matched samples

Variable	Standardized difference	Weighted Standardized difference
Birthdate	0.368	0.001
Mothers age at 1st birth	0.160	0.004
Family size	0.097	0.109
SEFI2 at birth	0.041	0.095
SEFI2 at Index date	0.103	0.041
Residential Mobility	0.138	0.124
Age at Follow-up	0.353	0.002
Male sex	0.013	0.000
Income Assistance	0.199	0.054
CFS	0.057	0.004
CFS but never in care	0.066	0.064
Younger sibling	0.053	0.011
Major Childhood Illness	0.021	0.002
FASD referral	0.025	0.018
Intellectual Disability	0.002	0.021
ADHD	0.028	0.019
Autism	0.022	0.006
Mental Illness	0.033	0.032
Psychotropic Medication	0.091	0.018
Special needs funding	0.021	0.028

Table 10. Comparison of baseline characteristics between Grade grouping 2 ROE group and control group children in the original and matched samples

Variable	Standardized difference	Weighted Standardized difference
Birthdate	0.844	0.005
Mothers age at 1st birth	0.054	0.034
Family size	0.149	0.094
SEFI2 at birth	0.080	0.023
SEFI2 at Index date	0.095	0.003
Residential Mobility	0.117	0.080
Age at Follow-up	0.279	0.016
Male sex	0.012	0.000
Income Assistance	0.130	0.027
CFS	0.055	0.010
CFS but never in care	0.133	0.048
Younger sibling	0.081	0.031
Major Childhood Illness	0.054	0.036
FASD referral	0.057	0.002
Intellectual Disability	0.001	0.019
ADHD	0.022	0.007
Autism	0.004	0.021
Mental Illness	0.045	0.012
Psychotropic Medication	0.028	0.013
Special needs funding	0.074	0.008

Table 11. Comparison of baseline characteristics between Grade grouping 3 ROE group and control group children in the original and matched samples

Variable	Standardized difference	Weighted Standardized difference
Birthdate	0.697	0.020
Mothers age at 1st birth	0.125	0.058
Family size	0.013	0.055
SEFI2 at birth	0.011	0.083
SEFI2 at Index date	0.067	0.027
Residential Mobility	0.180	0.126
Age at Follow-up	0.078	0.096
Male sex	0.073	0.000
Income Assistance	0.234	0.042
CFS	0.072	0.039
CFS but never in care	0.150	0.064
Younger sibling	0.025	0.000
Major Childhood Illness	0.106	0.026
FASD referral	.	.
Intellectual Disability	0.085	0.049
ADHD	0.022	0.066
Autism	0.041	0.014
Mental Illness	0.046	0.020
Psychotropic Medication	0.002	0.010
Special needs funding	0.141	0.065

Weighted Variance Ratios

Variance ratios were calculated for the continuous variables in the original sample and compared to the weighted variance ratios in the matched samples with values closer to 1 representing greater unity (Table 12). The matched samples produced some ratios that were closer to unity (Date of Birth and Age at Follow-up), some that were further away (SEFI2 at Birth and Index Date), and some that were unchanged (Mothers age at 1st birth and Residential Mobility).

Table 12. Weighted Variance Ratios (control/ROE)

	Grade grouping 1		Grade grouping 2		Grade grouping 3	
Variable	Original Sample	Matched Sample	Original Sample	Matched Sample	Original Sample	Matched Sample
Date of Birth	2.72	1.00	2.00	1.00	1.00	1.00
Family size	1.06	1.10	1.38	1.01	1.01	1.15
SEFI2 at birth	1.25	1.36	1.13	1.21	1.14	0.98
SEFI2 at index	1.13	1.33	1.21	1.34	0.98	1.17
Mothers age at 1st birth	1.06	0.97	0.96	1.05	1.11	1.04
Residential Mobility	0.88	0.89	1.04	0.99	0.94	1.14
Age at Follow-up	1.16	1.03	1.10	1.03	1.12	1.16

Graphical summaries (Cumulative Density Functions, Boxplots)

The cumulative density functions and side-by-side boxplots for each continuous variable in the original and matched samples are shown in Appendix C. The density functions are similar between the samples for most variables in all three grade grade groupings. Most notably, matching improved the density functions for birthdate and age at follow-up. The side-by-side boxplots also demonstrate that the continuous variable distributions for ROE and control group children in the matched sample were similar to those in the original sample.

Unmatched Descriptive Statistics

There were 755 ROE group children in the Original sample for whom no matches could be found (Grade grouping 1 = 148; Grade grouping 2 = 434; Grade grouping 3 = 173). The descriptive statistics for these children and the standardized differences between them and the matched ROE group children are shown in Tables 13, 14, and 15. Many of the standardized differences were above 0.10. In each of the three Grade groupings, the unmatched children were older at the time of follow-up, had mothers who had their first child at a younger age, had larger family sizes, higher SEFI2 scores, moved residences more often, were more likely to have families who

received income assistance, and to have been in contact with the CFS system (in care or otherwise).

Table 13. Comparison of baseline characteristics between matched and unmatched ROE group children in Grade grouping 1

Variable	Unmatched n (%)* n = 148	Matched n (%)* n = 1,707	Std. Diff.
Birthdate (mean ± SD)	14,342 ± 464	14,636 ± 875	0.420
Mothers age at 1st birth (mean ± SD)	20.30 ± 3.51	25.03 ± 5.58	1.014
Family size (mean ± SD)	3.26 ± 1.90	2.47 ± 1.18	0.496
SEFI2 at birth (mean ± SD)	0.85 ± 1.17	0.06 ± 0.98	0.734
SEFI2 at Index date (mean ± SD)	0.89 ±1.13	0.07 ± 0.97	0.778
Residential Mobility (mean ± SD)	1.05 ± 1.18	0.80 ± 1.09	0.222
Age at Follow-up (mean ± SD)	8.01 ±1.22	7.90 ± 1.09	0.089
Male sex	72 (48.7)	884 (51.9)	0.064
Income Assistance	91 (61.5)	393 (23.1)	0.845
CFS	24 (16.2)	45 (2.64)	0.478
CFS but never in care	17 (11.5)	140 (8.21)	0.110
Younger sibling	76 (51.4)	749 (43.9)	0.149
Major Childhood Illness	39 (26.4)	457 (26.8)	0.010
FASD referral	Sup.	7 (0.41)	0.036
Intellectual Disability	0 (0.00)	9 (0.53)	0.103
ADHD	Sup.	19 (1.11)	0.021
Autism	0 (0.00)	Sup.	0.069
Mental Illness	13 (8.78)	165 (9.68)	0.031
Psychotropic Medication	10 (6.76)	85 (4.99)	0.075
Special needs funding	Sup.	32 (1.88)	0.011
Sup. = Suppressed due to small cell size (<5) *unless otherwise specified			

Table 14. Comparison of baseline characteristics between matched and unmatched ROE group children in Grade grouping 2

Variable	Unmatched n (%)* n = 173	Matched n (%)* n = 654	Std. Diff.
Birthdate (mean ± SD)	12,587 ± 805	12,372 ± 1225	0.207
Mothers age at 1st birth (mean ± SD)	22.98 ± 4.85	25.20 ± 5.31	0.436
Family size (mean ± SD)	3.11 ± 1.59	2.65 ± 1.29	0.315
SEFI2 at birth (mean ± SD)	0.47 ± 1.21	0.02 ± 1.08	0.397
SEFI2 at Index date (mean ± SD)	0.50 ± 1.13	-0.03 ± 1.00	0.503
Residential Mobility (mean ± SD)	2.05 ± 2.13	1.65 ± 2.12	0.188
Age at Follow-up (mean ± SD)	13.88 ± 0.78	13.69 ± 0.69	0.256
Male sex	84 (48.6)	304 (46.5)	0.041
Income Assistance	83 (48.0)	164 (25.1)	0.490
CFS	15 (8.67)	29 (4.43)	0.172
CFS but never in care	39 (22.5)	93 (14.2)	0.216
Younger sibling	107 (61.9)	337 (51.5)	0.209
Major Childhood Illness	85 (49.1)	269 (41.1)	0.161
FASD referral	0 (0.00)	0 (0.00)	.
Intellectual Disability	Sup.	11 (1.68)	0.045
ADHD	Sup.	16 (2.45)	0.009
Autism	Sup.	Sup.	0.041
Mental Illness	15 (8.67)	53 (8.10)	0.020
Psychotropic Medication	7 (4.05)	18 (2.75)	0.071
Special needs funding	13 (7.51)	29 (4.43)	0.130
Sup. = Suppressed due to small cell size (<5) *unless otherwise specified			

Table 15. Comparison of baseline characteristics between matched and unmatched ROE group children in Grade grouping 3

Variable	Unmatched n (%)* n = 434	Matched n (%)* n = 3,275	Std. Diff.
Birthdate (mean ± SD)	13,939 ± 921	14,004 ± 978	0.068
Mothers age at 1st birth (mean ± SD)	23.38 ± 5.42	25.36 ± 5.46	0.364
Family size (mean ± SD)	2.72 ± 1.45	2.59 ± 1.22	0.096
SEFI2 at birth (mean ± SD)	0.14 ± 1.11	-0.03 ± 1.00	0.158
SEFI2 at Index date (mean ± SD)	0.25 ± 1.21	-0.08 ± 0.93	0.299
Residential Mobility (mean ± SD)	1.38 ± 1.65	1.18 ± 1.51	0.125
Age at Follow-up (mean ± SD)	11.38 ± 0.84	10.75 ± 0.88	0.723
Male sex	202 (46.5)	1635 (49.9)	0.068
Income Assistance	176 (40.6)	741 (22.6)	0.393
CFS	31 (7.14)	119 (3.63)	0.156
CFS but never in care	82 (18.9)	421 (12.9)	0.166
Younger sibling	219 (50.5)	1574 (48.1)	0.048
Major Childhood Illness	172 (39.6)	1096 (33.5)	0.128
FASD referral	6 (1.38)	12 (0.37)	0.109
Intellectual Disability	7 (1.61)	22 (0.67)	0.089
ADHD	10 (2.30)	73 (2.23)	0.005
Autism	Sup.	9 (0.27)	0.031
Mental Illness	28 (6.45)	264 (8.06)	0.062
Psychotropic Medication	11 (2.53)	79 (2.41)	0.008
Special needs funding	26 (5.99)	102 (3.11)	0.138
Sup. = Suppressed due to small cell size (<5) *unless otherwise specified			

Observation Period

The lengths of observation calculated from the start of follow-up until censoring for reasons other than medication dispensation are shown in Table 16. For Grade groupings 1 and 3, the mean and median lengths were similar between the ROE and control groups. In Grade grouping 2, the ROE group children had slightly longer mean and median observation lengths compared to the control group, suggesting that there was a slightly higher proportion of control group children who were censored because they either moved or died.

Table 16. Lengths of observation periods (years)

	ROE					Control				
Grade grouping	Mean	SD	Min	Med	Max	Mean	SD	Min	Med	Max
1	7.62	2.63	0.17	8.42	12.4	7.41	2.70	0.08	8.42	12.4
2	5.83	2.00	0.25	6.27	9.16	5.51	2.11	0.01	5.63	9.17
3	4.03	0.82	0.17	4.10	5.80	4.01	0.87	0.08	4.07	6.06

Outcomes

Grade grouping 1: Kindergarten – Grade 3

There were 212 ROE group children (12.4%) and 860 control group children (11.6%) who were dispensed at least one psychotropic medication during the follow-up period (Table 17). Except for anxiolytic medications, the proportion of children in the ROE group dispensed at least one medication in each psychotropic classification was higher compared to the proportion in the control group. Within the ROE group, psychostimulants were most likely dispensed at least once (5.3%), and hypnotics and sedatives least likely (0.6%). Anxiolytic medications were the most likely dispensed at least once in the control group (5.1%), and hypnotics and sedatives were the least (0.3%).

Among males, 13.5% in the ROE group and 11.7% in the control group were dispensed at least one psychotropic medication. Males in the ROE group children were also more likely to be dispensed a psychostimulants or antipsychotic medication at least once compared to males in the control group, and less likely dispensed an antidepressant or anxiolytic medication. The proportion of females who were dispensed at least one psychotropic medication or antidepressant were similar between ROE and control groups (11.3% and 11.4%, respectively). Females in the ROE group were less likely dispensed at least one anxiolytic or psychostimulant and more commonly dispensed an antipsychotic. Within the ROE and control groups, females were more likely dispensed at least one antidepressant or anxiolytic medication compared to males, while males were more likely dispensed psychostimulants.

Table 17. Proportion of children dispensed at least one medication for each outcome in Grade grouping 1

	ROE (n, %)			Control (n, %)		
Event	Male	Female	Total	Male	Female	Total
Any Psychotropic	119 (13.5)	93 (11.3)	212 (12.4)	443 (11.7)	417 (11.4)	860 (11.6)
Antidepressants	10 (1.13)	29 (3.53)	39 (2.29)	43 (1.13)	101 (2.77)	144 (1.93)
Anxiolytics	34 (3.85)	41 (4.99)	75 (4.40)	160 (4.22)	218 (5.97)	378 (5.08)
Psychostimulants	67 (7.58)	23 (2.80)	90 (5.28)	254 (6.69)	111 (3.04)	365 (4.90)
Antipsychotics	33 (3.73)	22 (2.68)	55 (3.23)	80 (2.11)	82 (2.25)	162 (2.18)
Hypnotics & Sedatives	Sup.	Sup.	10 (0.59)	88 (0.21)	16 (0.44)	24 (0.32)
Sup. = Suppressed due to small cell size (<5)						

Kaplan-Meier survival curves for ROE and control group children are shown in Figures 3 to 8. Visual comparison of the curves for each group indicates that after 5 years of follow-up, the survival probabilities under each of the outcomes, except for anxiolytics, were lower for ROE group children than control group children. Calculating the absolute difference in survival probabilities after 1, 3, 5, 7, 9, and 11 years of follow-up indicate that the probability of being

dispensed at least one psychotropic medication is small along the entire follow-up period (Table 18). This is confirmed in the stratified log-rank tests, which revealed the only statistically different survival curve was for antipsychotic dispensations (p = 0.026; Figure 7). In this case, the absolute difference in the probability of being dispensed one of these medications after 11 years of follow-up between the ROE group and control group was still only 0.012 (Table 18).

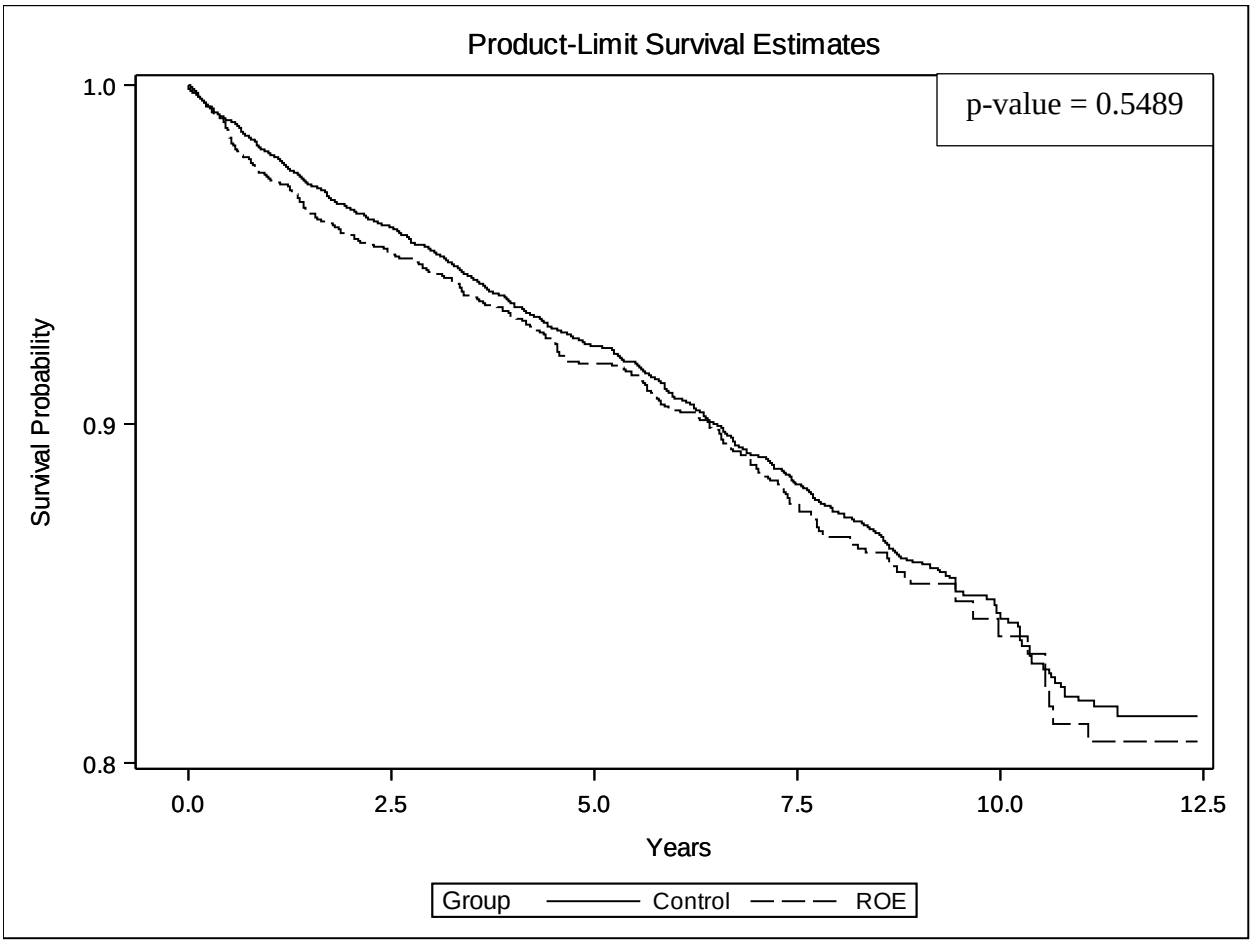

Figure 3. Survival curves for time to first psychotropic dispensation in Grade grouping 1

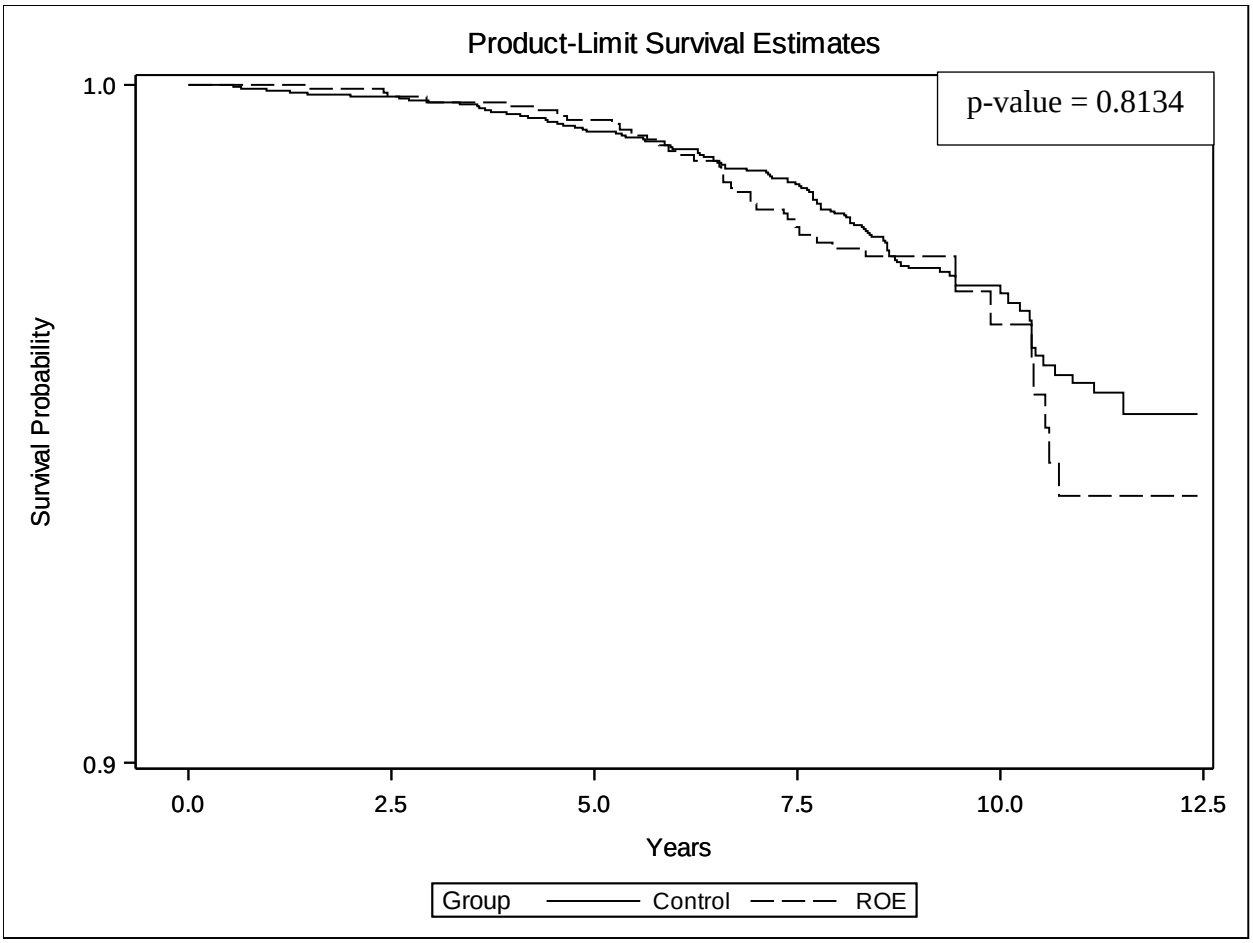

Figure 4. Survival curves for time to first antidepressant dispensation in Grade grouping 1

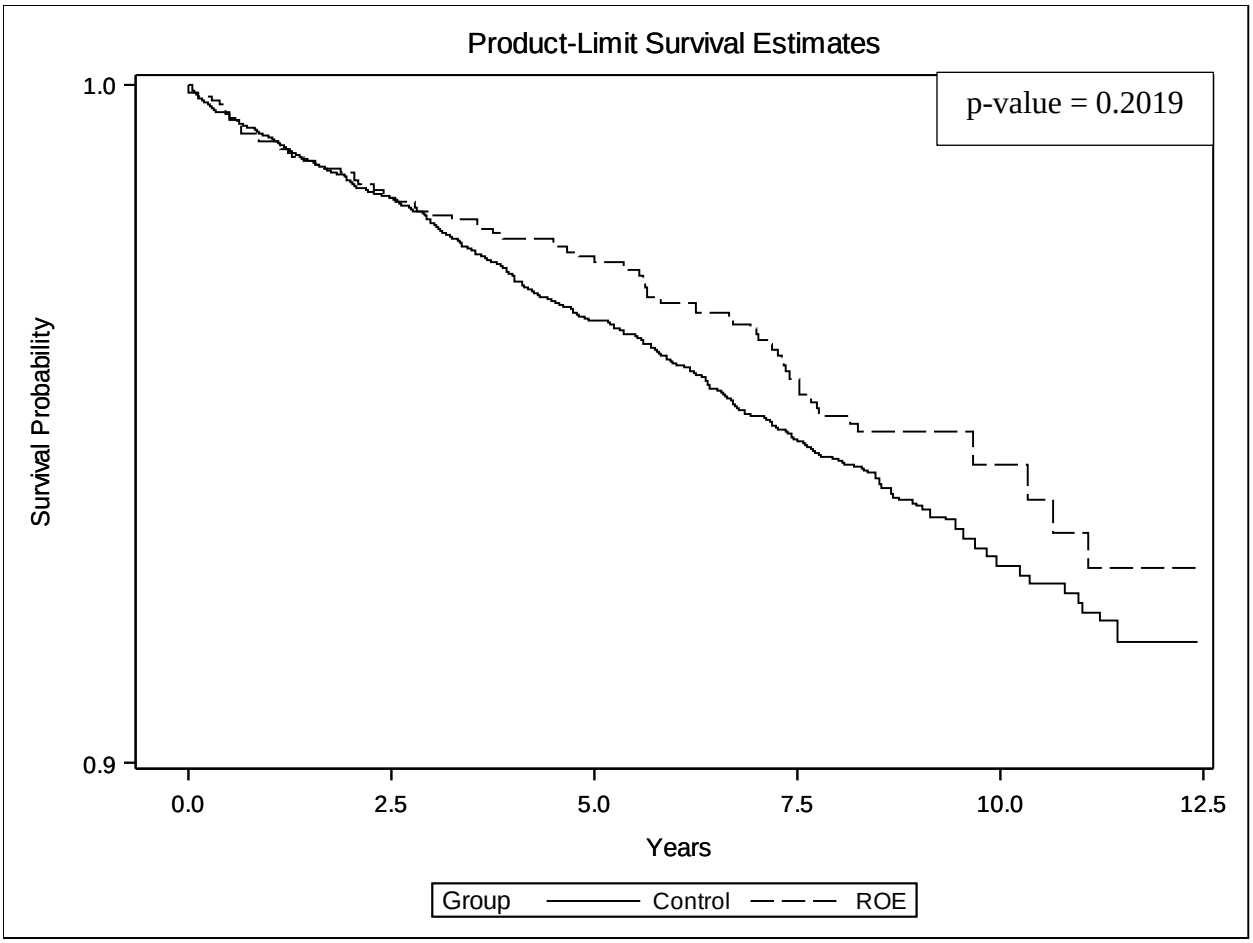

Figure 5. Survival curves for time to first anxiolytic dispensation in Grade grouping 1

Figure 6. Survival curves for time to first psychostimulant dispensation in Grade grouping 1

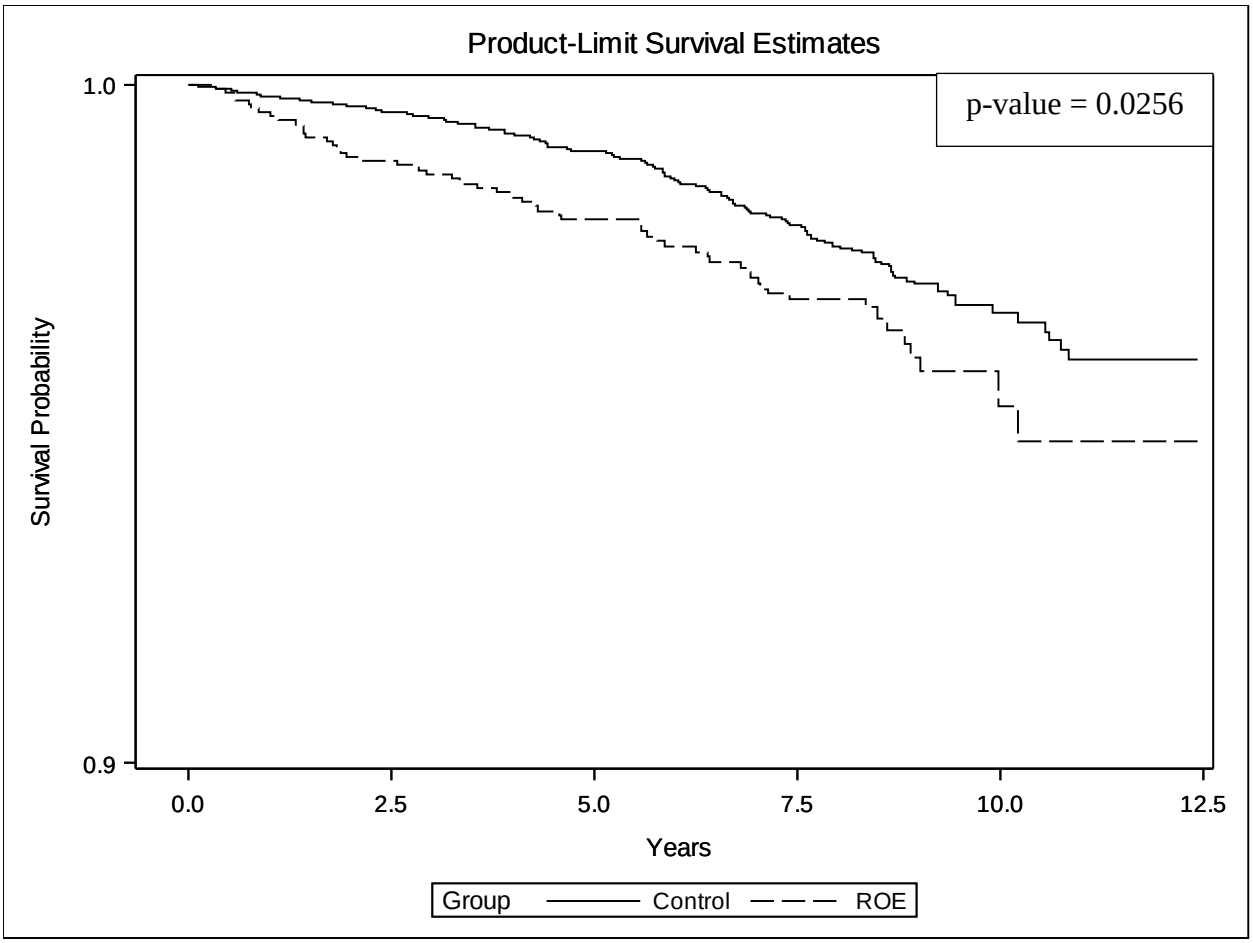

Figure 7. Survival curves for time to first antipsychotic dispensation in Grade grouping 1

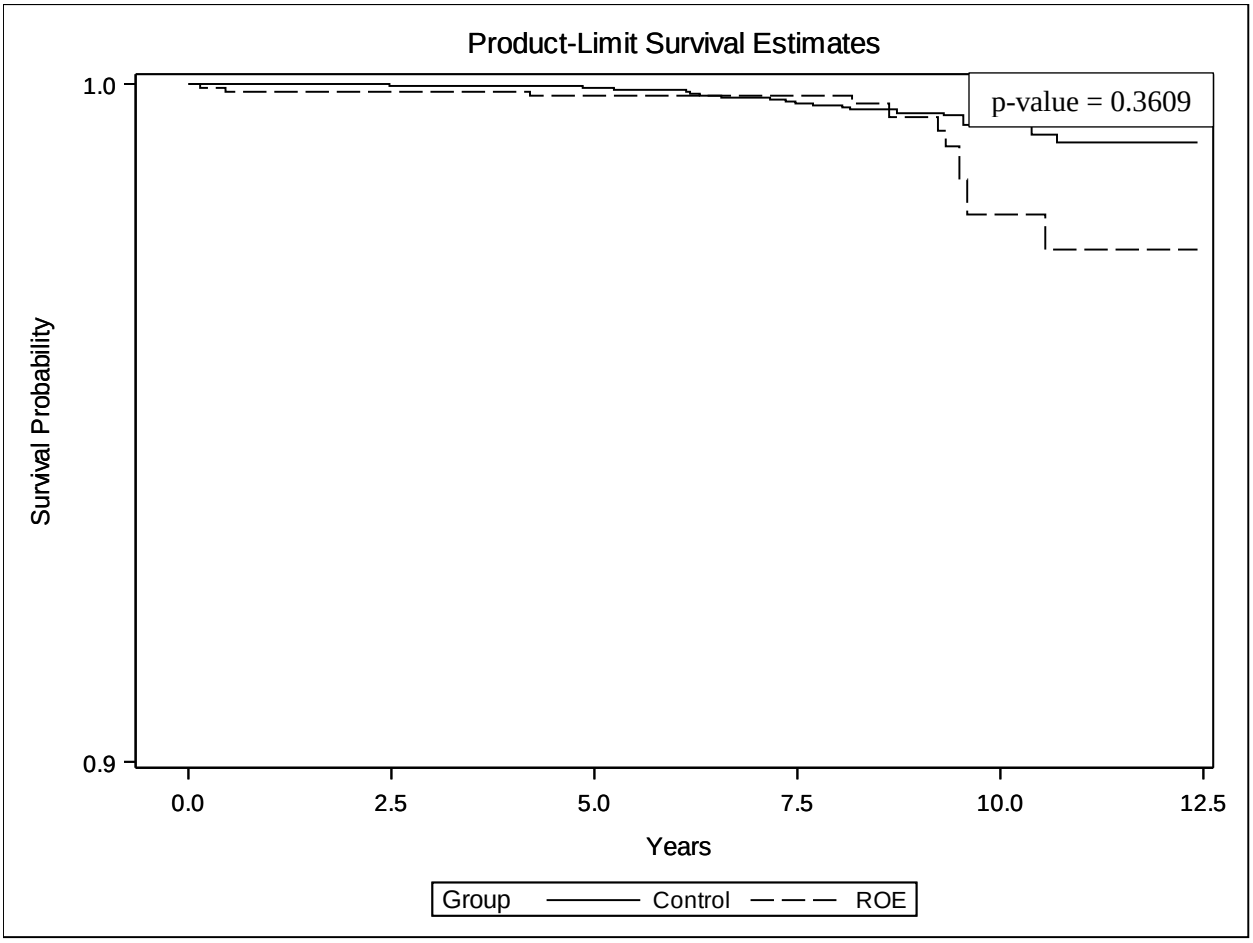

Figure 3. Survival curves for time to first hypnotic & sedative dispensation in Grade grouping 1

Table 18. Absolute difference in survival probabilities at 1, 3, 5, 7, 9, 11, and 12 years of follow-up in Grade grouping 1

Years of Follow-up	ROE	Control	
Any Psychotropic	Survival Probability		Difference
1	0.9723	0.9797	0.0074
3	0.9449	0.9512	0.0063
5	0.9180	0.9236	0.0056
7	0.8870	0.8907	0.0037
9	0.8527	0.8590	0.0063
11	0.8242	0.8180	0.0062
Antidepressants			
1	1.0000	0.9992	-0.0008
3	0.9975	0.9975	0.0000
5	0.9948	0.9932	-0.0016
7	0.9825	0.9874	0.0049
9	0.9746	0.9729	-0.0017
11	0.9393	0.9560	0.0167
Anxiolytics			
1	0.9917	0.9925	0.0008
3	0.9807	0.9796	-0.0011
5	0.9740	0.9651	-0.0089
7	0.9632	0.9513	-0.0119
9	0.9488	0.9378	-0.0110
11	0.9339	0.9236	-0.0103
Psychostimulants			
1	0.9823	0.9886	0.0063
3	0.9702	0.9739	0.0037
5	0.9542	0.9619	0.0077
7	0.9487	0.9512	0.0025
9	0.9391	0.9427	0.0036
11	0.9339	0.9328	-0.0011
Antipsychotics			
1	0.9959	0.9984	0.0025
3	0.9868	0.9951	0.0083
5	0.9801	0.9903	0.0102
7	0.9715	0.9809	0.0094
9	0.9599	0.9706	0.0107
11	0.9476	0.9596	0.012
Hypnotics & Sedatives			
1	0.9988	1.0000	0.0012
3	0.9988	0.9997	0.0009
5	0.9982	0.9994	0.0012
7	0.9982	0.9979	-0.0003
9	0.9752	0.9958	0.0206
11	0.9755	0.9913	0.0158

Tables 19 and 20 display the hazard ratios, 95% confidence intervals, and p-values for both the unadjusted and adjusted models. The only statistically significant differences between ROE and control group children in the unadjusted models occurred for antipsychotic dispensations where the hazard among all children (HR = 1.45, p = 0.008) and among males (HR = 1.81, p = 0.002) were higher in the ROE group (Table 19). After adjusting for the annual physician visit rates, only the difference among males remained significant (HR = 1.67, p = 0.013; Table 20). The adjusted models also revealed that children in the ROE group had a lower hazard of being dispensed an anxiolytic medication at least once (hazard ratio = 0.75, p = 0.033). In this case, children in the ROE group were at a 25% lower hazard of being dispensed an anxiolytic medication than children in the control group. Similar hazard ratios were estimated for males and females analyzed separately as that estimated when all children were analyzed; however, neither of these sex-specific differences reached statistical significance (Table 20).

Table 19. Unadjusted Hazard Ratio and 95% confidence intervals generated for each psychotropic medication classification with Cox regression models in Grade grouping 1

Event	HR	95% CI	p-value
All Children			
Any Psychotropic	1.05	0.91 – 1.21	0.490
Antidepressants	1.05	0.75 – 1.46	0.781
Anxiolytics	0.84	0.66 – 1.07	0.157
Psychostimulants	1.07	0.87 – 1.32	0.530
Antipsychotics	**1.45**	**1.10 – 1.91**	**0.008**
Hypnotics & Sedatives	1.43	0.80 – 2.59	0.223
Males			
Any Psychotropic	1.15	0.96 – 1.39	0.140
Antidepressants	0.90	0.47 – 1.73	0.755
Anxiolytics	0.94	0.67 – 1.33	0.731
Psychostimulants	1.10	0.86 – 1.41	0.445
Antipsychotics	**1.81**	**1.25 – 2.60**	**0.002**
Hypnotics & Sedatives	1.90	0.80 – 4.54	0.149
Females			
Any Psychotropic	0.94	0.76 – 1.17	0.584
Antidepressants	1.11	0.76 – 1.64	0.579
Anxiolytics	0.77	0.56 – 1.07	0.124
Psychostimulants	0.99	0.65 – 1.51	0.968
Antipsychotics	1.11	0.72 – 1.70	0.634
Hypnotics & Sedatives	1.15	0.52 – 2.56	0.728
Note. Control group was the reference			

Table 20. Adjusted Hazard Ratio and 95% confidence intervals generated for each psychotropic medication classification with Cox regression models in Grade grouping 1

Event	HR	95% CI	p-value
All Children			
Any Psychotropic	0.94	0.81 - 1.10	0.460
Antidepressants	1.06	0.75 - 1.49	0.755
Anxiolytics	**0.75**	**0.57 - 0.98**	**0.033**
Psychostimulants	0.96	0.74 - 1.23	0.726
Antipsychotics	1.26	0.94 - 1.68	0.126
Hypnotics & Sedatives	1.07	0.44 - 2.56	0.886
Males			
Any Psychotropic	0.98	0.79 - 1.21	0.849
Antidepressants	1.03	0.52 - 2.03	0.941
Anxiolytics	0.79	0.55 - 1.13	0.198
Psychostimulants	0.91	0.67 - 1.23	0.538
Antipsychotics	**1.67**	**1.12 - 2.49**	**0.013**
Hypnotics & Sedatives	1.41	047 - 4.22	0.540
Females			
Any Psychotropic	0.91	0.72 - 1.14	0.398
Antidepressants	1.09	0.73 - 1.63	0.663
Anxiolytics	0.72	0.51 - 1.04	0.078
Psychostimulants	1.08	0.69 - 1.68	0.185
Antipsychotics	0.94	0.59 - 1.45	0.775
Hypnotics & Sedatives	0.76	0.18 - 3.15	0.704
Note: Cox regression models included a time-dependant variable that adjusted for each child's annual physician rate. Control group was the reference.			

Grade grouping 2: Grade 4-6

There were 337 ROE group children (10.3%) and 679 control group children (8.9%) who were dispensed at least one psychotropic medication during the follow-up period (Table 21). The ROE group also had slightly higher proportions of children who were dispensed at least one medication in each of the psychotropic classifications. Anxiolytics were the most common medication dispensed at least once for both the ROE and control groups (4.2% and 3.9%), while hypnotics and sedatives were the least likely dispensed (0.6% and 0.5%).

The proportion of males who were dispensed at least one psychotropic medication was higher in the ROE group compared to the control group (9.4% and 8.0%, respectively). Proportions of antidepressant, psychostimulant, antipsychotic, and hypnotic and sedative dispensations among males were also higher in the ROE group compared to those in the control group, but were lower for anxiolytic dispensations (2.8% vs. 3.3%). The proportion of females who were dispensed at least one psychotropic medication was higher in the ROE group compared to the control group (11.2% vs. 9.8%). The proportion of females dispensed at least one either anxiolytics, antipsychotics, and hypnotic and sedatives, classification was higher in the ROE group and lower for psychostimulants compared to the proportion of females dispensed those medications in the control group. Similar proportions were observed for an antidepressant dispensation between groups. Within ROE and control groups, the proportion of females (vs males) that were dispensed at least one medication was higher in all classifications, except for psychostimulants, where males were more likely to be dispensed one of those medications.

Table 21. Proportion of children dispensed at least one medication for each outcome in Grade grouping 2

	ROE (n, %)			Control (n, %)		
Event	Male (1,559)	Female (1,575)	Total (3,134)	Male (3,573)	Female (3,570)	Total (7,143)
Any Psychotropic	154 (9.4)	183 (11.2)	337 (10.3)	308 (7.99)	371 (9.76)	679 (8.87)
Antidepressants	21 (1.35)	42 (2.67)	63 (2.01)	35 (0.98)	95 (2.66)	130 (1.82)
Anxiolytics	44 (2.82)	87 (5.52)	131 (4.18)	119 (3.33)	157 (4.40)	276 (3.86)
Psychostimulants	69 (4.43)	30 (1.90)	99 (3.16)	125 (3.50)	75 (2.10)	200 (2.80)
Antipsychotics	31 (1.99)	37 (2.35)	68 (2.17)	55 (1.54)	76 (2.13)	131 (1.83)
Hypnotics & Sedatives	9 (0.58)	11 (0.70)	20 (0.64)	15 (0.42)	20 (0.56)	35 (0.49)

Kaplan-Meier survival curves for ROE and control group children are shown in Figures 8 to 13. Visual comparison of the curves for each group indicates that the survival probabilities under each of the outcomes were similar between ROE and control group children during the follow-up periods. The absolute difference in the survival probabilities measured after 1, 3, 5, 7, and 9 years of follow-up indicate that the probability of being dispensed at least one medication in each of the outcomes was small (Table 22). The stratified log-rank tests did not detect any statistically significant differences in the survival curves for any of the other outcomes (Figures 8 to 13).

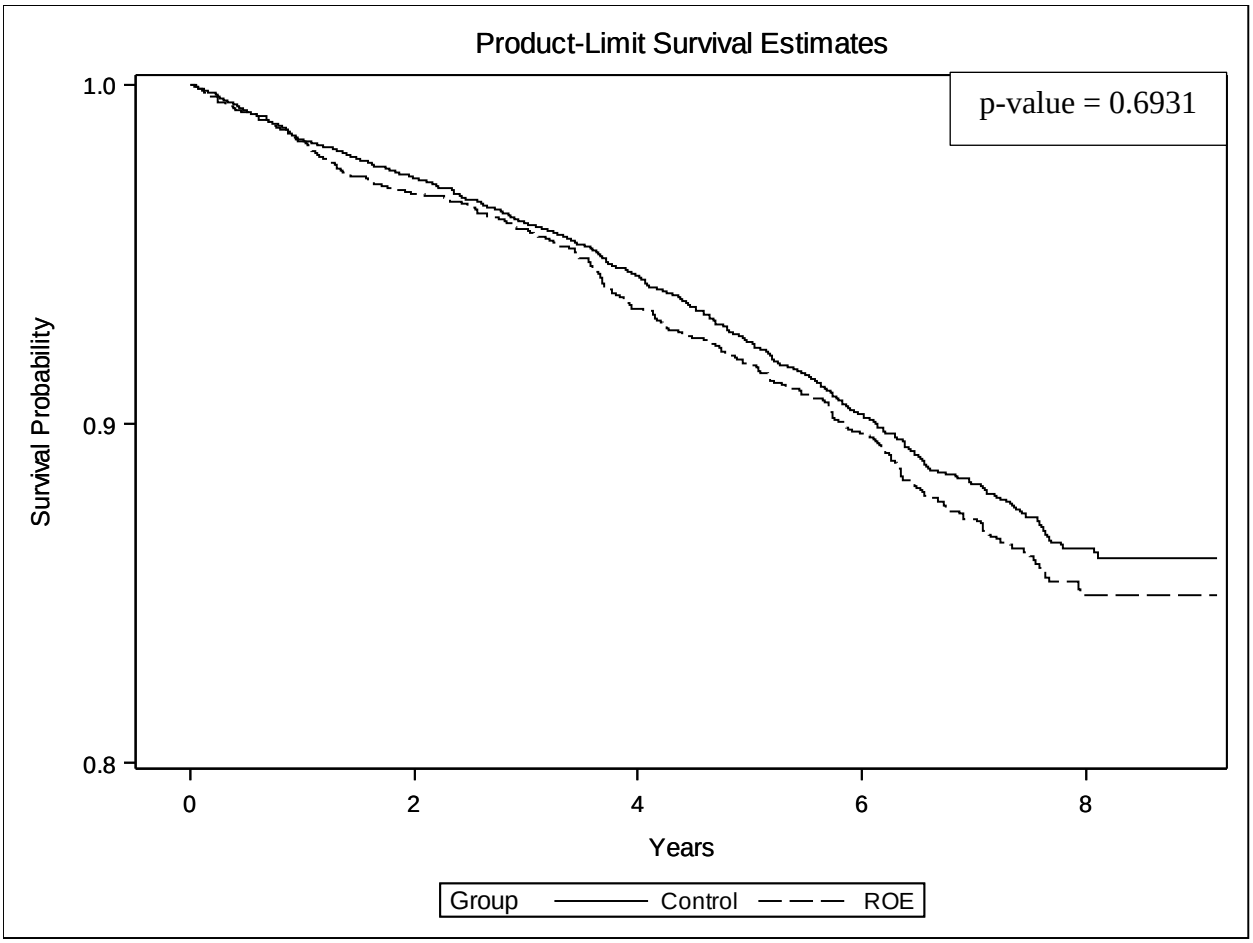

Figure 8. Survival curves for time to first psychotropic dispensation in Grade grouping 2

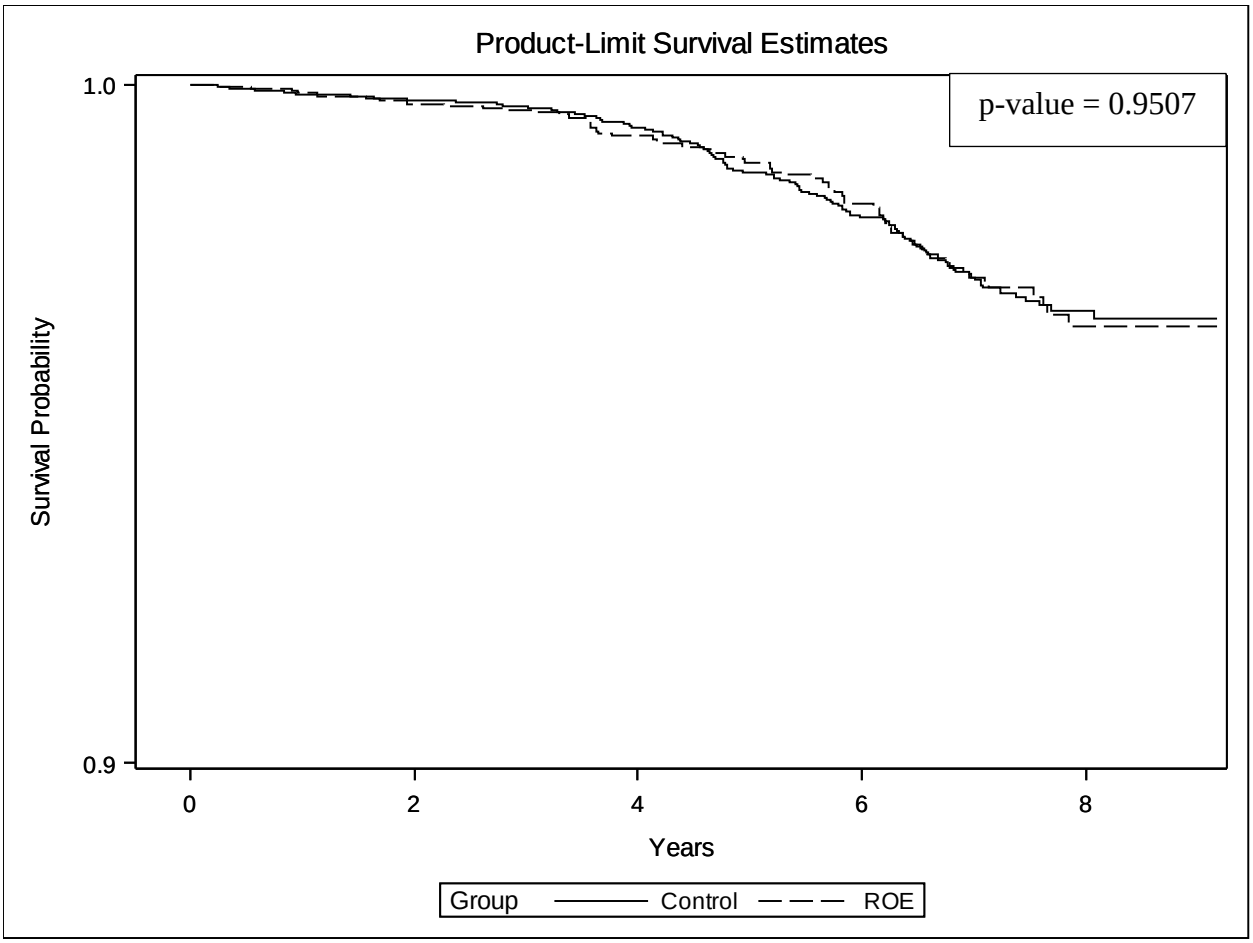

Figure 9. Survival curves for time to first antidepressant dispensation in Grade grouping 2

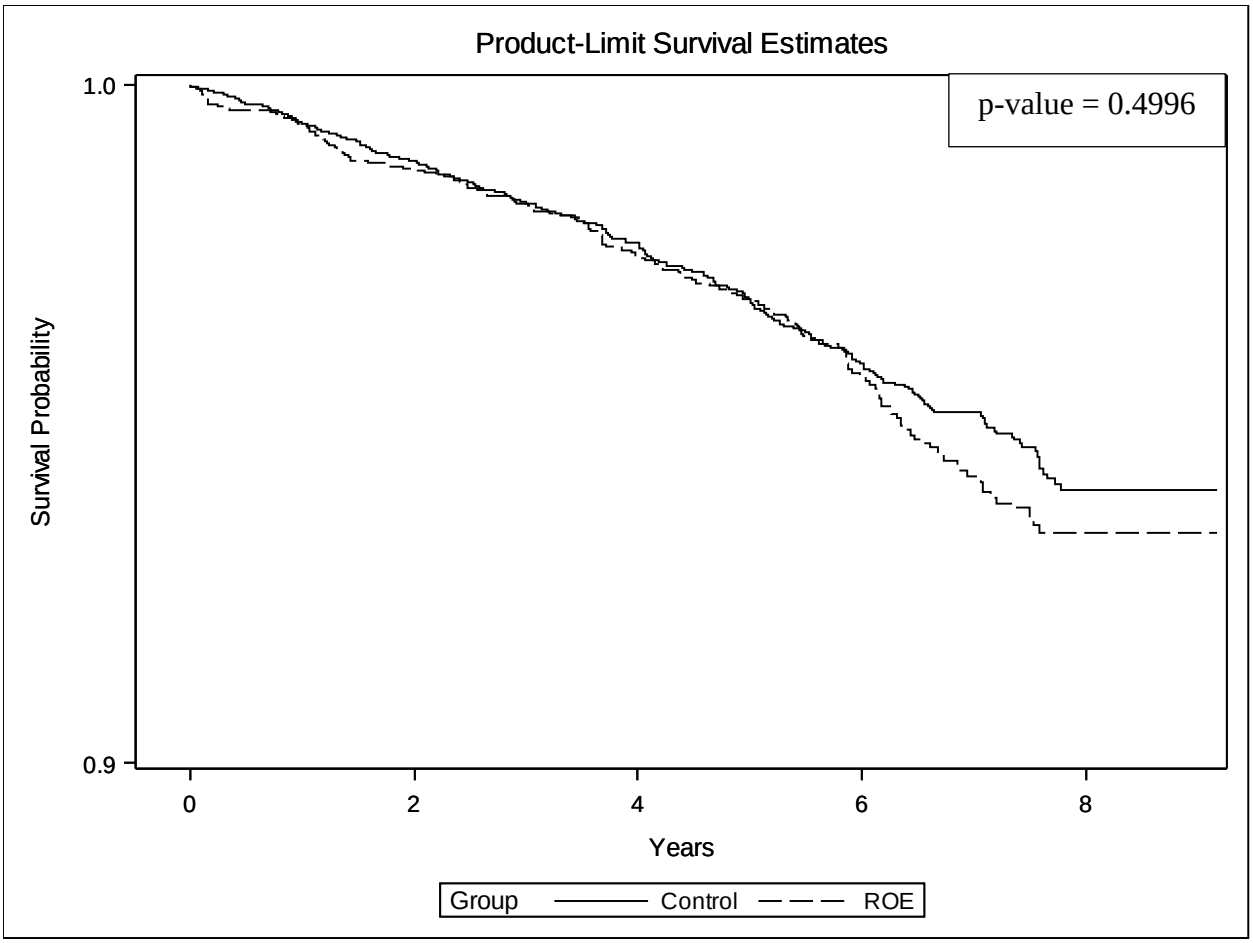

Figure 10. Survival curves for time to first anxiolytic dispensation in Grade grouping 2

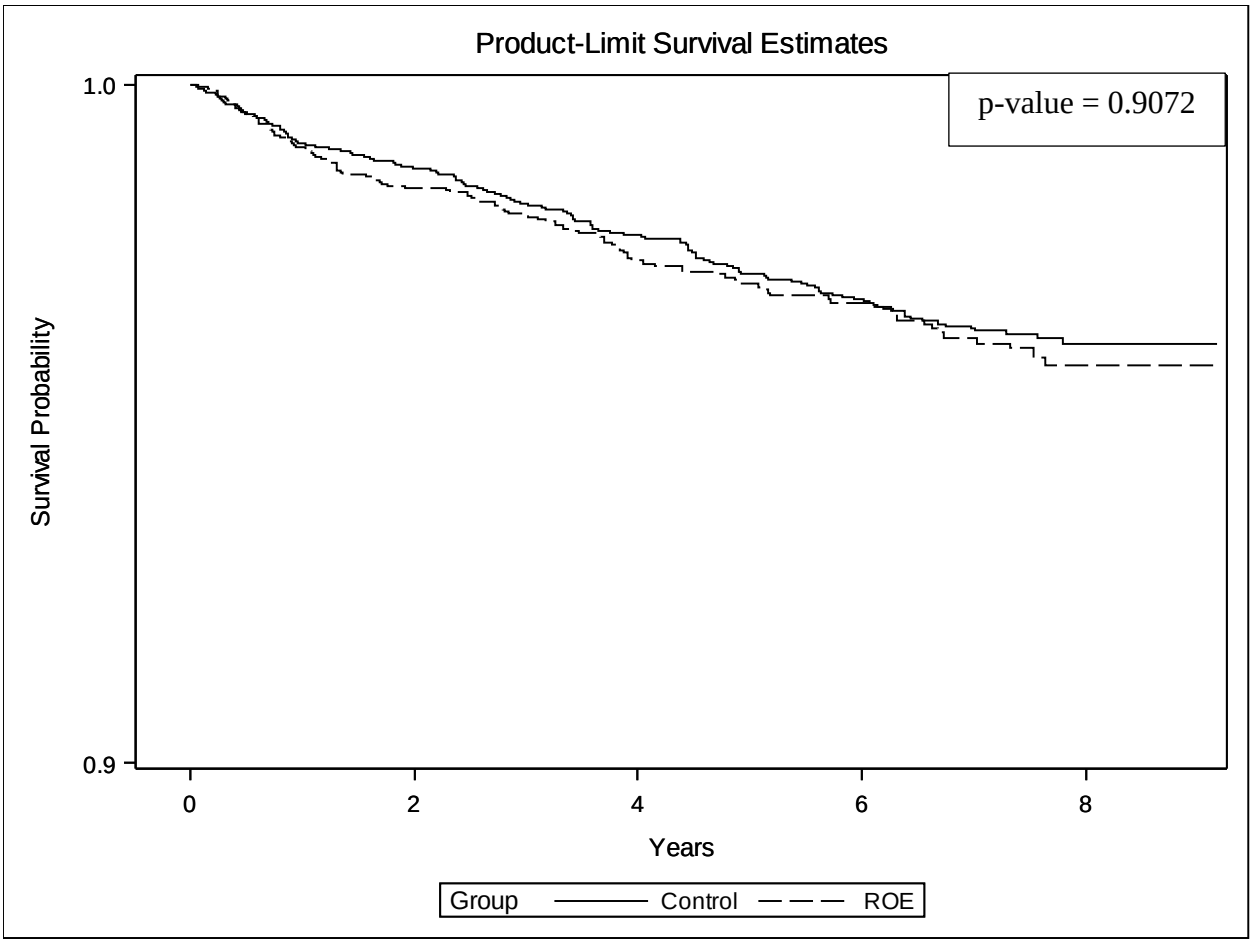

Figure 11. Survival curves for time to first psychostimulant dispensation in Grade grouping 2

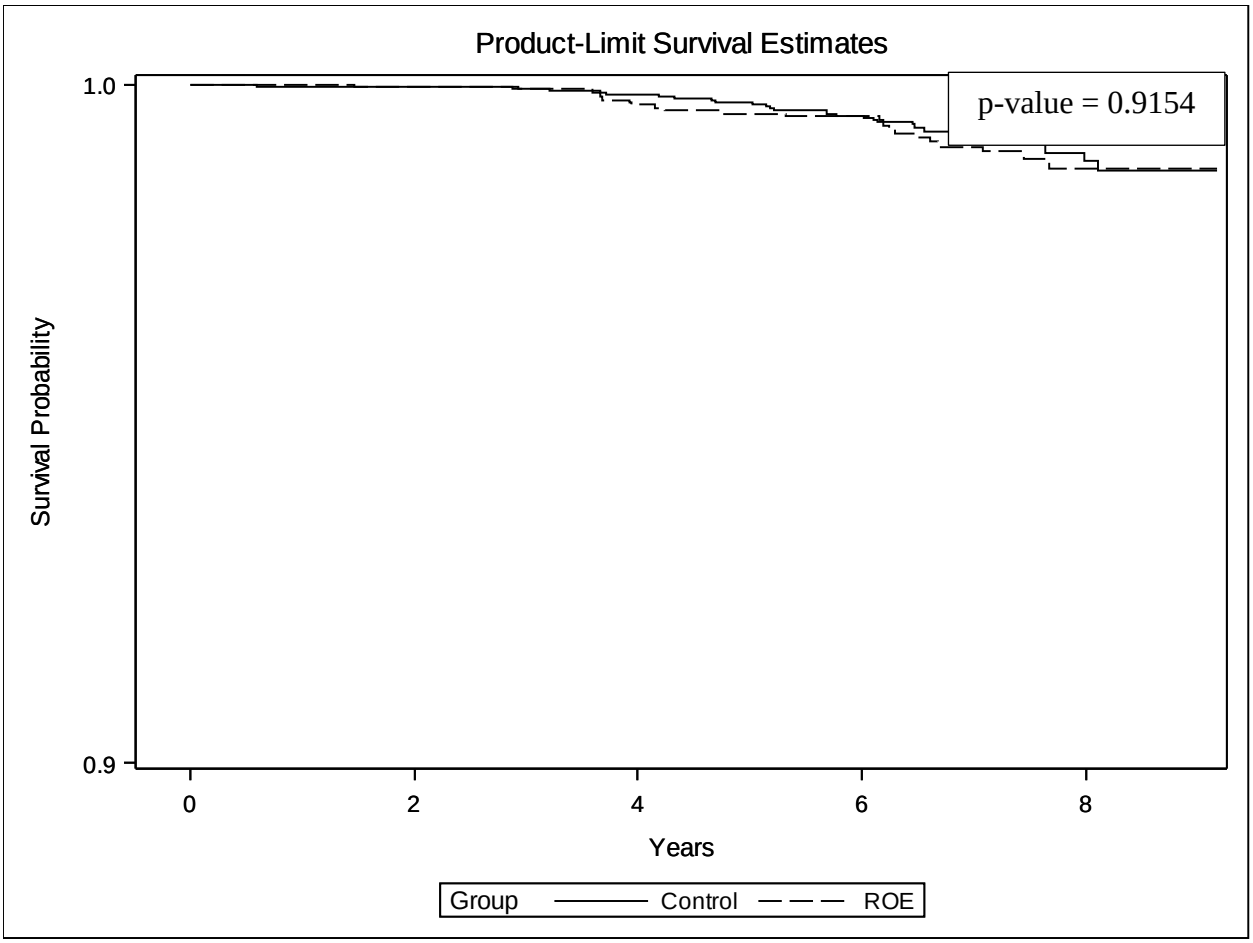

Figure 12. Survival curves for time to first antipsychotic dispensation in Grade grouping 2

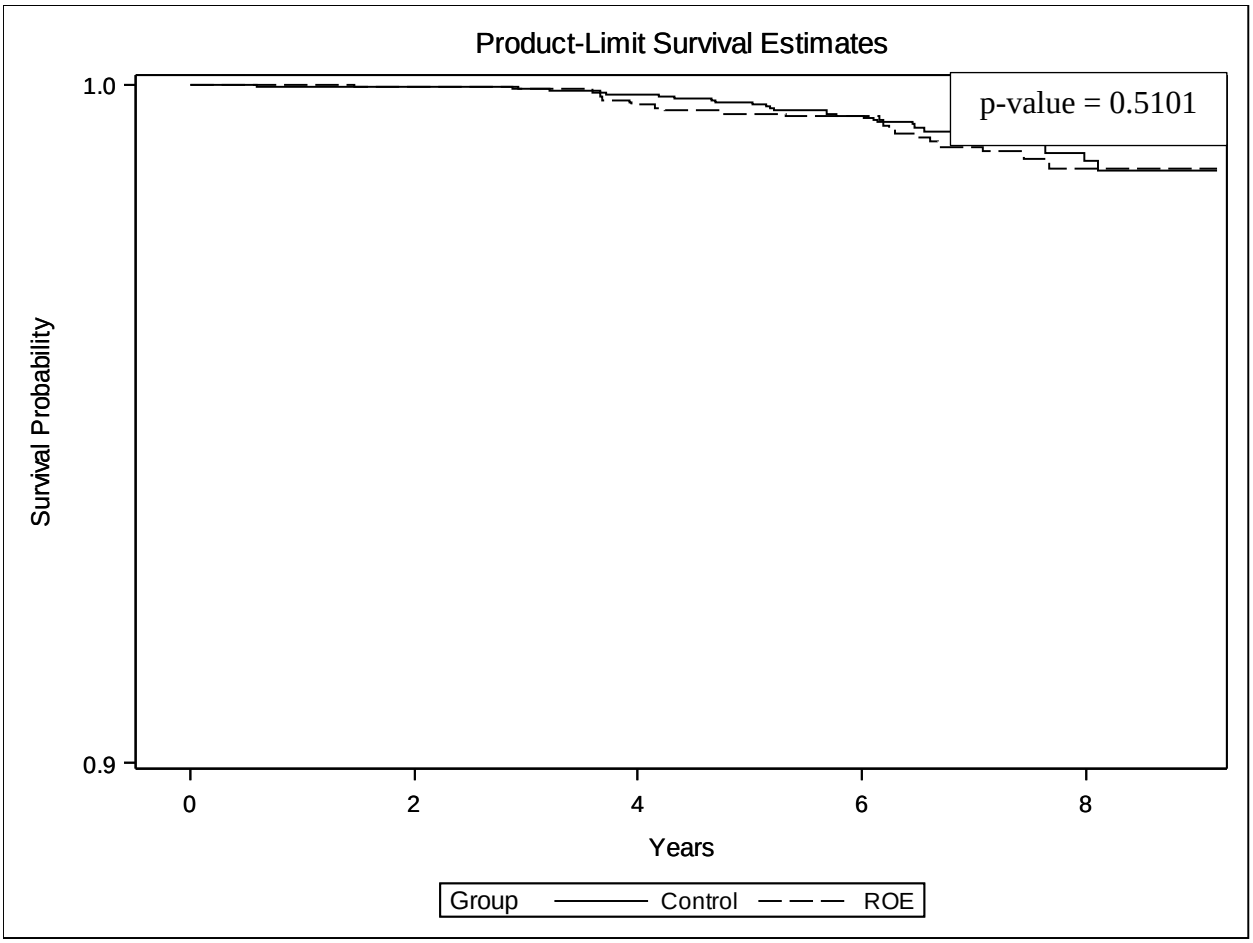

Figure 13. Survival curves for time to first hypnotic & sedative dispensation in Grade grouping 2

Table 22. Absolute difference in survival probabilities at 1, 3, 5, 7, and 9years of follow-up in Grade grouping 2

Any Psychotropic	ROE	Control	
Years of Follow-up	Survival Probability		Difference
1	0.9832	0.9837	0.0005
3	0.9573	0.9593	0.0020
5	0.9170	0.9242	0.0072
7	0.8721	0.8823	0.0102
9	0.8493	0.8605	0.0112
Antidepressants			
1	0.9988	0.9987	-0.0001
3	0.9962	0.9967	0.0005
5	0.9886	0.9871	-0.0015
7	0.9716	0.9716	0
9	0.9643	0.9654	0.0011
Anxiolytics			
1	0.9939	0.9943	0.0004
3	0.9825	0.9827	0.0002
5	0.9680	0.9681	0.0001
7	0.9423	0.9517	0.0094
9	0.9339	0.9403	0.0064
Psychostimulants			
1	0.9908	0.9913	0.0005
3	0.9809	0.9824	0.0015
5	0.9707	0.9720	0.0013
7	0.9619	0.9641	0.0022
9	0.9585	0.9618	0.0033
Antipsychotics			
1	0.9982	0.9983	0.0001
3	0.9940	0.9927	-0.0013
5	0.9806	0.9860	0.0054
7	0.9690	0.9716	0.0026
9	0.9607	0.9624	0.0017
Hypnotics & Sedatives			
1	1.0000	0.9997	-0.0003
3	0.9993	0.9994	0.0001
5	0.9957	0.9974	0.0017
7	0.9909	0.9929	0.0020
9	0.9875	09873	-0.0002

There was no difference in the unadjusted hazards for being dispensed at least one psychotropic medication, or any of the classifications of psychotropic medications (Table 23). In the adjusted models, the only statistically significant difference between ROE and control group children was estimated among males being dispensed antipsychotic medications (HR = 1.10, p = 0.04; Table 24). Males in the ROE group had a 10% higher hazard of being dispensed an antipsychotic medication at least once compared to males in the control group.

Table 23. Unadjusted Hazard Ratio and 95% confidence intervals generated for each psychotropic medication classification with Cox regression models in Grade grouping 2

Event	HR	95% CI	p-value
All Children			
Any Psychotropic	1.03	0.92 – 1.15	0.621
Antidepressants	1.01	0.78 – 1.31	0.940
Anxiolytics	1.08	0.91 – 1.27	0.396
Psychostimulants	1.02	0.83 – 1.25	0.888
Antipsychotics	1.02	0.80 – 1.29	0.895
Hypnotics & Sedatives	1.21	0.79 – 1.86	0.386
Males			
Any Psychotropic	1.07	0.90 – 1.27	0.829
Antidepressants	1.29	0.79 – 2.13	0.308
Anxiolytics	0.89	0.67 – 1.19	0.427
Psychostimulants	1.21	0.94 – 1.56	0.140
Antipsychotics	0.93	0.65 – 1.34	0.705
Hypnotics & Sedatives	1.18	0.62 – 2.27	0.618
Females			
Any Psychotropic	1.00	0.86 – 1.16	0.994
Antidepressants	0.91	0.67 – 1.23	0.542
Anxiolytics	1.20	0.97 – 1.48	0.087
Psychostimulants	0.73	0.51 – 1.05	0.092
Antipsychotics	1.08	0.79 – 1.49	0.628
Hypnotics & Sedatives	1.23	0.69 – 2.19	0.474
Note. Control group was the reference			

Table 24. Adjusted Hazard Ratio and 95% confidence intervals generated for each psychotropic medication classification with Cox regression models in Grade grouping 2

Event	HR	95% CI	p-value
All Children			
Any Psychotropic	0.96	0.88 - 1.14	0.960
Antidepressants	0.94	0.72 - 1.24	0.679
Anxiolytics	1.07	0.87 - 1.31	0.518
Psychostimulants	0.99	0.76 - 1.28	0.917
Antipsychotics	1.03	0.79 - 1.35	0.820
Hypnotics & Sedatives	0.92	0.57 - 1.48	0.740
Males			
Any Psychotropic	1.08	0.89 - 1.32	0.570
Antidepressants	1.33	0.77 - 2.32	0.311
Anxiolytics	0.92	0.65 - 1.30	0.632
Psychostimulants	1.24	0.90 - 1.71	0.182
Antipsychotics	**1.10**	**1.00 - 1.20**	**0.040**
Hypnotics & Sedatives	0.95	0.48 - 1.90	0.884
Females			
Any Psychotropic	0.95	0.80 - 1.12	0.391
Antidepressants	0.82	0.60 - 1.12	0.207
Anxiolytics	1.19	0.93 - 1.53	0.176
Psychostimulants	0.66	0.41 - 1.04	0.074
Antipsychotics	0.87	0.61 - 1.26	0.466
Hypnotics & Sedatives	0.90	0.47 - 1.72	0.751
Note: Cox regression models included a time-dependant variable that adjusted for each child's annual physician rate. Control group was the reference.			

Grade grouping 3: Grade 7-8

There were 58 ROE group children (8.9%) and 160 control group children (8.0%) in Group 3 who were dispensed at least one psychotropic medication during the follow-up period (Table 25). Anxiolytic medications were the most likely to be dispensed at least once for both groups (ROE = 3.7%; control = 4.2%). Hypnotics and sedatives were the least likely dispensed among both groups (ROE = 0.9%; control = 0.8%). The ROE group had lower proportions of children who were dispensed at least one medication in the antidepressant and anxiolytic classifications

compared to the control group and higher proportions in the psychostimulant, antipsychotic and hypnotic and sedative classes.

The proportion of males who were dispensed at least one psychotropic medication was also higher in the ROE group (8.9% vs. 5.8%). Proportions of antipsychotic dispensations were higher for males in the ROE group compared to those in the control group and similar for anxiolytic dispensations. The proportion of females who were dispensed at least one psychotropic medication was lower for the ROE group compared to the control group (8.9% vs. 10.1%). Females in the ROE group were less likely dispensed an anxiolytic and more often dispensed an antipsychotic. Within the ROE group, the proportion of females that were dispensed at least one anxiolytic medication was higher than for males, whereas it was lower for antipsychotics. Females in the control group were more likely dispensed medications in each classification than were males.

Table 25. Proportion of children dispensed at least one medication for each outcome in Grade grouping 3

	ROE (n, %)			Control (n, %)		
Event	Male (295)	Female (346)	Total (641)	Male (939)	Female (1,001)	Total (1,940)
Any Psychotropic	27 (8.88)	31 (8.86)	58 (8.87)	57 (5.76)	103 (10.1)	160 (7.96)
Antidepressants	Sup.	Sup.	10 (1.56)	11 (1.17)	35 (3.50)	46 (2.37)
Anxiolytics	7 (2.37)	17 (4.91)	24 (3.74)	22 (2.34)	59 (5.89)	81 (4.18)
Psychostimulants	Sup.	Sup.	13 (2.03)	15 (1.60)	17 (1.70)	32 (1.65)
Antipsychotics	9 (3.05)	10 (2.89)	19 (2.96)	17 (1.81)	21 (2.10)	38 (1.96)
Hypnotics & Sedatives	Sup.	Sup.	6 (0.94)	Sup.	Sup.	15 (0.77)
Sup. = Suppressed due to small cell size (<5)						

Kaplan-Meier survival curves for ROE and control group children are shown in Figures 14 to 19. Visual comparison of the curves for each group indicates slightly lower survival probabilities

under the psychostimulants outcome for the ROE group children compared to the control group children (Figure 18). For the antidepressant and anxiolytic outcomes, the survival probabilities were slightly higher for the ROE group (Figures 15 and 16). The calculated absolute differences in the survival probabilities measured after 1, 3, and 5 years of follow-up confirm the small differences observed in the survival curves (Table 26), and the stratified log-rank tests did not detect any statistically significant differences for any of the outcomes assessed (Figures 14 to 19).

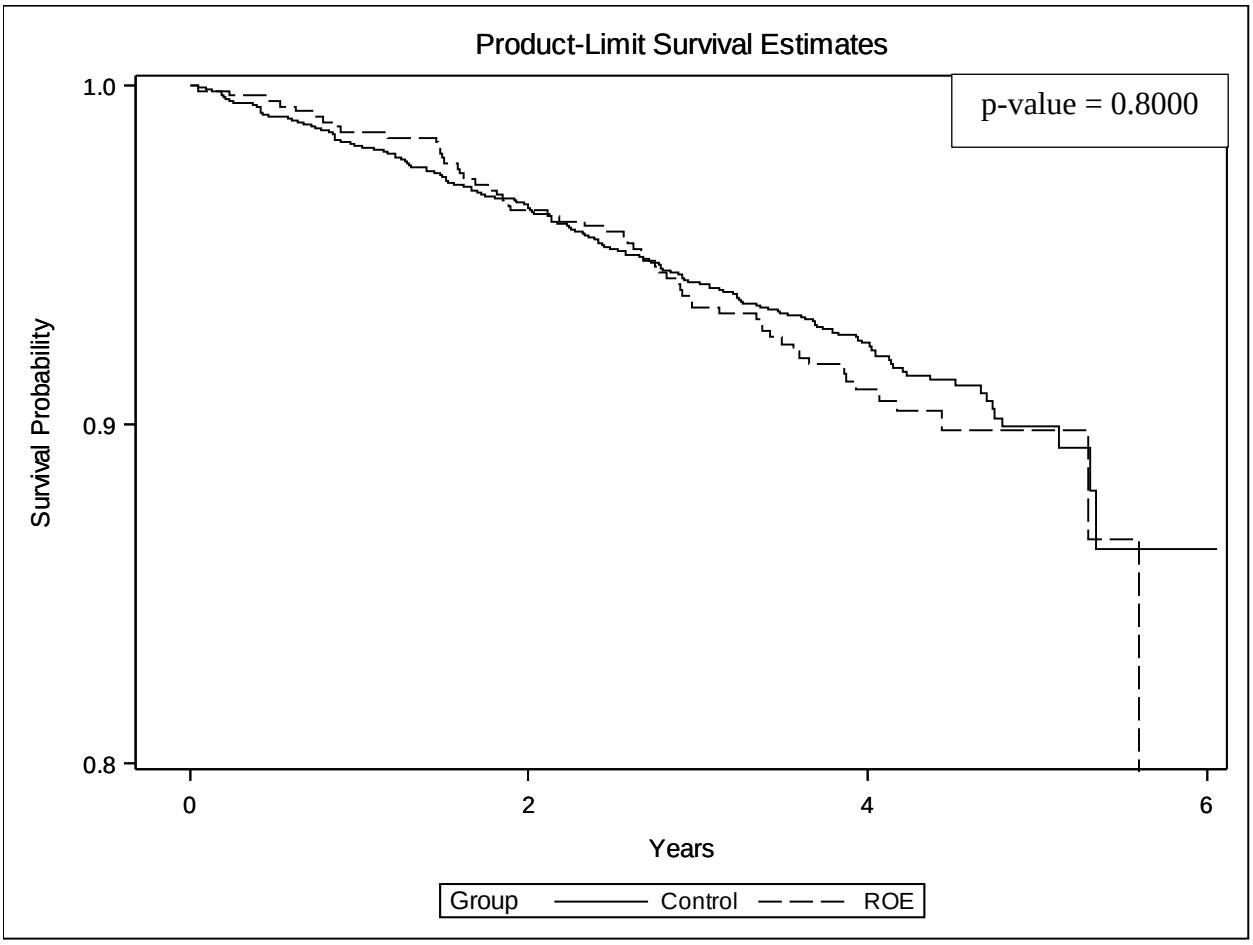

Figure 14. Survival curves for time to first psychotropic in Grade grouping 3

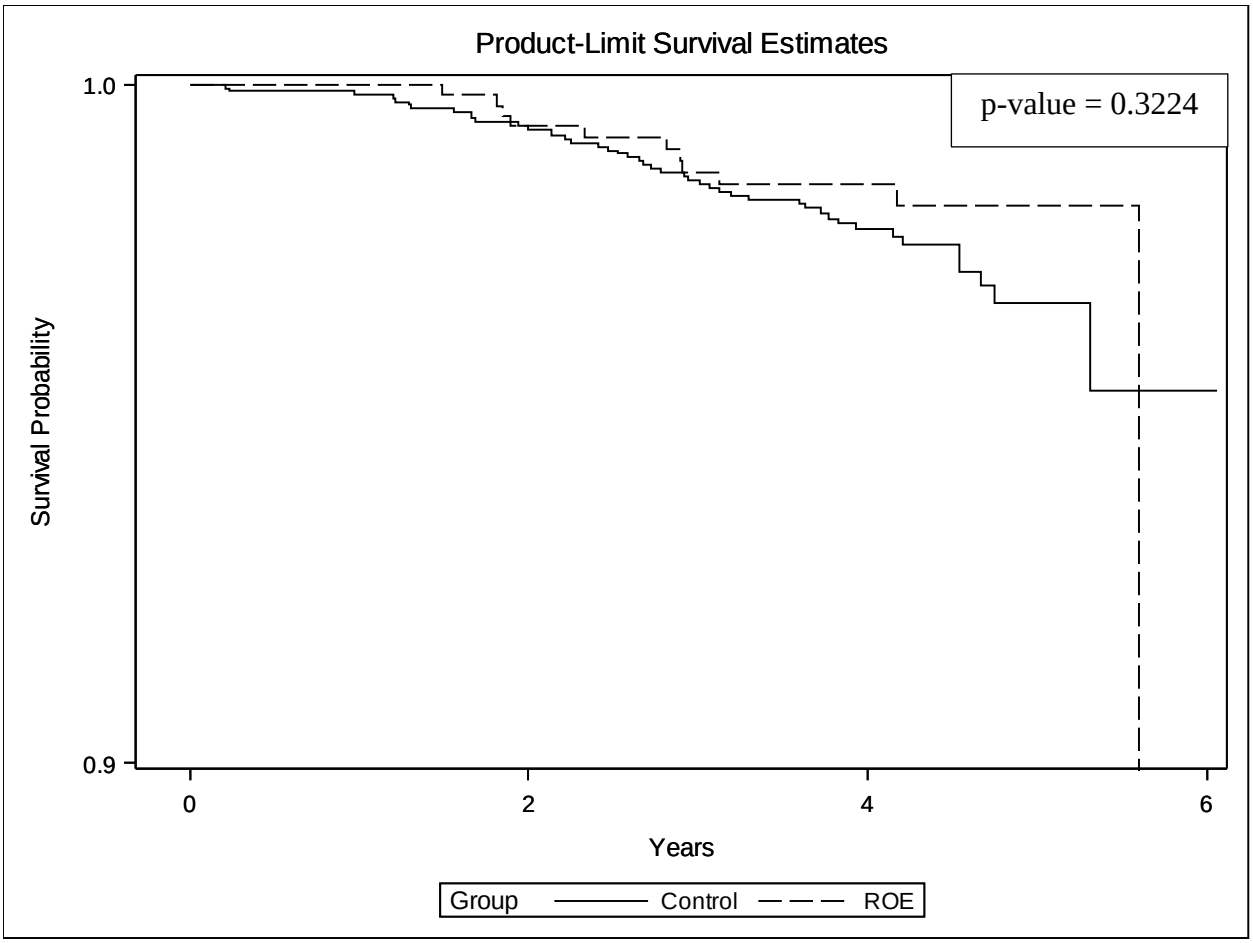

Figure 15. Survival curves for time to first antidepressant dispensation in Grade grouping 3

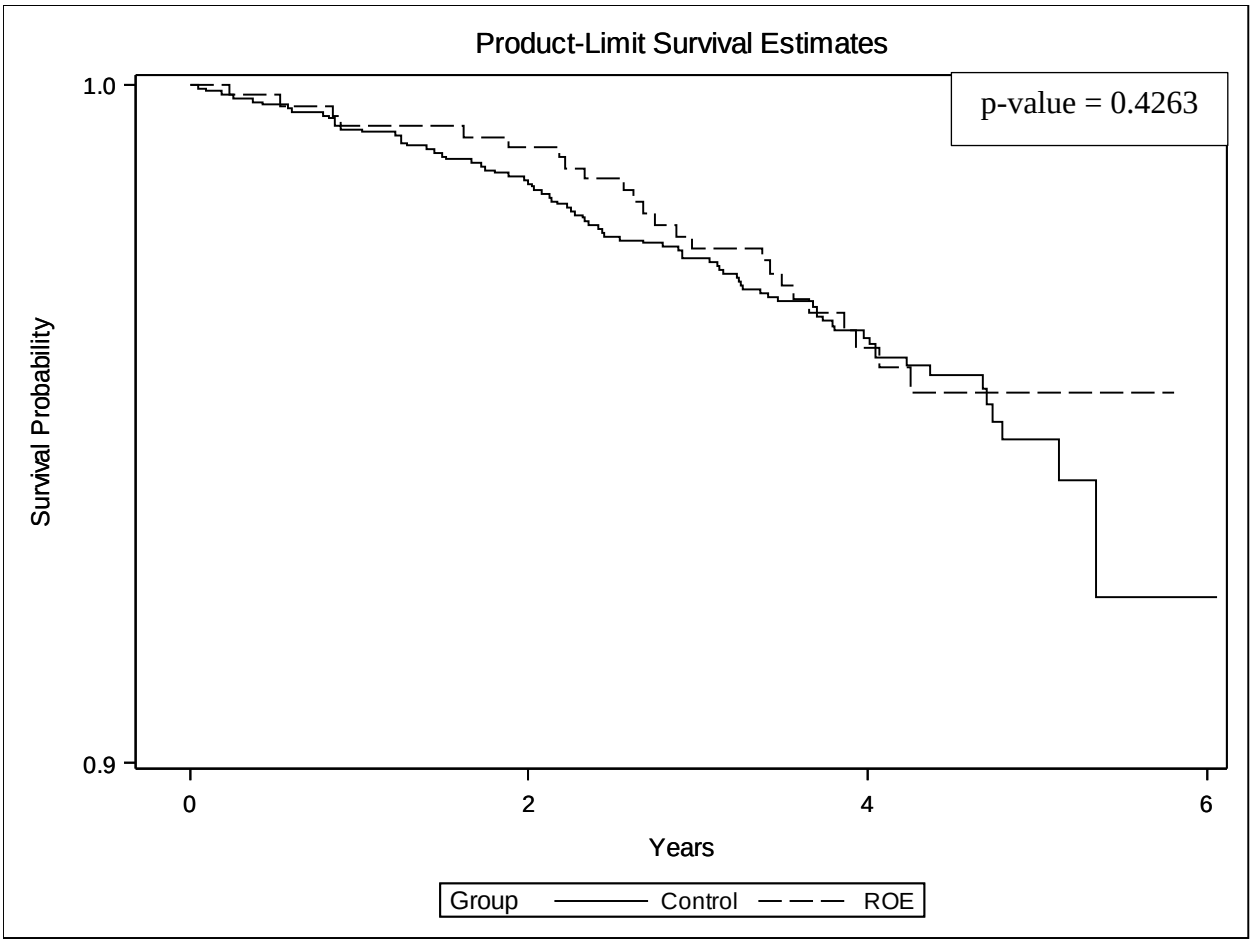

Figure 16. Survival curves for time to first anxiolytic dispensation in Grade grouping 3

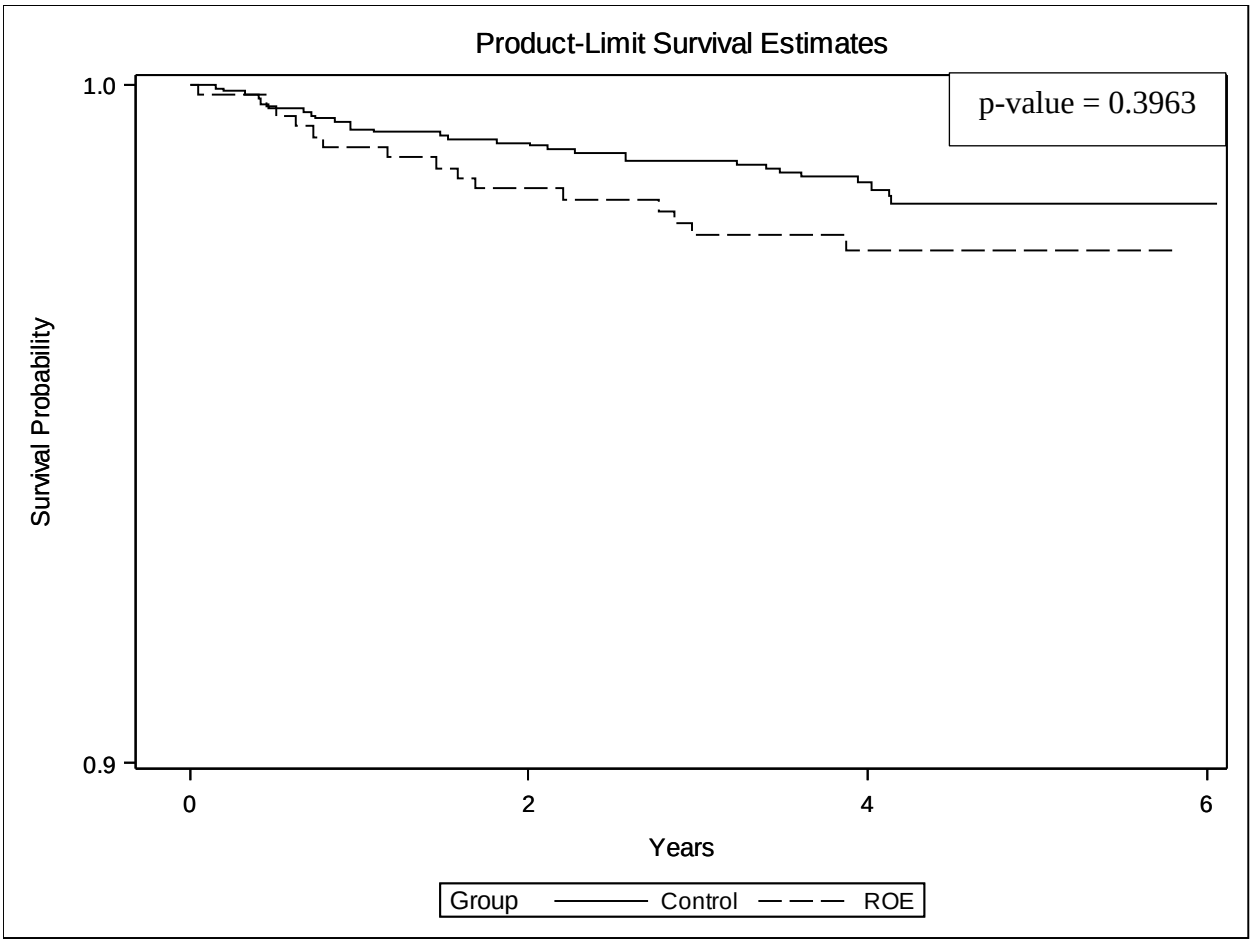

Figure 17. Survival curves for time to first psychostimulant dispensation in Grade grouping 3

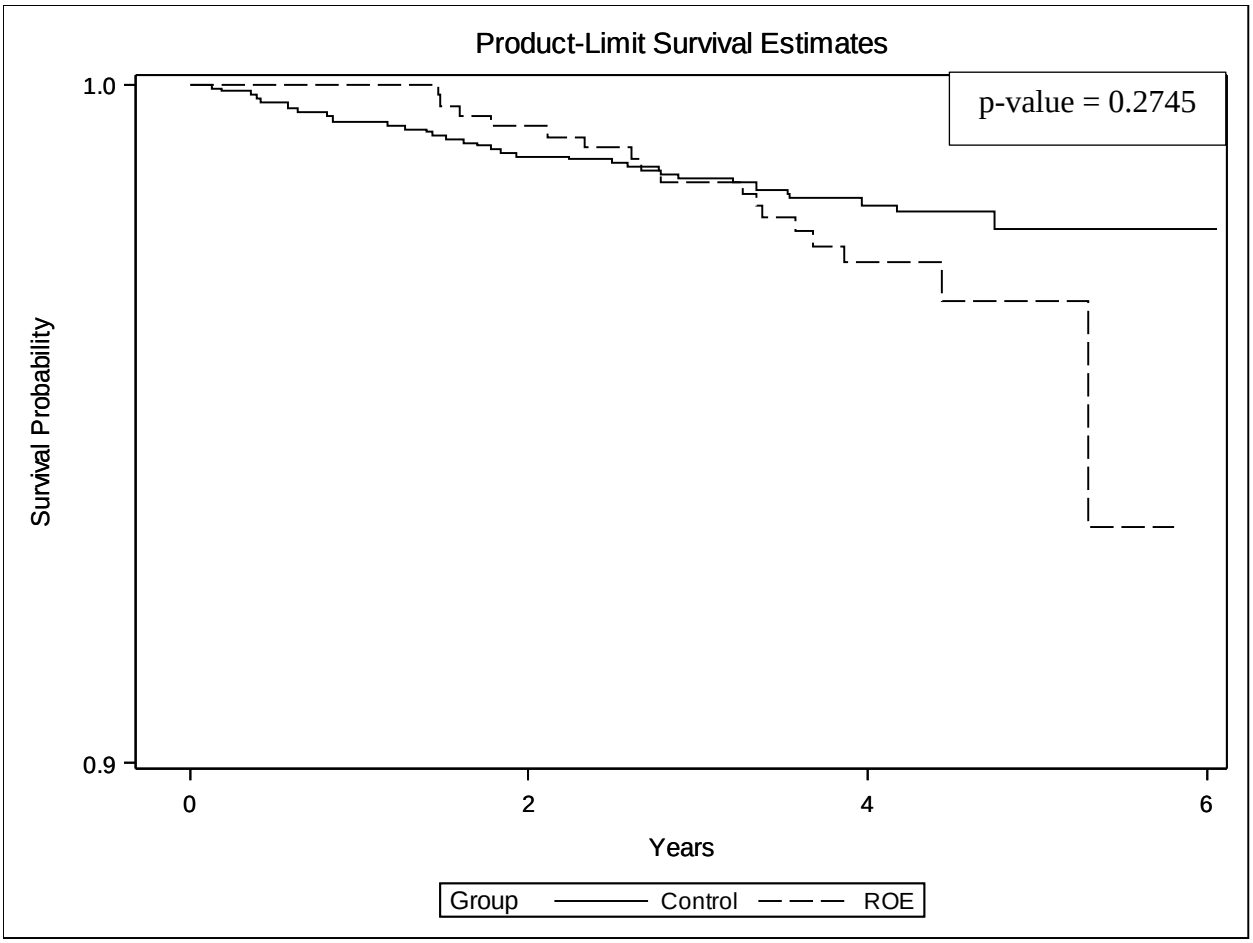

Figure 18. Survival curves for time to first antipsychotic dispensation in Grade grouping 3

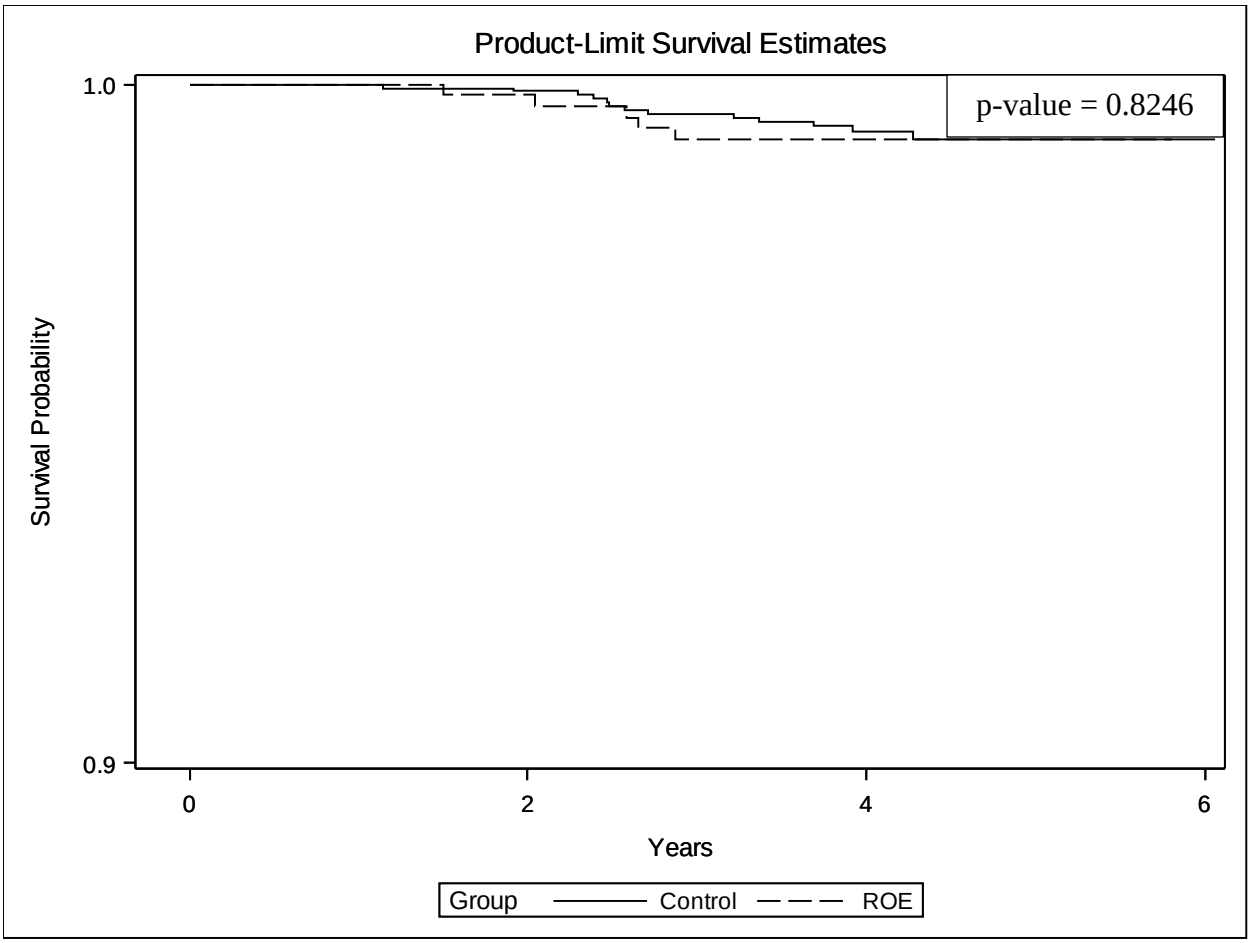

Figure 19. Survival curves for time to first hypnotic & sedative dispensation in Grade grouping 3

Table 26. Absolute difference in survival probabilities at 1, 3, and 5 years of follow-up in Grade grouping 3

Any Psychotropic	ROE	Control	
Years of Follow-up	Survival Probability		Difference
1	0.9862	0.9815	-0.0047
3	0.9346	0.9415	0.0069
5	0.8983	0.8934	-0.0049
Antidepressants			
1	1.0000	0.9985	-0.0015
3	0.9872	0.9859	-0.0013
5	0.9821	0.9679	-0.0142
Anxiolytics			
1	0.9939	0.9935	-0.0004
3	0.9759	0.9744	-0.0015
5	0.9547	0.9478	-0.0069
Psychostimulants			
1	0.9908	0.9935	0.0027
3	0.9780	0.9889	0.0109
5	0.9755	0.9825	0.007
Antipsychotics			
1	1.0000	0.9945	-0.0055
3	0.9857	0.9862	0.0005
5	0.9682	0.9787	0.0105
Hypnotics & Sedatives			
1	1.0000	1.0000	0
3	0.9918	0.9958	0.004
5	0.9918	0.9918	0

There were no significant differences in the unadjusted hazard ratios for any of the outcomes, or any sex-specific outcomes (Table 27). The only significant difference in the adjusted models was observed for antipsychotics, where children in the ROE group had a higher hazard (HR = 2.39, p = 0.006; Table 28). Sex-specific analyses revealed that among males, the ROE group children had a higher hazard of being dispensed an antipsychotic medication than the children in the

control group (HR = 2.75, p = 0.025), and there were no significant differences observed among females for any outcome (Table 28).

Table 27. Unadjusted Hazard Ratio and 95% confidence intervals generated for each psychotropic medication classification with Cox regression models in Grade grouping 3

Event	HR	95% CI	p-value
Any Psychotropic	0.96	0.74 – 1.25	0.754
Antidepressants	0.70	0.39 – 1.25	0.227
Anxiolytics	0.82	0.56 – 1.20	0.304
Psychostimulants	1.33	0.79 – 2.24	0.285
Antipsychotics	1.41	0.86 – 2.31	0.179
Hypnotics & Sedatives	1.13	0.50 – 2.55	0.763
Any Psychotropic	1.20	0.80 – 1.80	0.389
Antidepressants	0.40	0.12 – 1.29	0.124
Anxiolytics	0.97	0.52 – 1.81	0.916
Psychostimulants	1.41	0.74 – 2.69	0.295
Antipsychotics	1.76	0.88 – 3.52	0.113
Hypnotics & Sedatives	1.78	0.53 – 5.94	0.349
Any Psychotropic	0.83	0.58 – 1.17	0.281
Antidepressants	0.83	0.43 – 1.61	0.579
Anxiolytics	0.76	0.48 – 1.22	0.259
Psychostimulants	1.21	0.49 – 2.95	0.683
Antipsychotics	1.09	0.54 – 2.20	0.819
Hypnotics & Sedatives	0.93	0.31 – 2.77	0.891
Note. Control group was the reference.			

Table 28. Adjusted Hazard Ratio and 95% confidence intervals generated for each psychotropic medication classification with Cox regression models in Grade grouping 3

Event	HR	95% CI	p-value
All Children			
Any Psychotropic	1.08	0.81 - 1.44	0.608
Antidepressants	0.71	0.38 - 1.32	0.280
Anxiolytics	0.73	0.47 - 1.13	0.152
Psychostimulants	1.51	0.75 - 3.06	0.250
Antipsychotics	**2.39**	**1.29 - 4.43**	**0.006**
Hypnotics & Sedatives	1.35	0.51 - 3.63	0.548
Males			
Any Psychotropic	1.25	0.79 - 1.99	0.341
Antidepressants	0.68	0.19 - 2.44	0.347
Anxiolytics	0.46	0.16 - 1.28	0.134
Psychostimulants	1.65	0.65 - 4.19	0.294
Antipsychotics	**2.75**	**1.14 - 6.66**	**0.025**
Hypnotics & Sedatives	7.00	0.29 - 171.85	0.233
Females			
Any Psychotropic	0.99	0.69 - 1.43	0.961
Antidepressants	0.76	0.38 - 1.55	0.559
Anxiolytics	0.78	0.48 - 1.28	0.325
Psychostimulants	1.56	0.55 - 4.41	0.407
Antipsychotics	2.05	0.89 - 4.72	0.093
Hypnotics & Sedatives	1.10	0.40 - 1.38	0.859
Note: Cox regression models included a time-dependant variable that adjusted for each child's annual physician rate. Control group was the reference.			

Chapter 4. Discussion

This is the first known study evaluating the association between a school-based social and emotional learning (SEL) program and the use of psychotropic medications, and the first time the Roots of Empathy (ROE) program has been evaluated on a health outcome beyond 3 years of follow-up. Psychotropic medication use was defined as the first time a child or youth was dispensed a psychotropic medication after receiving the ROE program. There were not consistent

differences in the use of psychotropic medications between children who received ROE and children who did not in Manitoba. This finding was generally the same when psychotropic medications were measured as a composite of psychotropic medications or separated by ATC medication class. Despite the statistically non-significant results regarding medication use, there were some interesting observations from this study that suggest that the program may be positively influencing children's mental health and well being. Potential reasons for the non-significant findings and areas for further research regarding the association between the ROE program and psychotropic medication use are discussed below.

Approximately 12.4% of the children who received ROE any year between kindergarten and grade 3 were dispensed at least one psychotropic medication during the follow-up period. The proportion was lower among children who received ROE in either grade 4 to 6 (10.2%) or in grade 7 or 8 (8.9%), likely related to the shorter follow-up time available in this study (children were censored at age 18 or on March 31, 2015, whichever came first – see Methods). These proportions were all slightly higher than those observed in the respective matched control groups. For the individual medication classes, the ROE group had greater proportions than the control group across most drug classes, except for anxiolytic and antidepressant dispensations for children who received ROE in grade 7 or 8, and anxiolytic dispensations for children receiving ROE in kindergarten to grade 3. This finding is interesting given that the symptoms these medications are typically prescribed for would seem more amenable to change from such a program (i.e. anxiety-related symptoms). Expected dispensation patterns were seen within the ROE and control groups, where a greater proportion of males were dispensed psychostimulants and a greater proportion of females were dispensed anxiolytic and antidepressants.

Despite the slight differences in the proportion of children in each grade group receiving a medication, the comparison of survival estimates and hazards for medication dispensation revealed few significant differences between children who received ROE and those who did not. Significant differences were observed for anxiolytic medications in children in the kindergarten to grade 3 grade group, for antipsychotics in the grade 7 - 8 group, and antipsychotic medications among males compared to females in all three grade groups. The association between the program and anxiolytic medication use in the kindergarten to grade 3 children may be explained by the idea that the medications in this classification are typically used for conditions and illnesses that are more likely to be prevented by improving an individual's social and emotional skills. The fact that this was observed for the group of children who received the program in the earliest grades also aligns with the recommendation of implementing programs early for improving adult health (Campbell, 2014). This and other comparisons among the kindergarten – grade 4 group were the most statistically powerful comparisons in this study, as they involved to the longest follow-up time. Despite the significant difference in the adjusted hazard, the absolute difference in the survival probability (i.e., likelihood of not being dispensed an anxiolytic medication) between the two groups after 11 years of follow up was only 1%. Therefore, since this outcome (and each outcome when analyzed by individual medication classification) is rare, the clinical significance of this finding is small. The significantly higher adjusted hazards for antipsychotic medications among males in the ROE group was interesting, given that it was observed in each of the three grade groupings. While the relatively wide 95% confidence intervals estimated for each of these antipsychotic outcomes prompt interpreting these results with caution, there may be a feature of the program that may help identify children who may need these mediations, but might otherwise have gone untreated. However, it should also be

noted that given the number of statistical tests performed (54 models), and the chosen Alpha level ($p<0.05$), one or more of these significant findings may have simply occurred due to chance.

Overall, there was not enough evidence to reject the null hypothesis that no difference in the use of psychotropic medications exists between the group of children who received ROE and the group who did not. Given that SEL programs have been shown to be associated with positive outcomes from multiple domains, including indicators for mental health and well-being, it was expected that the ROE group would be less likely to use psychotropic medications. Indeed, one possible explanation may be that the program did not have a significant impact on preventing mental illness of the children who received it and, therefore, there would be no reason for the use of psychotropic medication to be different between groups. However, this may be too simplistic and presumptive of a conclusion to draw from this study. The remainder of this section discusses potential alternate explanations for the results while considering the design and methods that were used.

First, the results of this study suggest that the social and emotional benefits of the ROE program may not translate to a decrease in the reliance on psychotropic medications. However, this interpretation fails to consider that mental health and mental illness are two distinct states, each with their own continuum. Our study operated under the assumption that any effect of the program would be experienced similarly by all children who received ROE regardless of where they might fall on the continuum of mental illness severity. It may be possible that the program resulted in a lower proportion of children with more mild symptoms, and a higher proportion of children with more severe symptoms, who filled a prescription. Measuring medication use in

relation to mental illness severity may illustrate the different ways that the program may be promoting mental health.

Second, while considerable research has demonstrated a positive relationship between SEL programs and many immediate or intermediate outcomes, there has been limited research on mental illness outcomes, such as incidence rates and mental health service use, and even less on the relationship between social and emotional skills and psychotropic medication. Research studies evaluating universal programs have generally used indicators of mental health, such as social and emotional skills, attitudes towards self and others, conduct problems and emotional distress as their outcome measures. Furthermore, a meta-analysis of SEL programs investigating these outcomes demonstrated a positive effect; however, the effect sizes were modest at best, and quite low for the outcome of self-reported symptoms of depression and anxiety (R. D. Taylor et al., 2017). Similar conclusions were drawn following a systematic review of universal, indicated and targeted in-school programs, where the demonstrated effect of reducing depression and anxiety was cautioned due to small effect sizes. These studies suggest that, while effective from a statistical point of view, the differences on the outcomes between those who receive the program and those who do not is not clinically or practically significant. Given that the number of children who are dispensed a psychotropic medication should, theoretically, be less than the number of children who report mental illness symptoms or receive a mental illness diagnosis, it may be even more difficult to detect a difference, especially involving a singular, universal program that focuses on overall child development rather than child mental health (Kieling et al., 2011).

Third, the intention of this study was to examine medication use while children were still under the age of 18 years, to address the concern that most of these medications are not indicated for

this population. Any reduction in the use of these medications may be viewed as a positive outcome, as any side effects or unknown long-term effects would be avoided. However, this may not have been an adequate length of follow-up for the differences between groups to appear, as research has shown evidence of positive outcomes measured in adulthood following early childhood programs and interventions. Hawkins et al. (2008) found that mental health outcomes measured at 24 and 27 years of age were improved in individuals who received an in-school program in grades 1 to 6 aimed at increasing positive functioning in school and decrease problems related to mental health compared to individuals who did not. Similarly, an early adolescent drug use prevention program (marijuana use) was shown to reduce mental health service use in adulthood (Riggs & Pentz, 2009). Therefore, it is possible that differences between ROE group children and controls may emerge later, in their adult years. And while it is natural to study outcomes among the children who receive the program, the overarching goal of the program is to improve future generations and societies through responsible citizenship and responsive parenting (Rootsofempathy.org, n.d. About us). Therefore, the program's impact on psychotropic medication use may be more completely realized in children whose parents received the program, because of better family relationships and environments that may evolve. Given that providing young children with a range of positive experiences is an important part of promoting mental health (Government of Canada, 2006, p. 6) the ROE program may have its largest impact on the next generation of children on a range of outcomes, including psychotropic medication use.

Fourth, this study measured medication use as the first time a child was dispensed a psychotropic medication. The total number of prescriptions filled during the follow-up period, and the dose of medication dispensed were not measured. Therefore, this study can only

conclude that the proportion of children who received the program and were later dispensed a psychotropic medication was not different from that for children who did not receive the program. However, it is possible that they had a lower total number of dispensations, or had prescriptions written for lower doses, both of which would indicate less use. This would be an area for further study that would add another layer to overall ability of the program to influence psychotropic medication use.

Fifth, because of the way ROE class lists were collected, the children in the ROE group for this study received the program the first time their instructor implemented the program. Due to the inability to identify all children who received ROE, this study is only able to comment on the children who received the program by a first-time instructor. It is possible that the magnitude of the program's impact is a function of the instructor's experience and ability to deliver the program – which may increase over time.

Sixth, the children from both the ROE and control groups may have been exposed to other SEL interventions throughout their school years that may have had an influence on their use of psychotropic medications. While not required, schools in Manitoba are expected to provide environments that promote mental health through a holistic approach outlined in their comprehensive school health framework (Mental Health Promotion in Schools). For example, the framework outlines initiatives that focus on school-based suicide prevention, and intervention that addresses issues associated with suicide, such as bullying. Children involved in bullying, both the victims and perpetrators of bullying, have been shown to have elevated levels of anxiety and depression compared to non-participating children (Craig, 1998; Kaltiala-Heino, Rimpelä, Rantanen, & Rimpelä, 2000), with effects lasting well into adulthood (Kumpulainen & Räsänen, 2000; Takizawa, Maughan, & Arseneault, 2014). Therefore, the children who attend schools that

take a more active approach to creating caring and safe environments may be less likely to use psychotropic medications than children who do not attend similar schools. Therefore, if the children in the control group where more often exposed to those school environments, or other SEL programs, any effect of the ROE program may have been diminished.

Seventh, the causes of mental illness are complex, so initiatives aimed at reducing its burden may need to use multifaceted approaches that address the different pathological processes involved (Shirk, 2000). Traditionally, mental illness was thought to stem from only biological causes; however, more evidence for psychological and social pathologies have emerged, and a bio-psychosocial model that addresses the complex interplay between multiple factors now exists (Abera, Robbins, & Tesfaye, 2015; Yeh, Hough, McCabe, Lau, & Garland, 2004). This model describes the causes of mental illness as possessing elements of biology, psychology, and social environments. With over 400 diagnosable mental illnesses, the contributions of each element in the bio-psychosocial model varies across different illnesses. Therefore, ROE may address some of the psychosocial causes of mental illness, but altering the biological origins of mental illness may be more unlikely. In this respect, a single program or intervention of any kind is unlikely to be sufficient to reduce the use psychotropic medications. Supporting this idea is the observation that the hazard for being dispensed an antipsychotic medication was greater in the ROE group (especially among males) and was the only class of psychotropic medications that did show a statistically significant difference (although the 95% confidence intervals were quite wide).

Strengths

A major strength of this study is the care and effort taken to construct the matched sample, which allows for a direct comparison between children who received ROE and those who did not. Various models were created and compared in terms of how well they matched the ROE group

on baseline characteristics, to correctly assess the propensity score specification. The result was matched samples that were well balanced, and included a high success rate of identifying close matches for the children who received the ROE program (Grade grouping 1 = 92.0%; Grade grouping 2 = 88.3%; Grade grouping 3 = 79.1%). Another strength is the use of administrative data from multiple sources, which allowed for many potentially confounding variables to be controlled for with a propensity score. Another strength was the completeness of the drug dispensation data. This database contains client and medication information for all dispensations in Manitoba pharmacies, regardless of final payer. Therefore, other than medications dispensed from a hospital pharmacy or nursing station, all dispensations to the children in the study were captured in the database. Another strength was the use of stratified log-rank statistical testing and the inclusion of a robust variance estimator, which accounted for the lack of independence in outcomes that was induced by matching. Lastly, the children in this study were all non-users of any of the medications under investigation at the start of their follow-up, as established using a one-year washout period.

Limitations

The discussion of alternative explanations above addressed the major limitations of this study. Those include that medication use was defined as the first time a medication was dispensed, that other competing SEL programs were not controlled for, that the length of follow-up may not have been adequate for differences to be detected, and that only children of first-time ROE instructors were included in the ROE group. Other technical limitations are also worth noting. First, while the data sources and methods used provide for strong generalizability, potential threats to that remain. There were some children who received ROE that were not included because there was not a child in the pool of control group children who shared similar characteristics that would be considered a suitable match. Because a caliper matching process

was used, 11.8% of the ROE in the overall original sample were excluded because they had extreme values for the logit of propensity score based on their sets of characteristics. A comparison of the descriptive statistics between the excluded and included ROE group children revealed that the excluded children had some characteristics associated with poorer mental health (i.e. younger mothers, lower SES). If the ROE program has a greater influence on children with those characteristics, our results will be biased. An alternate approach to caliper matching is the nearest neighbor matching, which would include all children in the ROE group having a control assigned to them. While this approach would improve the external validity of the study, it would also lead to the selection of control group children who are quite different from ROE group children, confounding any intervention effect (Austin, 2014). Since the entry times vary randomly across individuals, and there was one study termination date, meant that a significant amount censoring in this study is considered random censoring. To avoid biased conclusions in such instances, it is important that this type of censoring be noninformative; a condition where an individual censored at a specific time should be representative of all subjects with the same values of the explanatory variables who survive to that same time (Allison, 2010). The randomly censored children in the study would have been children who moved out of province or died. Therefore, it is unlikely that the censored children, in the study were different from the other children who survived to the time they were censored. Lastly, the fidelity of program delivery was not measured, so while all the instructors had the same training, the actual implementation of the program in classrooms may have varied between instructors.

In conclusion, this study demonstrates that children who received the Roots of Empathy program in Manitoba between 2002/03 and 2012/13 were no more or less likely that those who did not to be subsequently dispensed a psychotropic medication. The program has demonstrated its

effectiveness in increasing important social and emotional skills that undoubtedly will serve children well into their future; however, this study found no association between program participation and the use of psychotropic medications. The study results and observations suggest that further research using other approaches to estimate psychotropic medication use may be warranted to obtain a more complete picture of any association between ROE and psychotropic medication use.

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Appendix

A. ICD-9-CM and ICD-10-CA codes used for Intellectual Disabilities variable

ICD-9-CM code	Condition
317	Mental Retardation (MR)
318	Other MR
319	Unspecified MR
758.0 – 758.3	Chromosomal Anomolies (includes Down's, Patau's and Edward's syndromes)
759.81 – 759.89	Other and unspecified congenital anomalies (includes Fragile X and Prader-willi syndromes)
ICD-10-CA code	Condition
F70.0, F70.1, F70.8, F70.9	Mild Mental Retardation (MR)
F71.0, F71.1, F70.8, F70.9	Moderate MR
F72.0, F71.1, F70.8, F70.9	Severe MR
F73.0, F73.1, F73.8, F73.9	Profound MR
F78.0, F78.1, F78.8, F78.9	Other MR
F79.0, F79.1, F79.8, F79.9	Unspecified MR
F84.0 – F84.9	Pervasive developmental disorders

B. WHO-ATC medication codes

Nervous System (N)				
Subgroups				
Level 2	Level 3	Level 4	ATC Code	Drug Name
Anti-epileptics (N03)	Anti-epileptics (N03A)	Benzodiazepine derivatives (N03AE)	N03AE01	Clonazepam
Psycholeptics (N05)	Antipsychotics (N05A)	Phenothiazines with aliphatic side-chain (N05AA)	N05AA01	chlorpromazine
			N05AA02	Levomepromazine

			N05AA03	Promazine
			N05AA04	Aepromazine
			N05AA05	triflupromazine
			N05AA06	Cyamemazine
			N05AA07	Chlorproethazine
Psycholeptics (N05)	Antipsychotics (N05A)	Phenothiazines with piperazine structure (N05AB)	N05AB01	Dixyrazine
			N05AB02	Fluphenazine
			N05AB03	Perphenazine
			N05AB04	Prochlorperazine
			N05AB05	Thiopropazate
			N05AB06	trifluoperazine
			N05AB07	Acetophenazine
			N05AB08	Thioproperazine
			N05AB09	Butaperazine

			N05AB10	Perazine
Psycholeptics (N05)	Antipsychotics (N05A)	Phenothiazines with piperidine structure (N05AC)	N05AC01	Periciazine
			N05AC02	Thioridazine
			N05AC03	Mesoridazine
			N05AC04	Pipotiazine
Psycholeptics (N05)	Antipsychotics (N05A)	Butyrophenone derivatives (N05AD)	N05AD01	Haloperidol
			N05AD02	Trifluperidol
			N05AD03	Melperone
			N05AD04	Moperone
			N05AD05	Pipamperone
			N05AD06	Bromperidol
			N05AD07	Benperidol
			N05AD08	Droperidol
			N05AD09	Fluanisone

Psycholeptics (N05)	Antipsychotics (N05A)	Indole derivatives (N05AE)	N05AE01	Oxypertine
			N05AE02	Molindone
			N05AE03	Sertindole
			N05AE04	Ziprasidone
			N05AE05	Lurasidone
Psycholeptics (N05)	Antipsychotics (N05A)	Thioxanthene derivatives (N05AF)	N05AF01	Flupentixol
			N05AF02	Clopenthixol
			N05AF03	Chlorprothixene
			N05AF04	Tiotixene
			N05AF05	Zuclopenthixol
Psycholeptics (N05)	Antipsychotics (N05A)	Diphenylbutylpiperidine derivatives (N05AG)	N05AG01	Fluspirilene
			N05AG02	Pimozide
			N05AG03	Penfluridol
Psycholeptics (N05)	Antipsychotics (N05A)	Diazepines, oxazepines,	N05AH01	Loxapine

		thiazepines and oxepines (N05AH)		
			N05AH02	Clozapine
			N05AH03	Olanzapine
			N05AH04	Quetiapine
			N05AH05	Asenapine
			N05AH06	Clotiapine
Psycholeptics (N05)	Antipsychotics (N05A)	Benzamides (N05AL)	N05AL01	Sulpiride
			N05AL02	Sultopride
			N05AL03	Tiapride
			N05AL04	Remoxipride
			N05AL05	Amisulpride
			N05AL06	Veralipride
			N05AL07	levosulpiride
Psycholeptics (N05)	Antipsychotics (N05A)	Other antipsychotics (N05AX)	N05AX07	Prothipendyl
			N05AX08	Risperidone

			N05AX10	Mosapramine
			N05AX11	Zotepine
			N05AX12	Aripiprazole
			N05AX13	Paliperidone
			N05AX14	Iloperidone
			N05AX15	cariprazine
Psycholeptics (N05)	Anxiolytics (N05B)	Benzodiazepine derivatives (N05BA)	N05BA01	Diazepam
			N05BA02	Chlordiazepoxide
			N05BA03	Medazepam
			N05BA04	Oxazepam
			N05BA05	Potassium clorazepate
			N05BA06	Lorazepam
			N05BA07	Adinazolam
			N05BA08	Bromazepam
			N05BA10	Ketazolam

			N05BA11	Prazepam
			N05BA12	Alprazolam
			N05BA13	Halazepam
			N05BA14	Pinazepam
			N05BA15	Camazepam
			N05BA16	Nordazepam
			N05BA17	Fludiazepam
			N05BA18	Ethyl loflazepate
			N05BA19	Etizolam
			N05BA21	Clotiazepam
			N05BA22	Cloxazolam
			N05BA23	Tofisopam
			N05BA5	Lorazepam, combinations
Psycholeptics (N05)	Anxiolytics (N05B)	Diphenylmethane derivatives (N05BB)	N05BB01	Hydroxyzine
			N05BB02	Captodiame

			N05BB51	Hydroxyzine, combinations
Psycholeptics (N05)	Anxiolytics (N05B)	Carbamates (N05BC)	N05BC01	Meprobamate
			N05BC02	Emylcamate
			N05BC03	Mebutamate
			N05BC51	Mebutamate, combinations
Psycholeptics (N05)	Anxiolytics (N05B)	Dibenzo-bicyclo-octadiene derivatives (N05BD)	N05BD01	benzoctamine
Psycholeptics (N05)	Anxiolytics (N05B)	Azaspirodecanedione derivatives (N05BE)	N05BE01	Buspirone
Psycholeptics (N05)	Anxiolytics (N05B)	Other anxiolytics (N05BX)	N05BX01	Mephenoxalone
			N05BX02	Gedocarnil
			N05BX03	Etifoxine
			N05BX04	fabomotizole
Psycholeptics (N05)	Hypnotics and Sedatives (N05C)	Benzodiazepine derivatives (N05CD)	N05CD01	Flurazepam
			N05CD02	Nitrazepam
			N05CD03	Flunitrazepam

			N05CD04	Estazolam
			N05CD05	Triazolam
			N05CD06	Lormetazepam
			N05CD07	Temazepam
			N05CD08	Midazolam
			N05CD09	Brotizolam
			N05CD10	Quazepam
			N05CD11	Loprazolam
			N05CD12	Doxefazepam
			N05CD13	cinolazepam
Psycholeptics (N05)	Hypnotics and Sedatives (N05C)	Benzodiazepine related drugs (N05CF)	N05CF01	Zopiclone
			N05CF02	Zolpidem
			N05CF03	Zaleplon
			N05CF04	eszopiclone
Psychoanaleptics (N06)	Antidepressants (N06A)	Non-selective monoamine reuptake inhibitors (N06AA)	N06AA01	Desipramine

			N06AA02	Imipramine
			N06AA03	Imipramine oxide
			N06AA04	Clomipramine
			N06AA05	Opipramol
			N06AA06	Trimipramine
			N06AA07	Lofepramine
			N06AA08	Dibenzepin
			N06AA09	Amitriptyline
			N06AA10	Nortriptyline
			N06AA11	Protiptyline
			N06AA12	Doxepin
			N06AA13	Iprindole
			N06AA14	Melitracen
			N06AA15	Butriptyline
			N06AA16	Dosulepin

			N06AA17	Amoxapine
			N06AA18	Dimetacrine
			N06AA19	Amineptine
			N06AA21	maprotiline
			N06AA23	Quinupramine
Psychoanaleptics (N06)	Antidepressants (N06A)	Selective serotonin reuptake inhibitors (N06AB)	N06AB02	Zimeldine
			N06AB03	Fluoxetine
			N06AB04	Citalopram
			N06AB05	Paroxetine
			N06AB06	Sertraline
			N06AB07	Alaproclate
			N06AB08	Fluvoxamine
			N06AB09	Etoperidone
			N06AB10	escitalopram

Psychoanaleptics (N06)	Antidepressants (N06A)	Monoamine oxidase inhibitors, non-selective (N06AF)	N06AF01	Isocarboxazid
			N06AF02	Nialamide
			N06AF03	Phenelzine
			N06AF04	Tranylcypromine
			N06AF05	iproniazide
			N06AF06	iproclozide
Psychoanaleptics (N06)	Antidepressants (N06A)	Monoamine oxidase A inhibitors	N06AG02	Moclobemide
			N06AG03	Toloxatone
Psychoanaleptics (N06)	Antidepressants (N06A)	Other antidepressants	N06AX01	oxitriptan
			N06AX02	Tryptophan
			N06AX03	Mianserin
			N06AX04	Nomifensine
			N06AX05	Trazodone
			N06AX06	Nefazadone

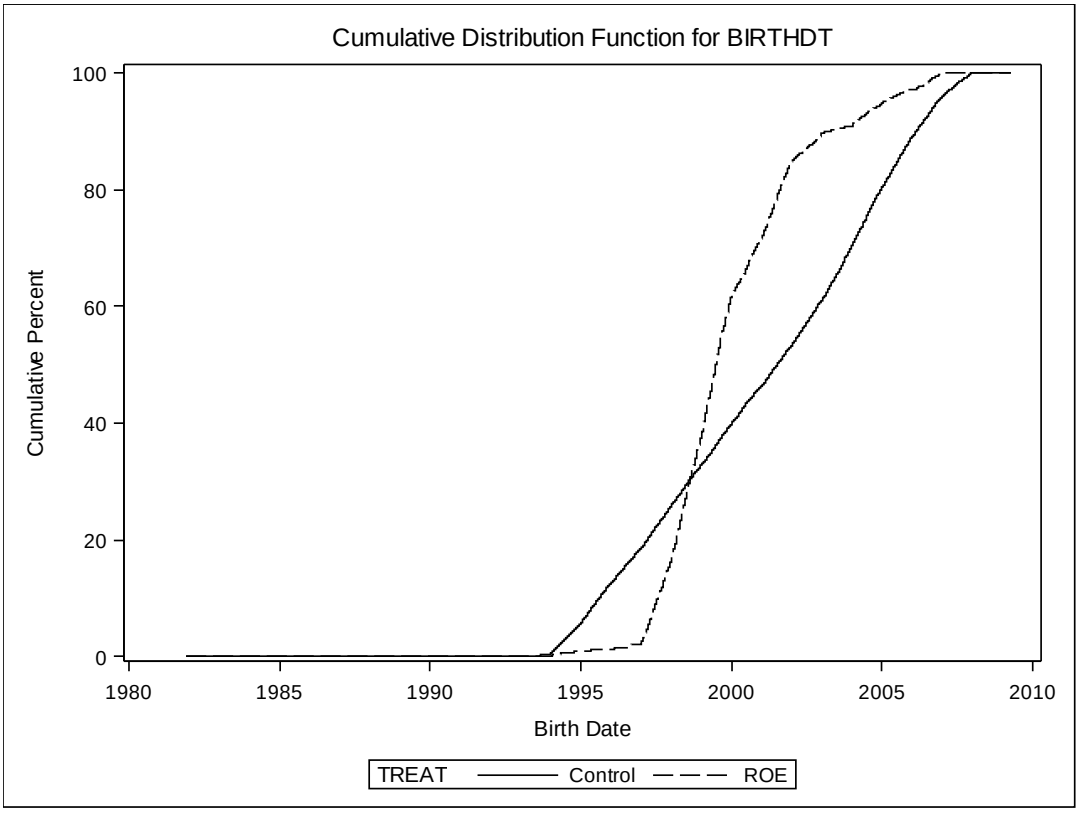
			N06AX07	Minaprine
			N06AX08	Bifemelane
			N06AX09	Viloxazine
			N06AX10	Oxaflozane
			N06AX11	Mirtazapine
			N06AX12	Bupropion
			N06AX13	Medifoxamine
			N06AX14	Tianeptine
			N06AX15	Pivagabine
			N06AX16	Venlafaxine
			N06AX17	Milnacipran
			N06AX18	Reboxetine
			N06AX19	Gepirone
			N06AX21	Duloxetine
			N06AX22	Agomelatine

			N06AX23	Desvenlafaxine
			N06AX24	Vilazodone
			N06AX25	Hyperici herba
			N06AX26	Vortioxetine
Psychoanaleptics (N06)	Psychostimulants (N06B)	Centrally acting sympathomimetics	N06BA01	Amfetamine
			N06BA02	Dexamfetamine
			N06BA03	Metamfetamine
			N06BA04	Methylphenidate
			N06BA05	Pemoline
			N06BA06	Fencamfamin
			N06BA07	Modafinil
			N06BA08	Fenozolone
			N06BA09	Atomoxetine
			N06BA10	Fenetylline
			N06BA11	Dexmethylphenidate

			N06BA12	Lisdexamfetamine
			N06BA13	Armodafnile

C. Baseline characteristic balance diagnostics of continuous variables. Graphical summaries (Cumulative Density Function, Boxplots)

Group 1. Birthdate



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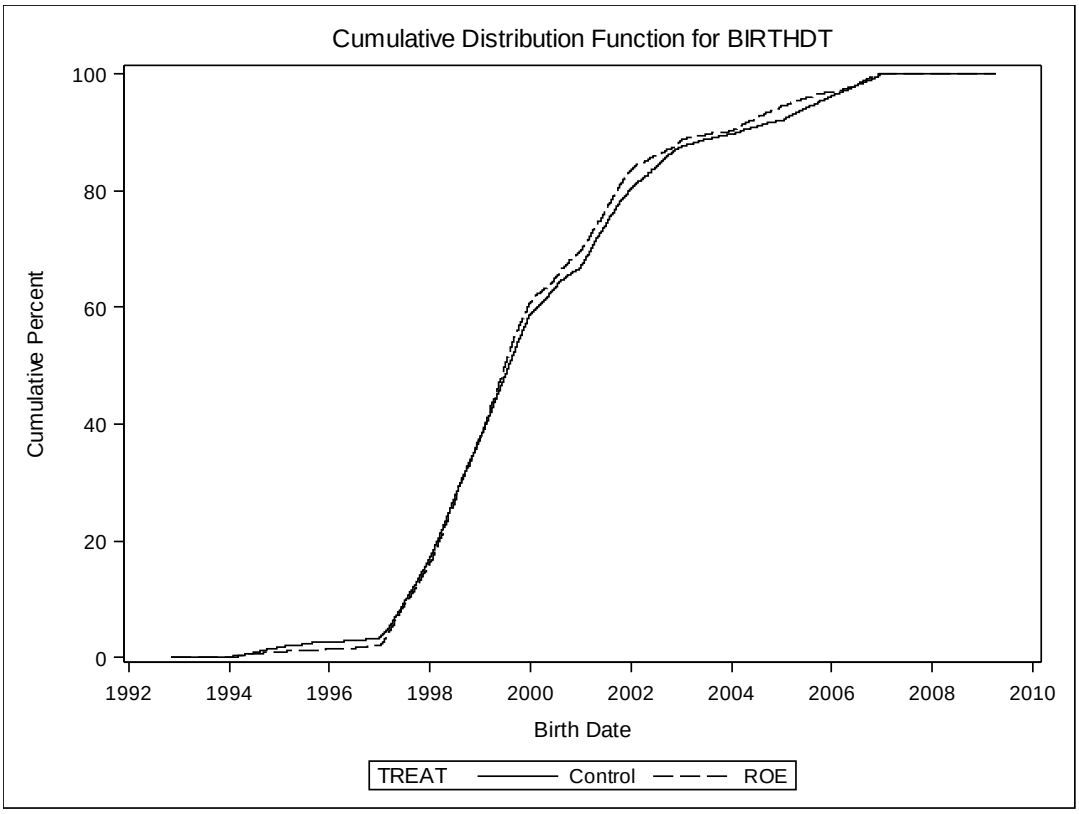

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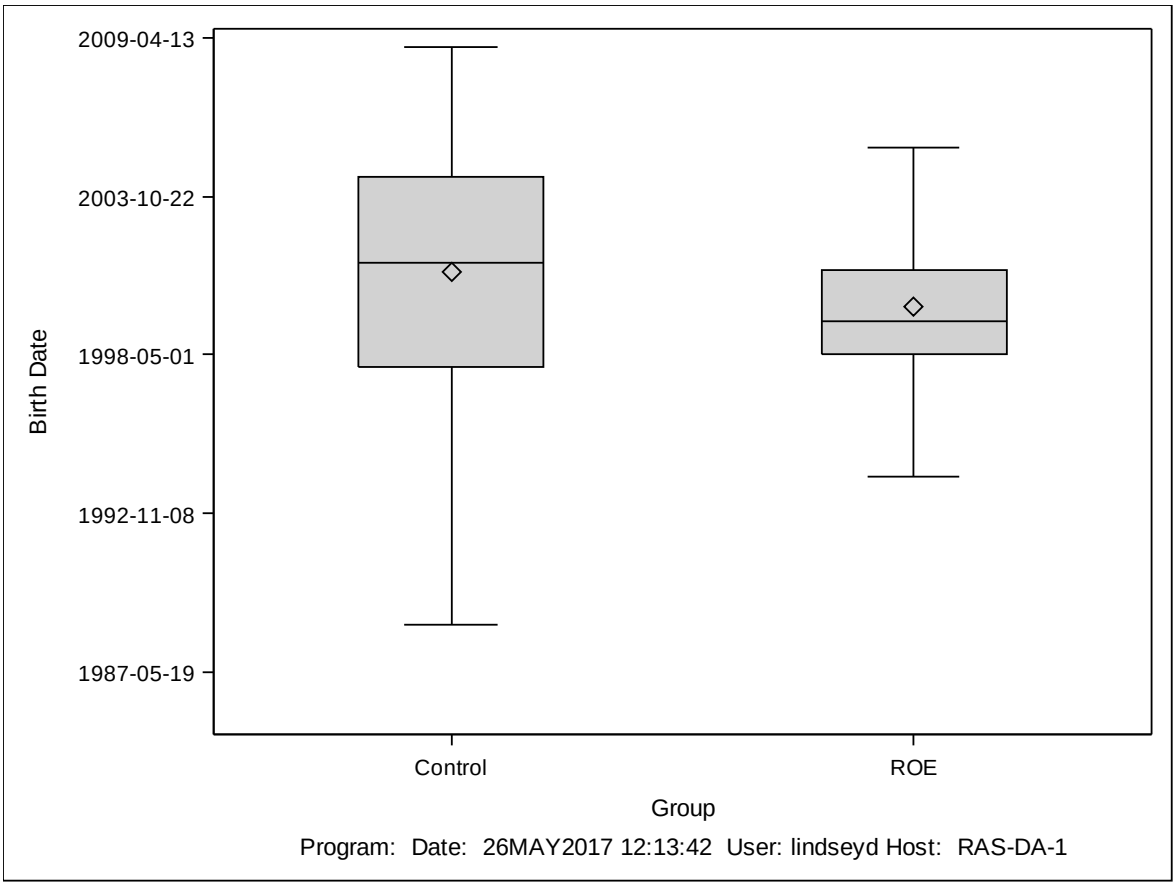

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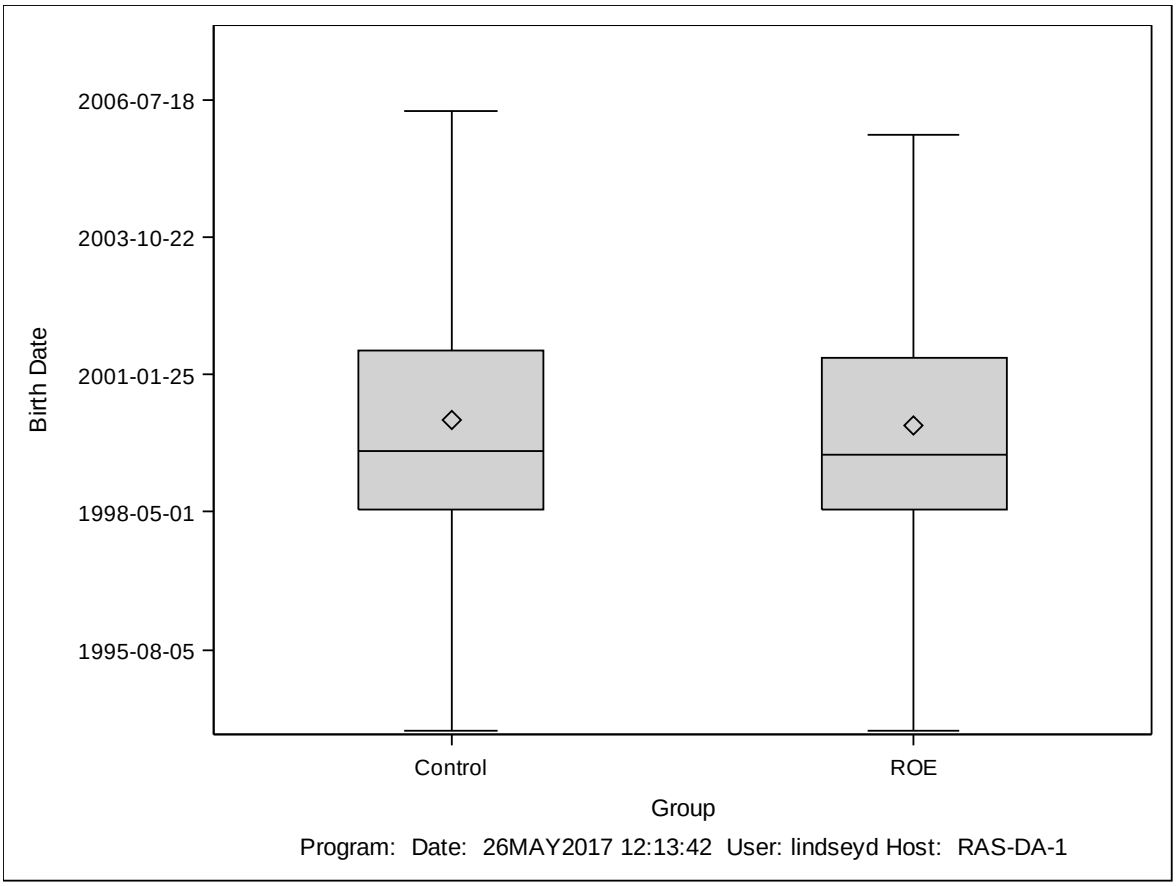
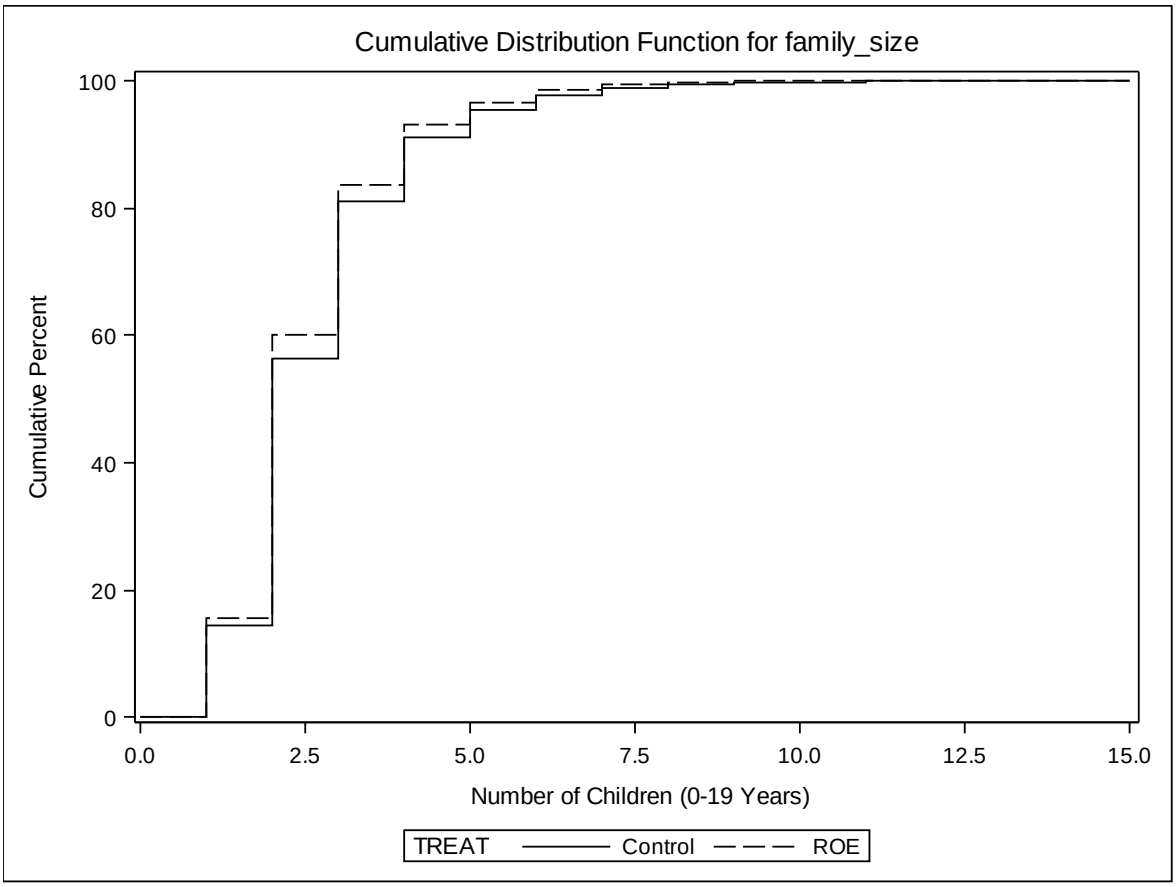


Matched Sample

Group 1. Family Size



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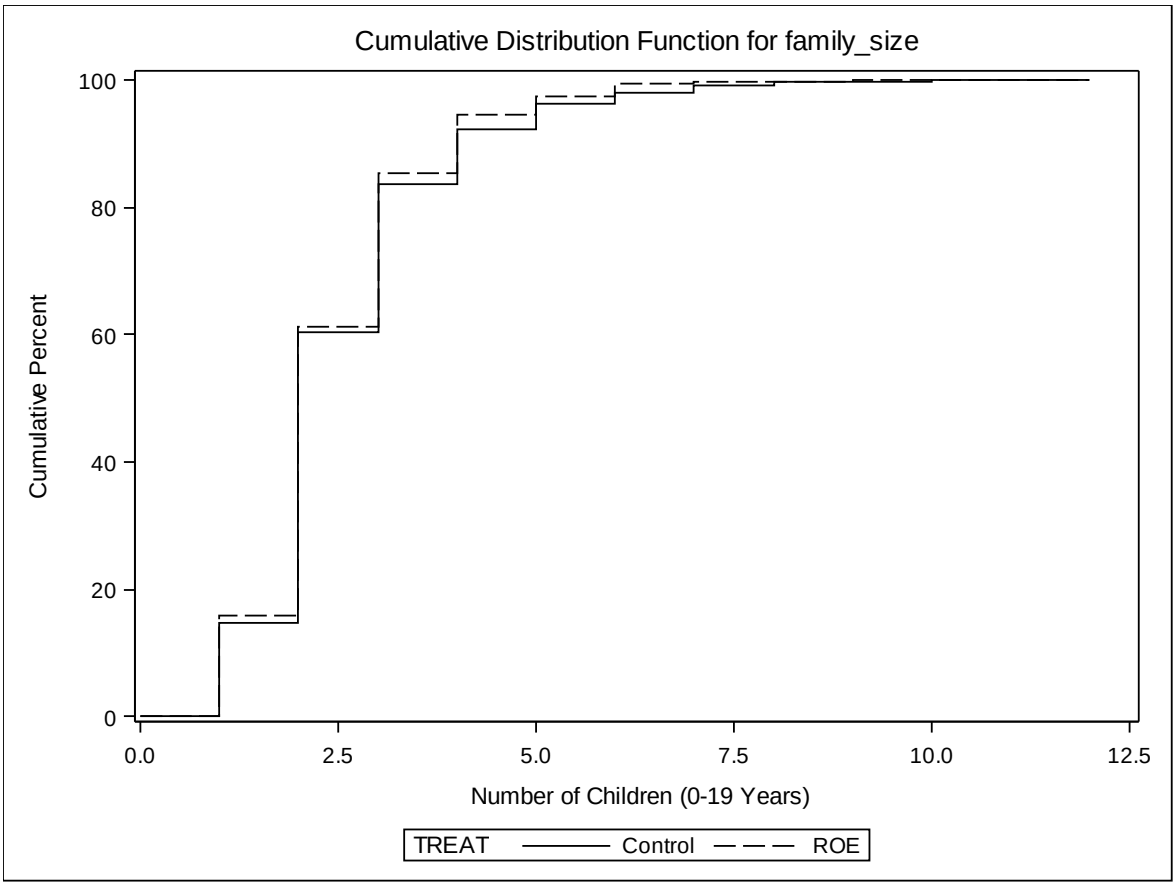

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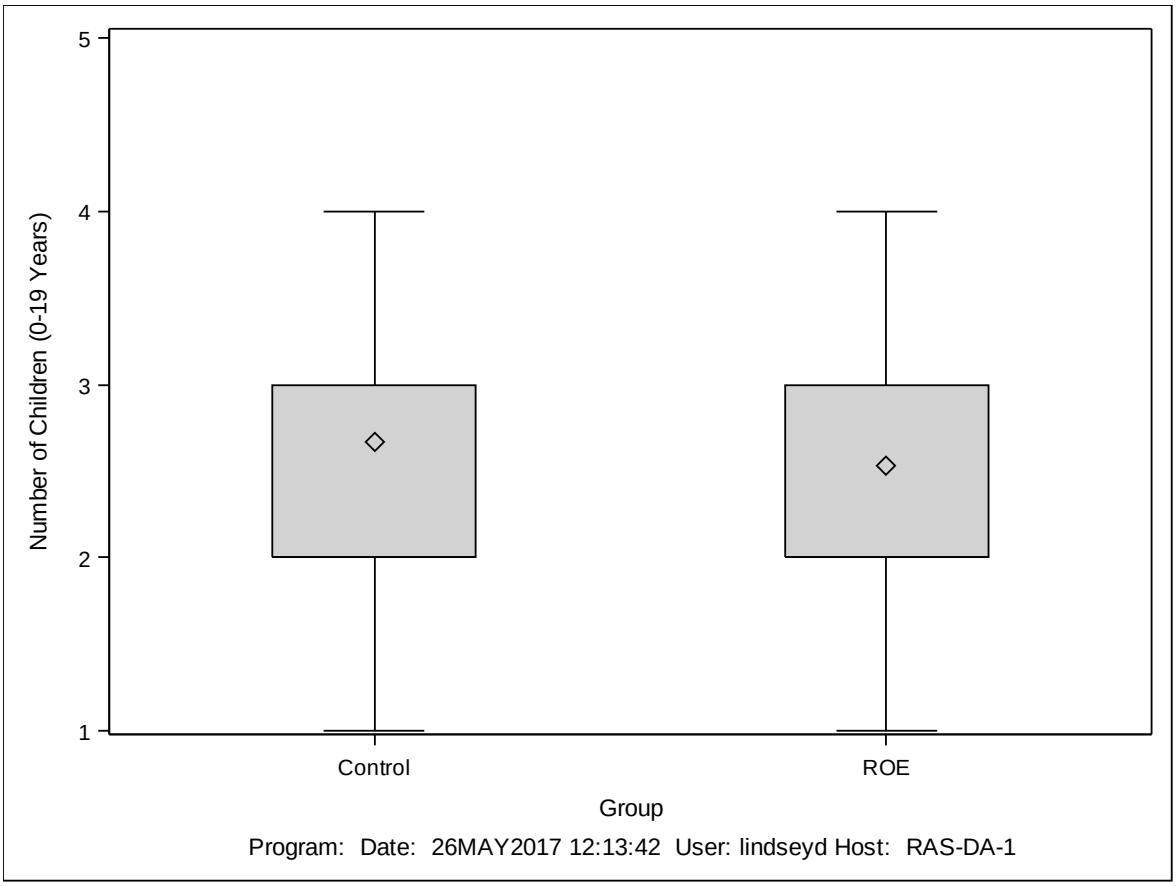

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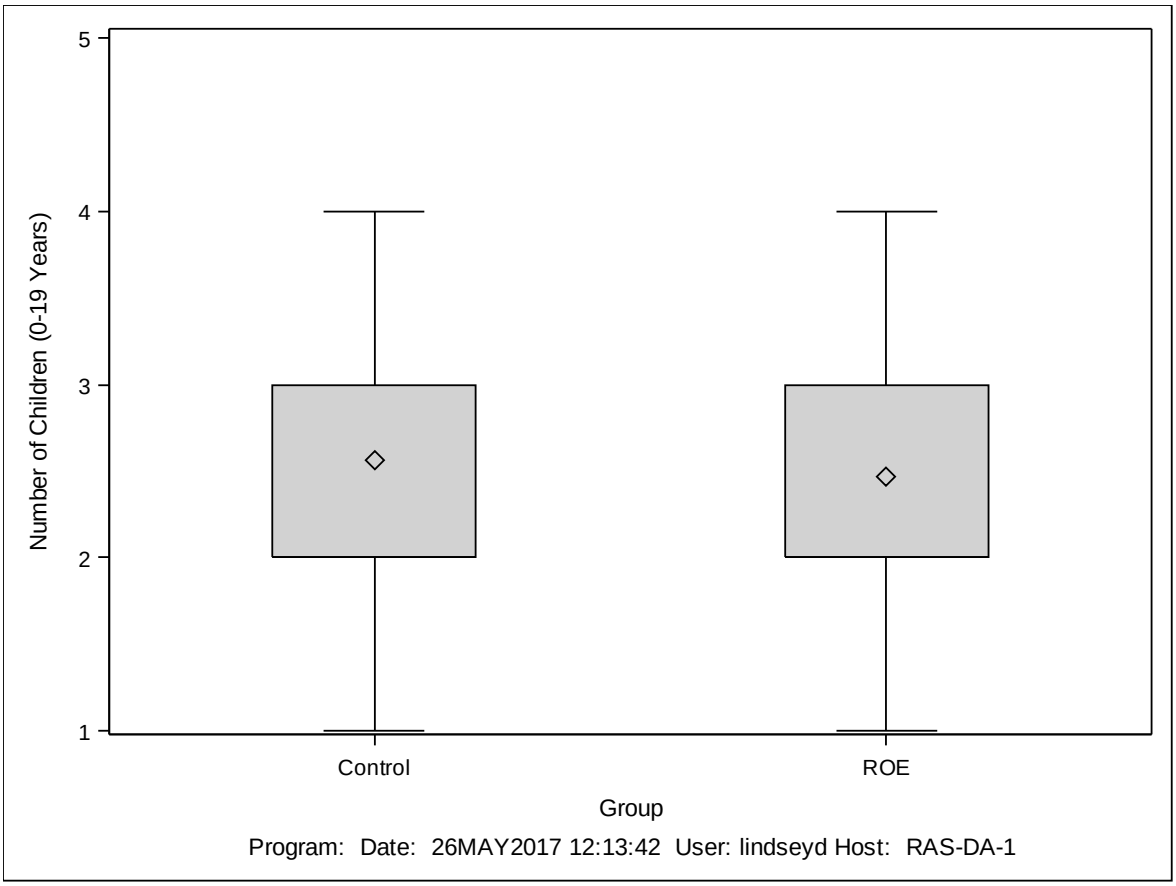
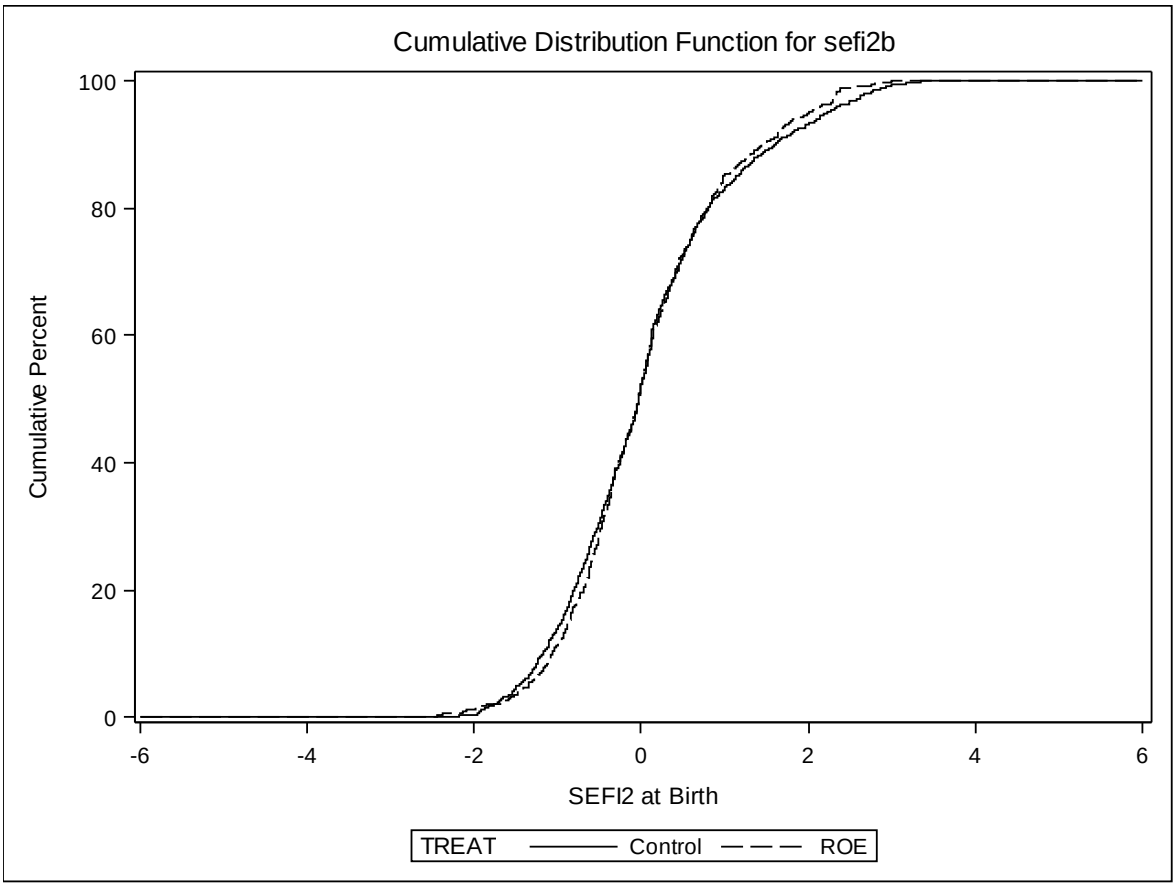


Matched Sample

Group 1. SEFI-2 at Birth



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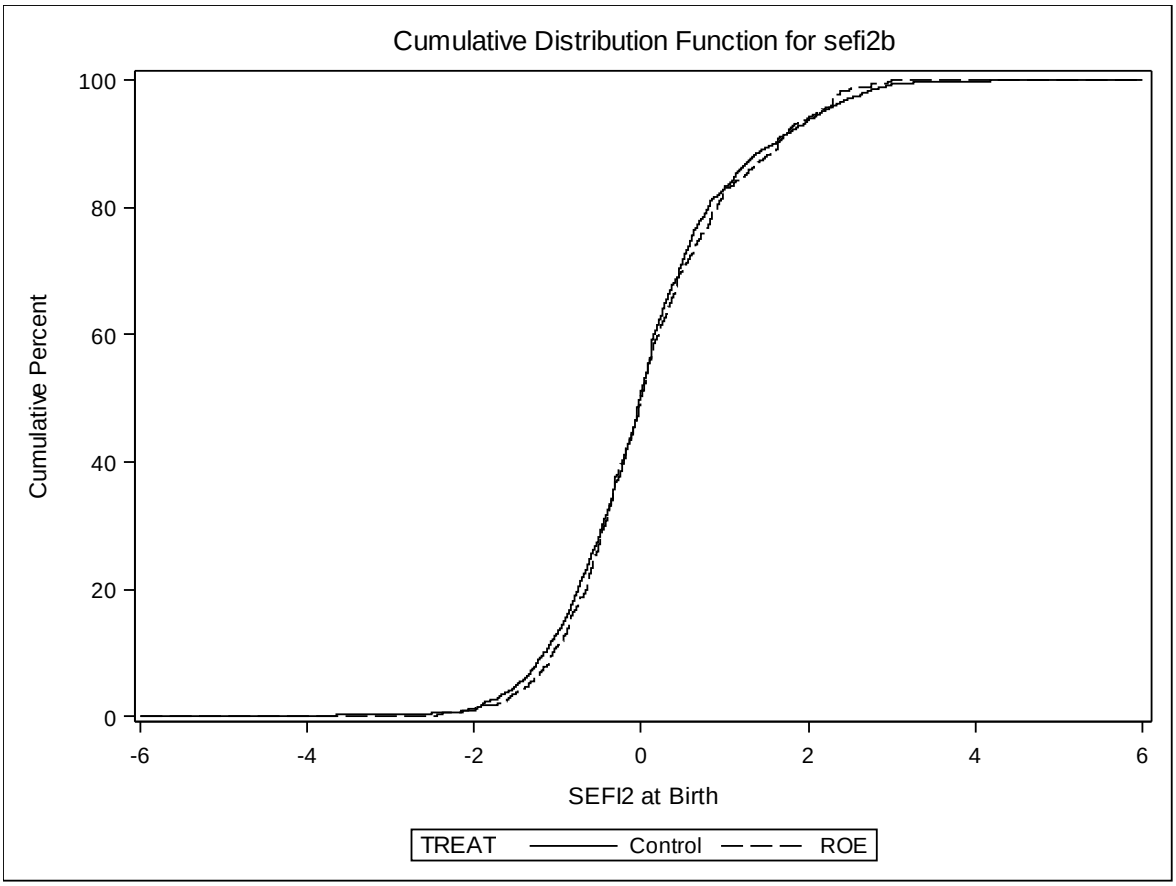

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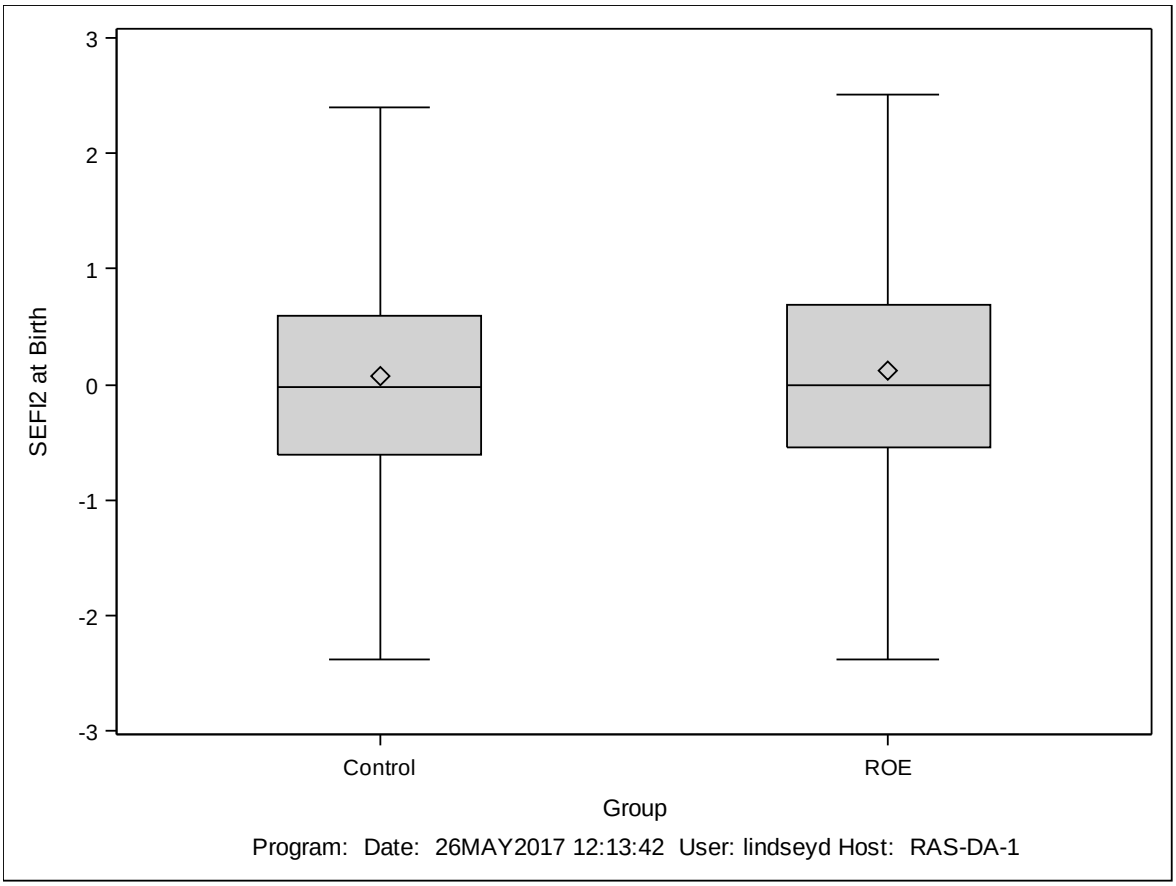

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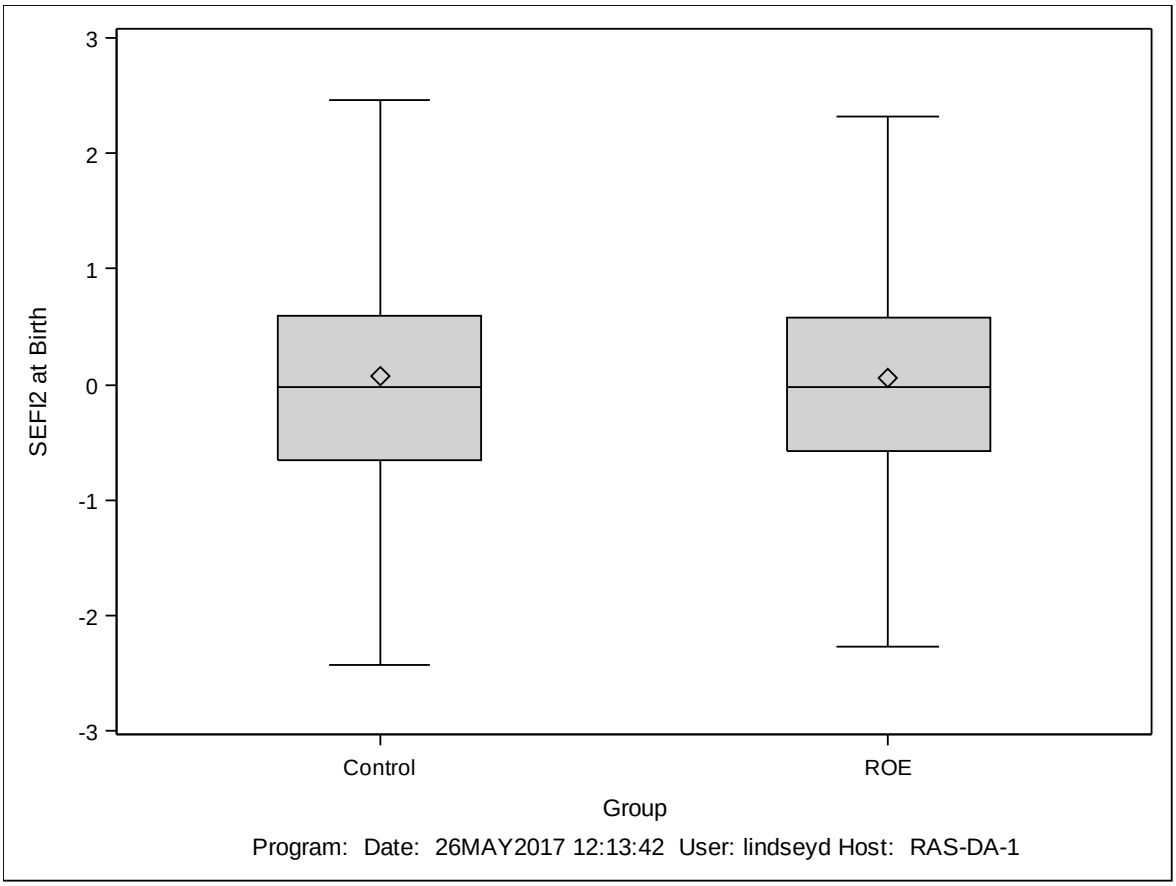
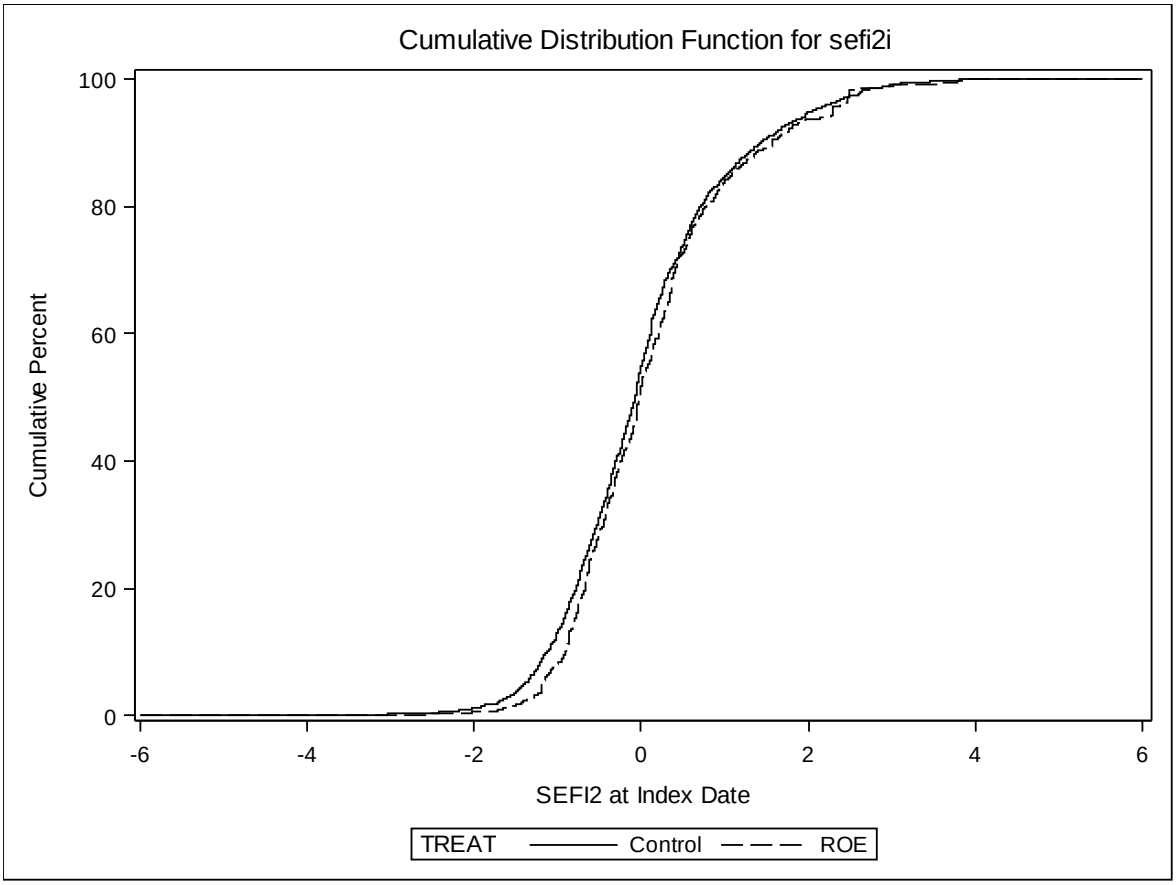


Matched Sample

Group 1. SEFI-2 at propensity score index date



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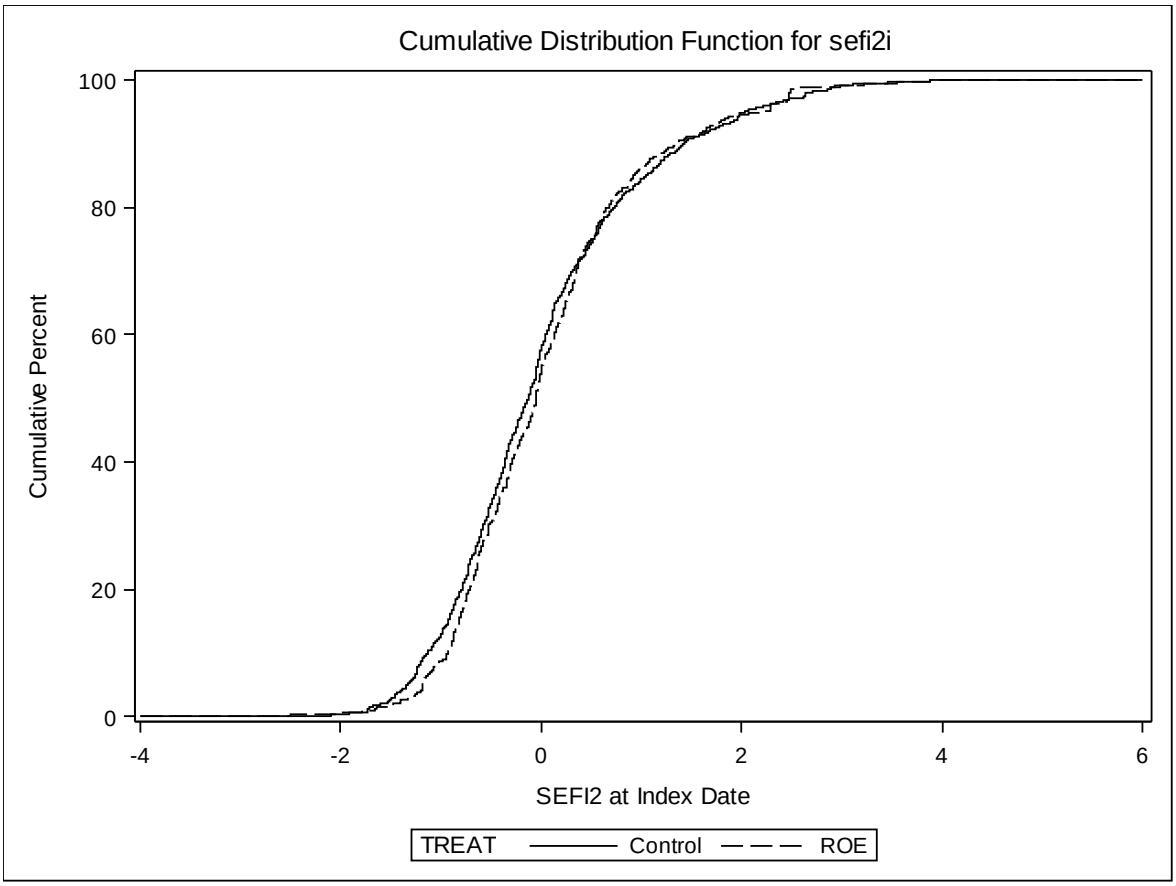

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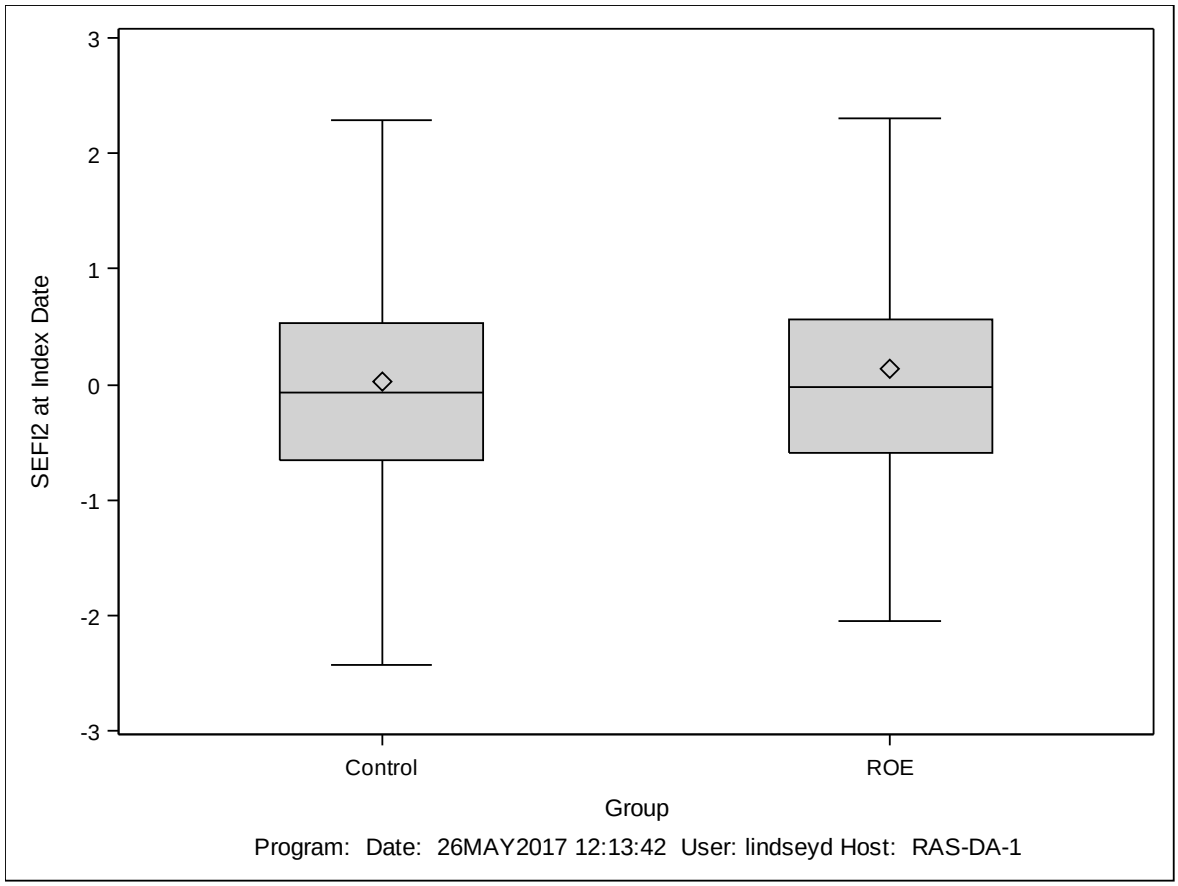

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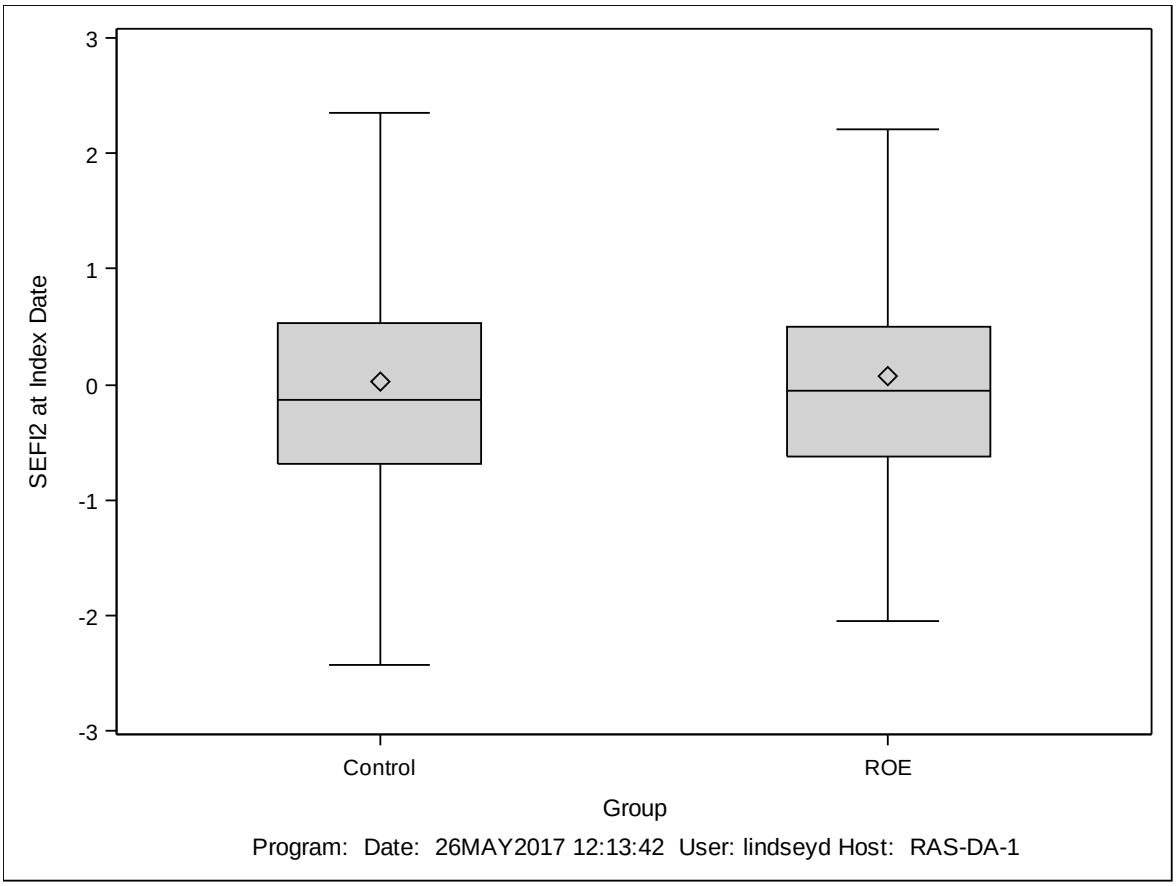
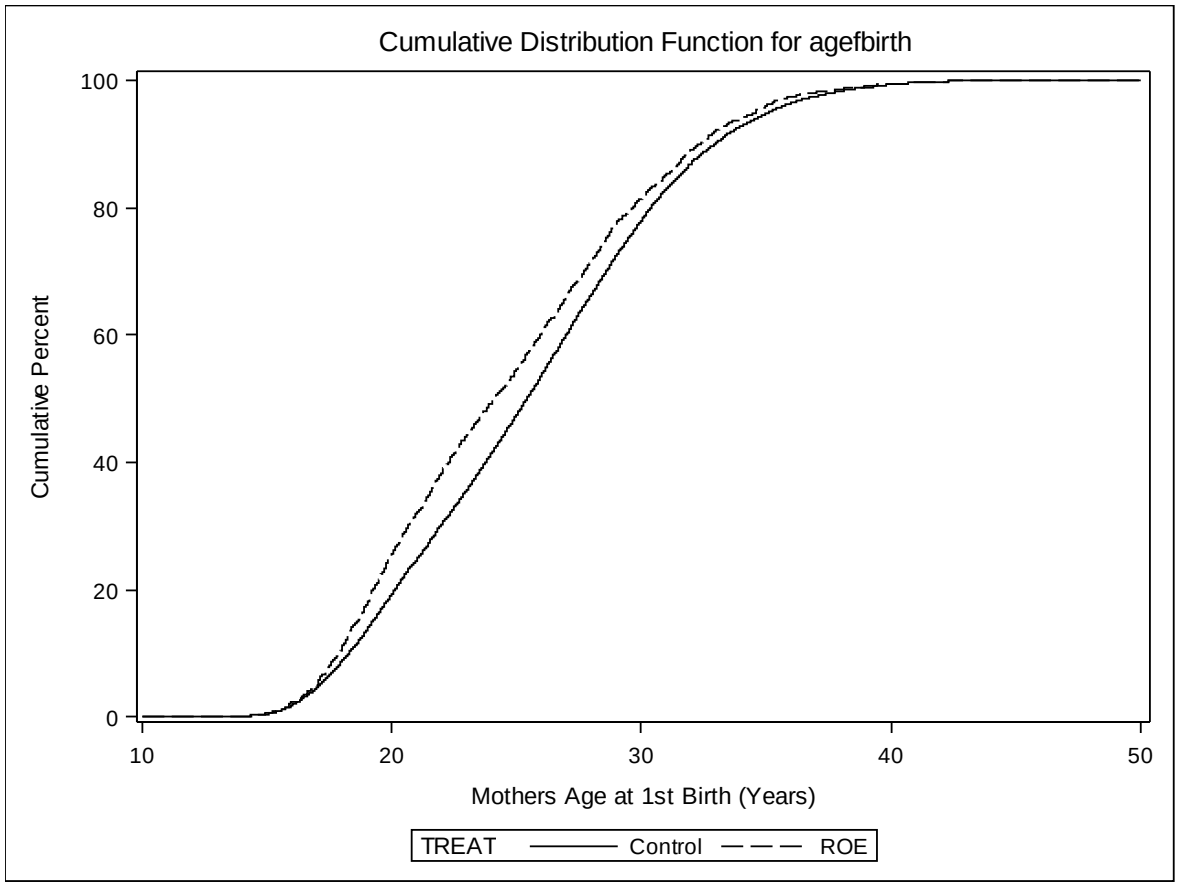


Matched Sample

Group 1. Mother's age at date of first birth



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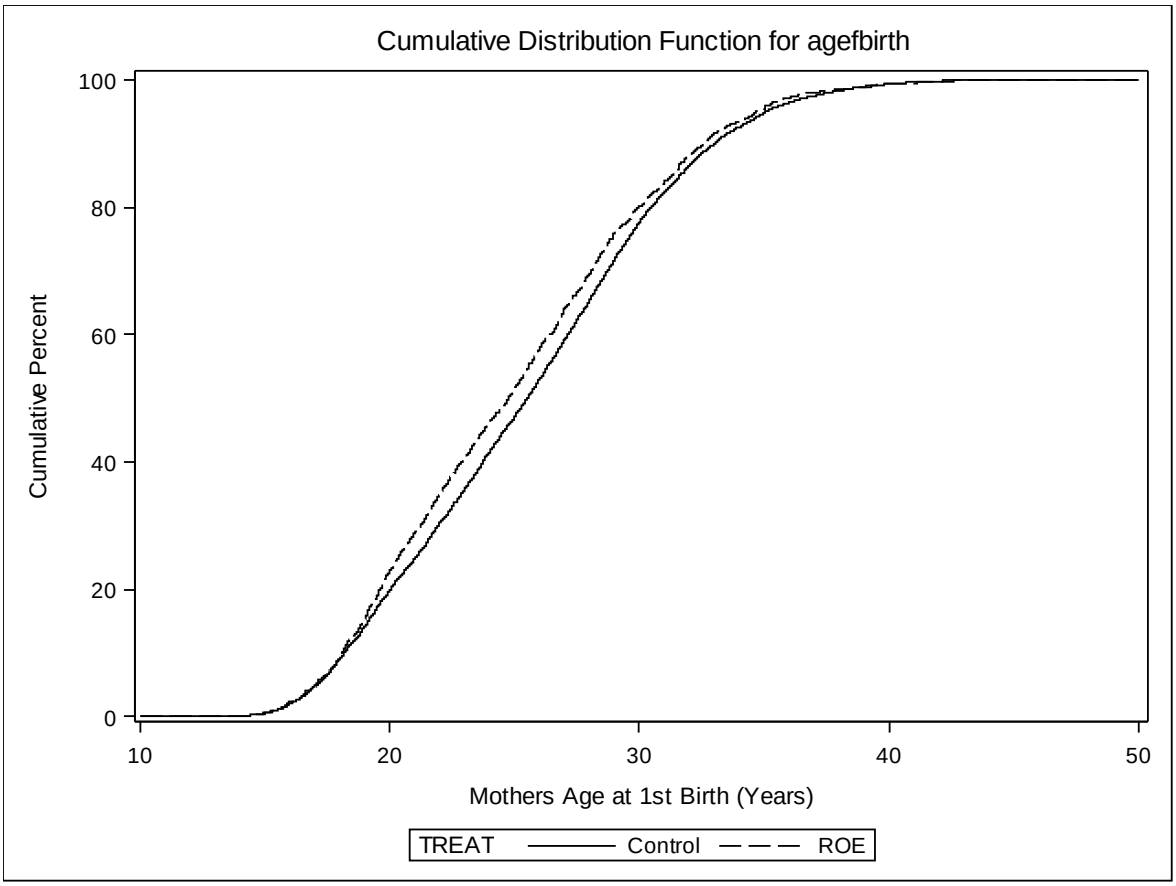
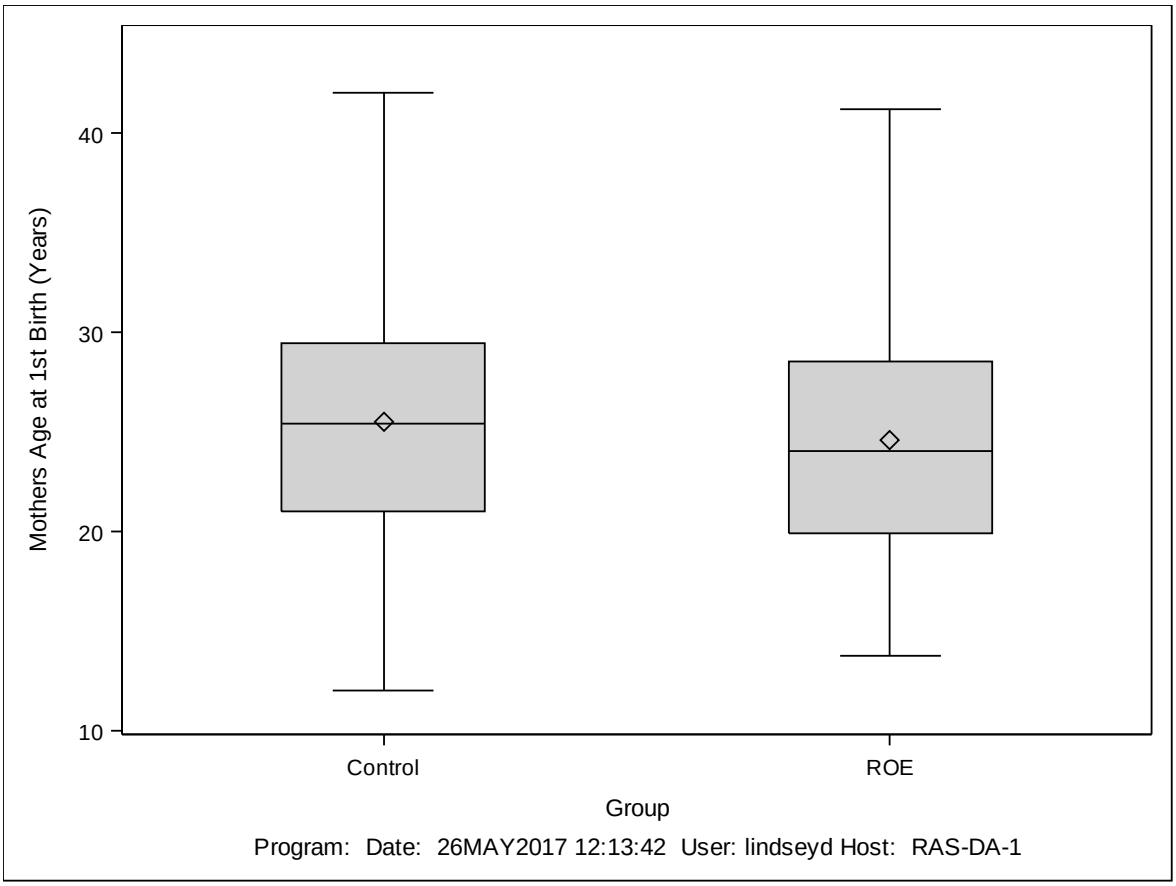
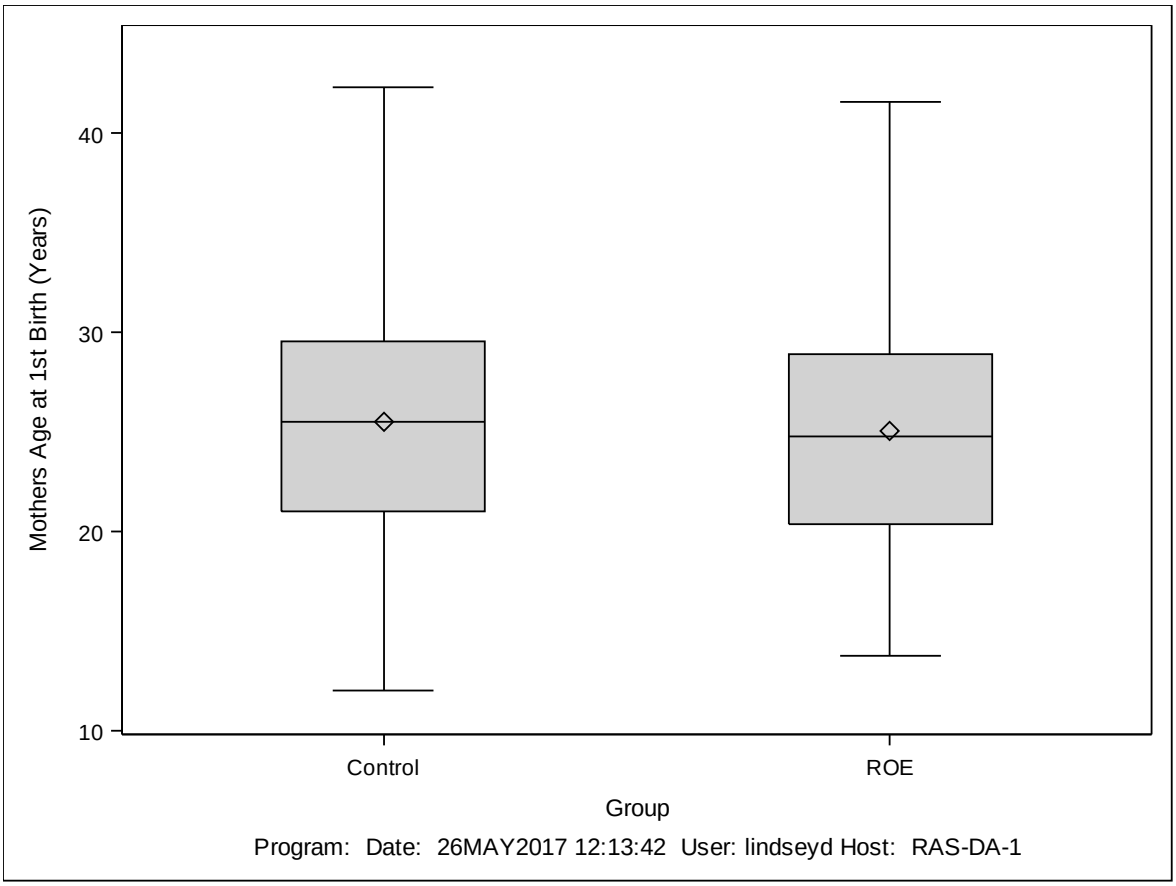


Matched Sample

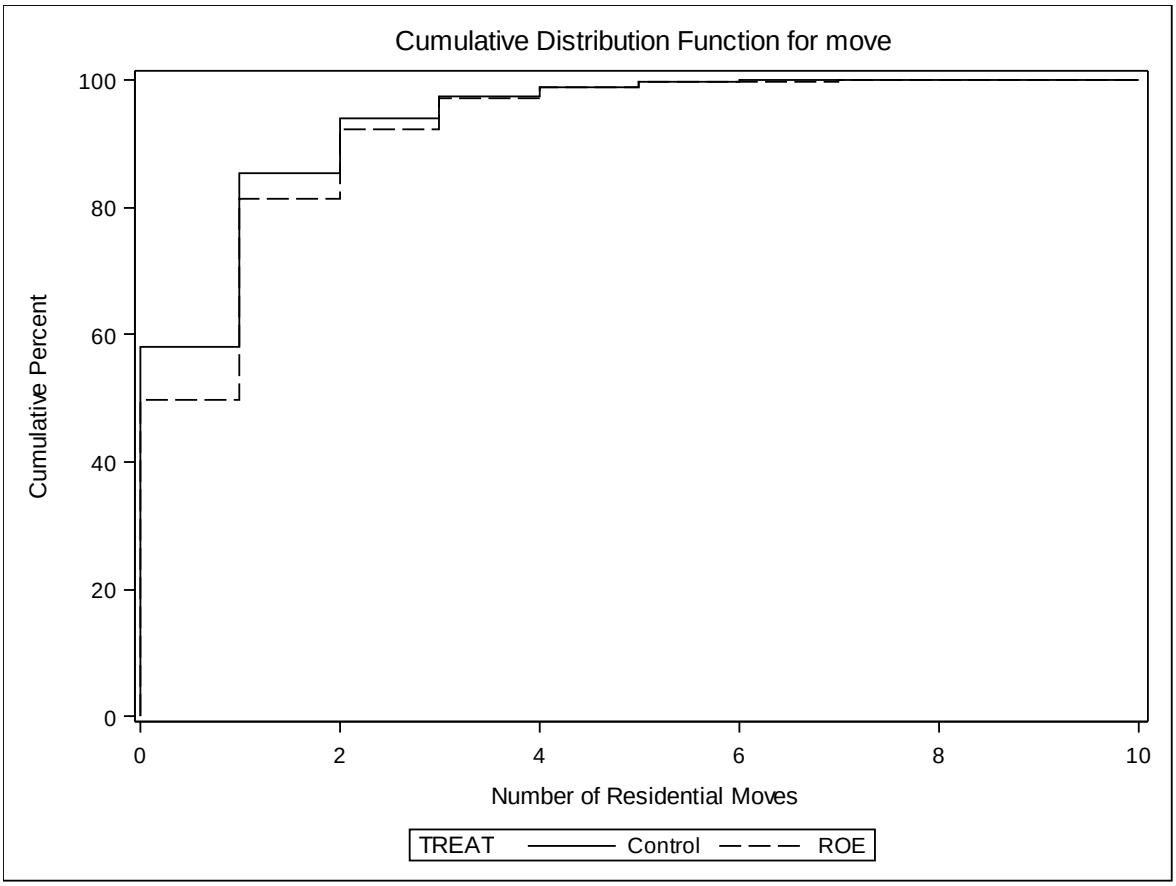


Original Sample

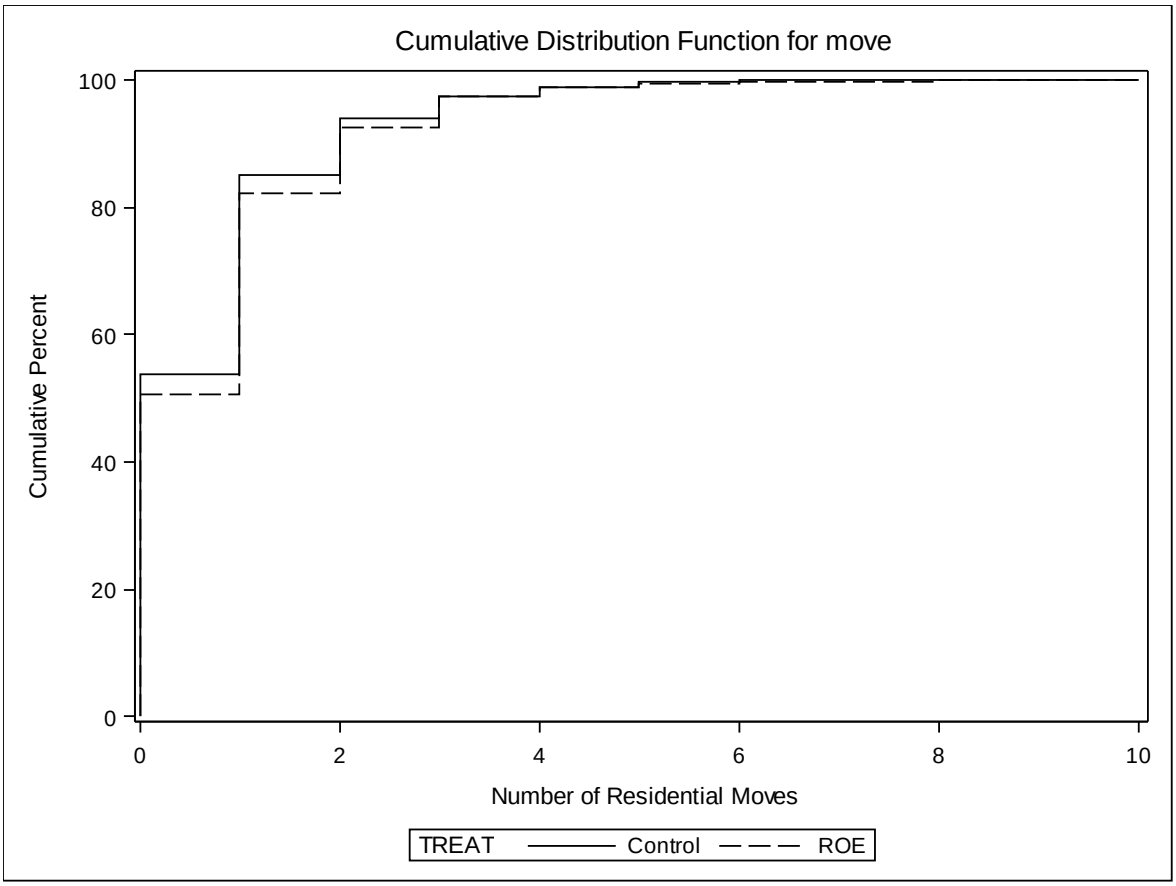


Matched Sample

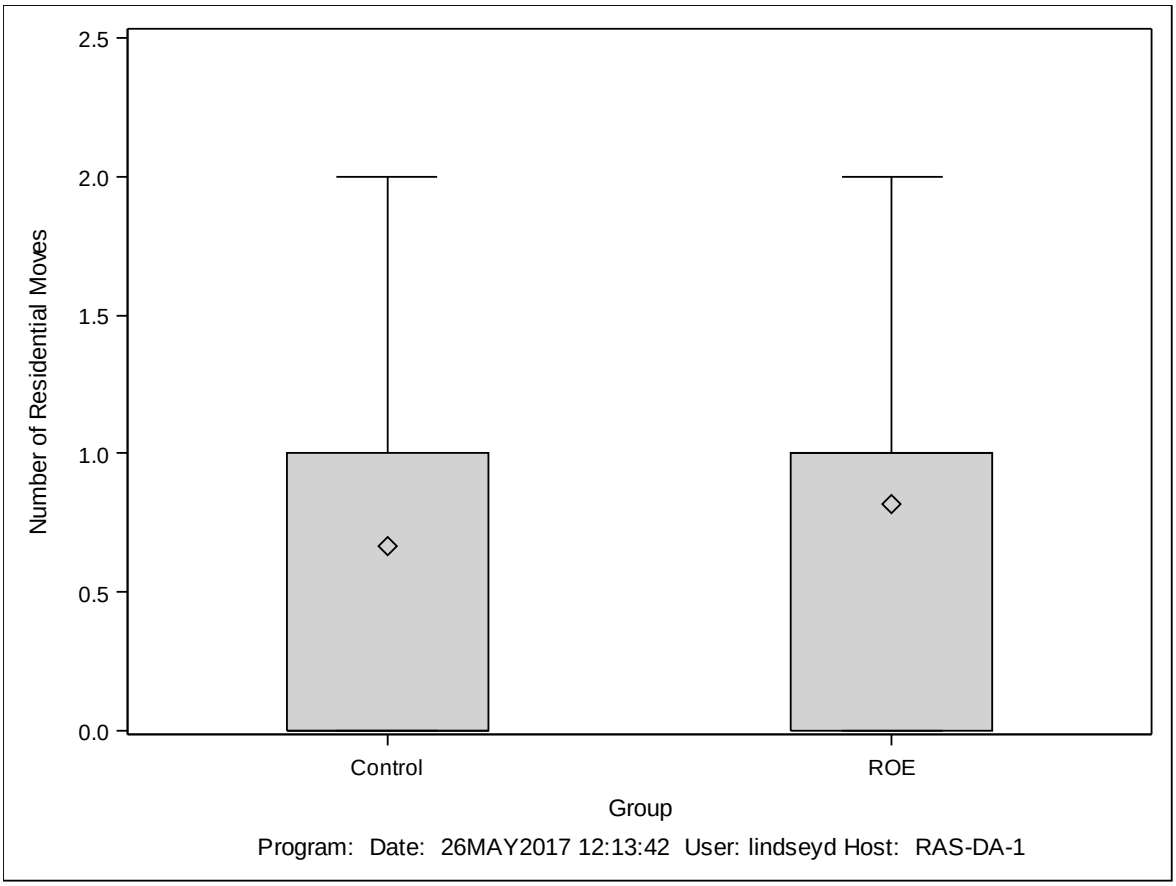
Group 1. Residential Mobility



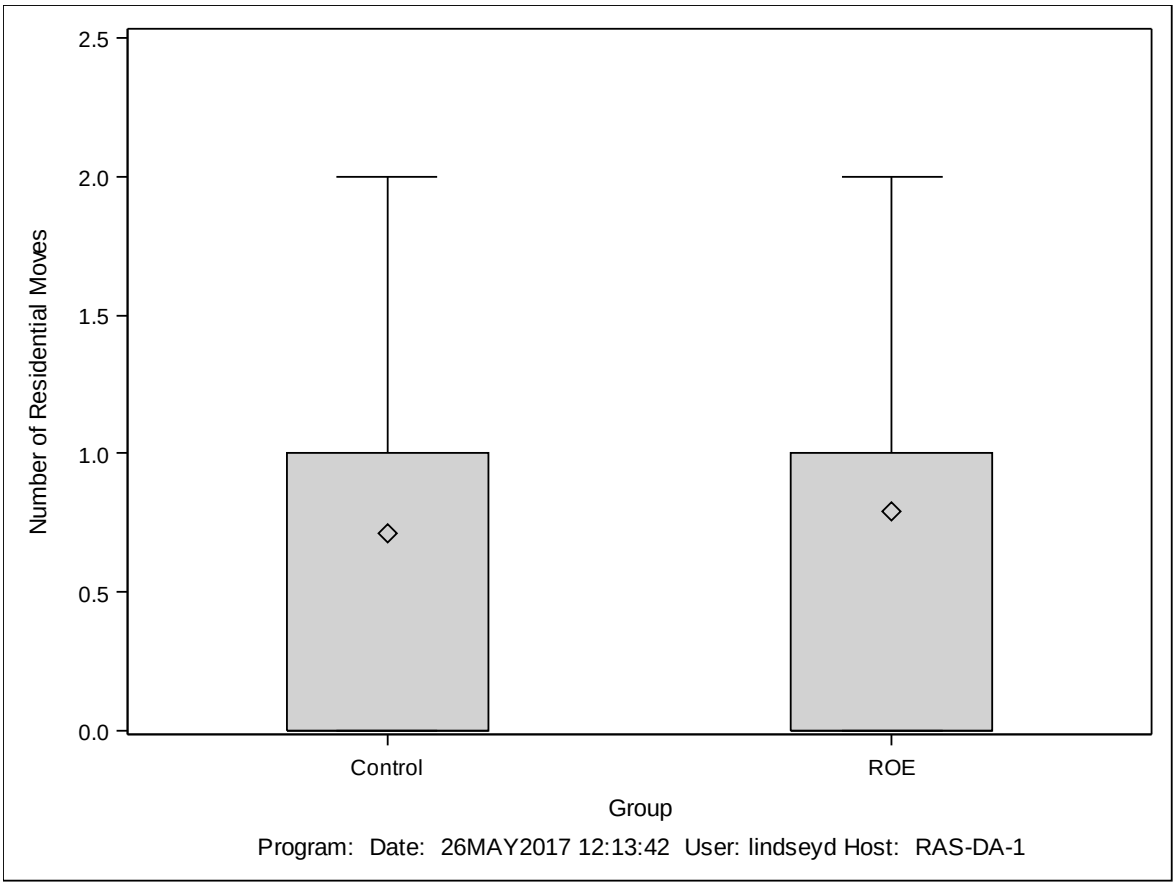
Original Sample



Matched Sample

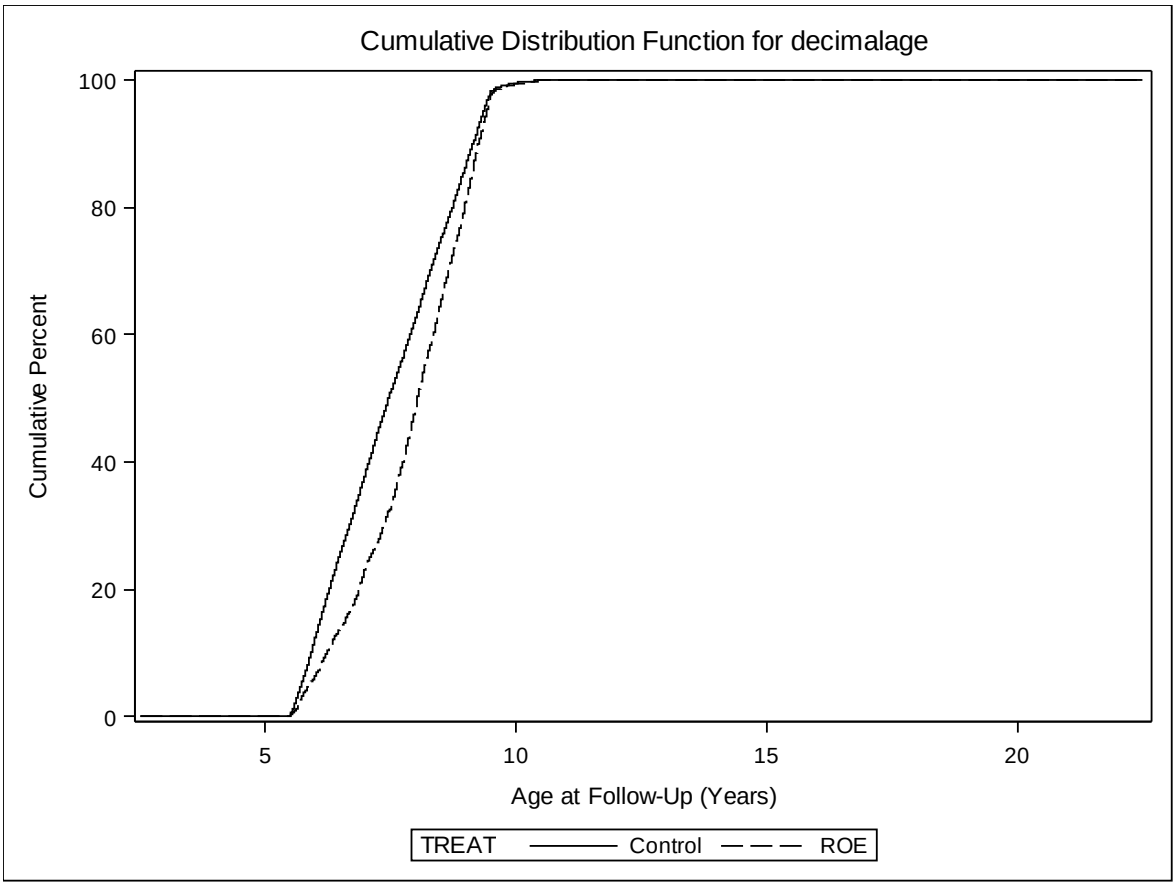


Original Sample

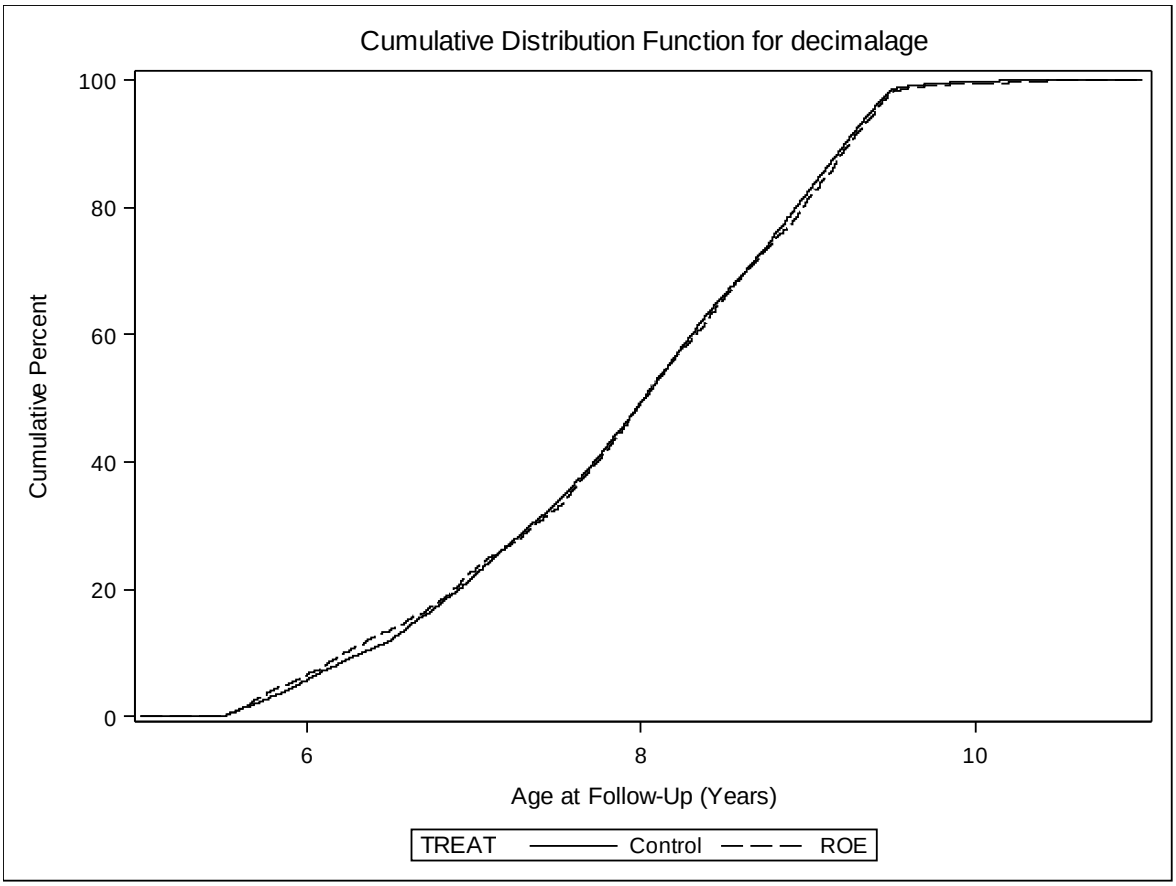


Matched Sample

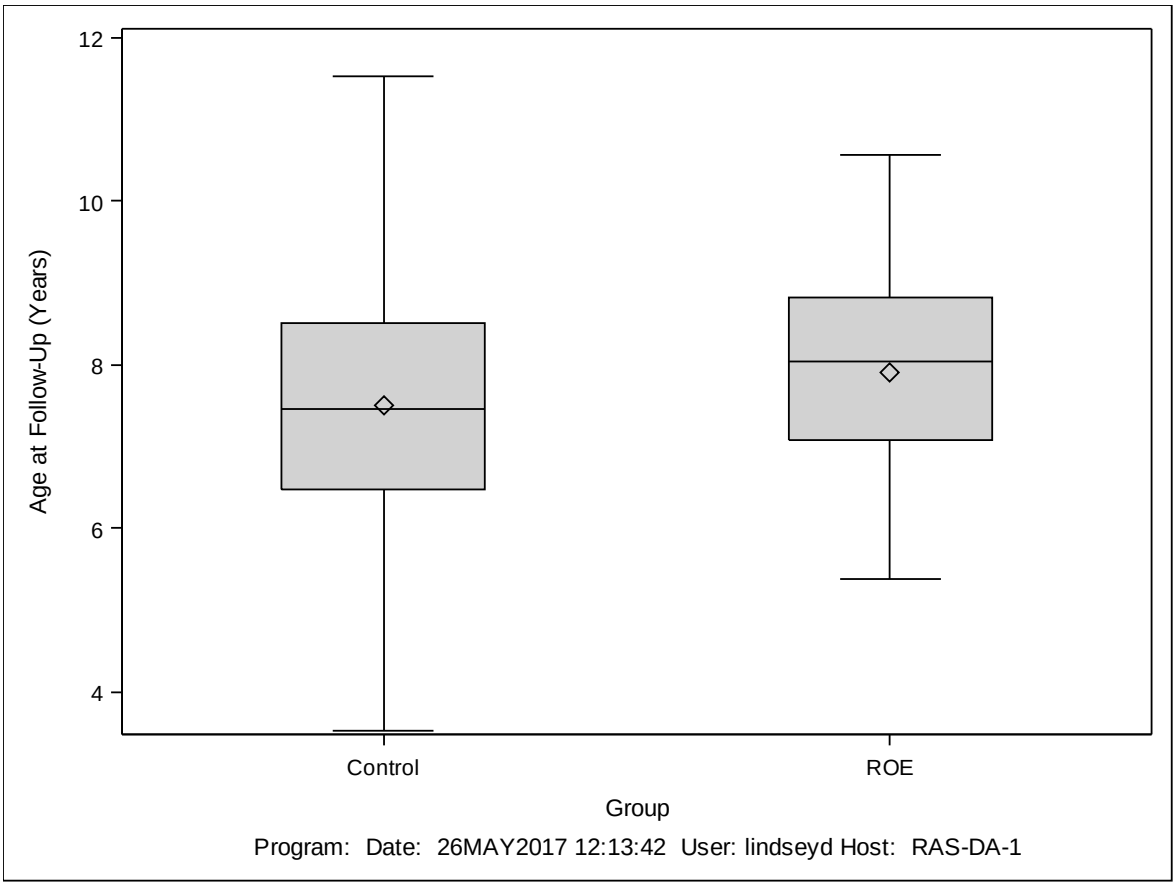
Group 1. Age at follow-up



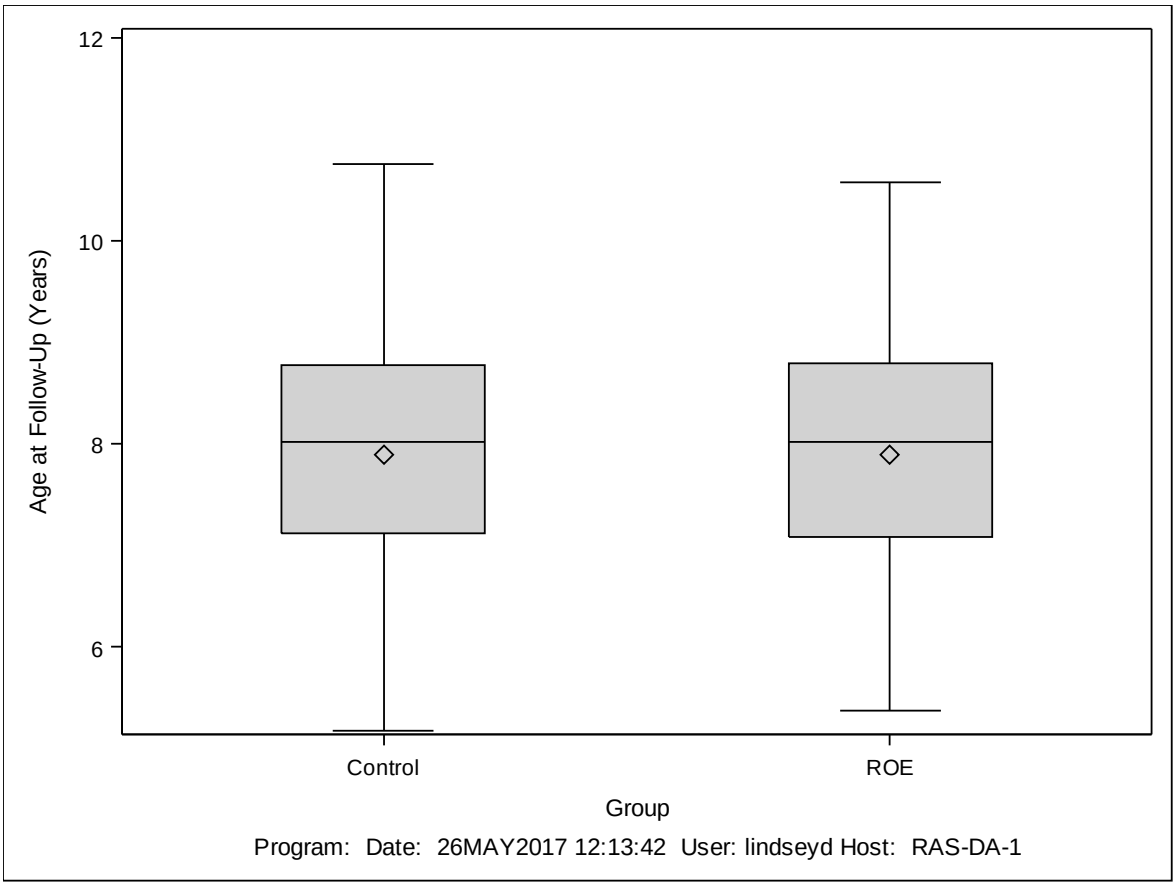
Original Sample



Matched Sample

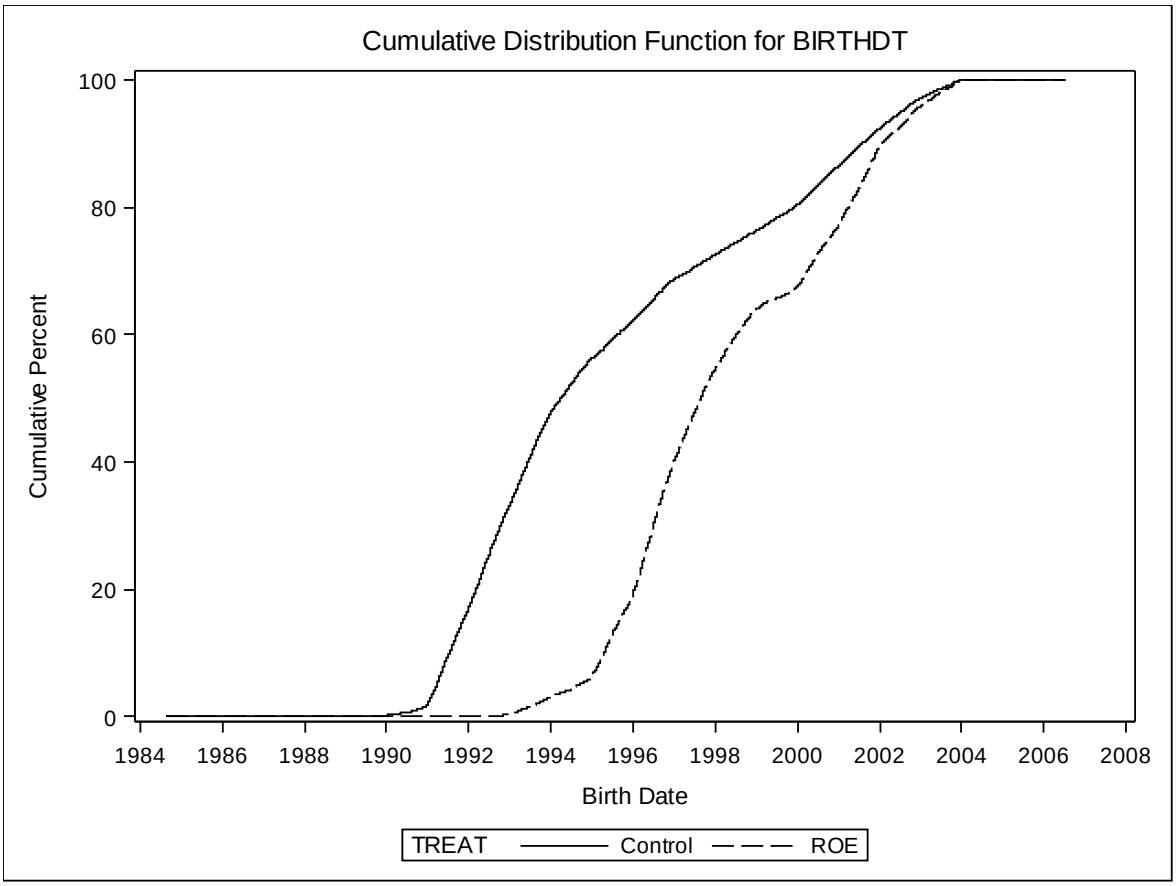


Original Sample

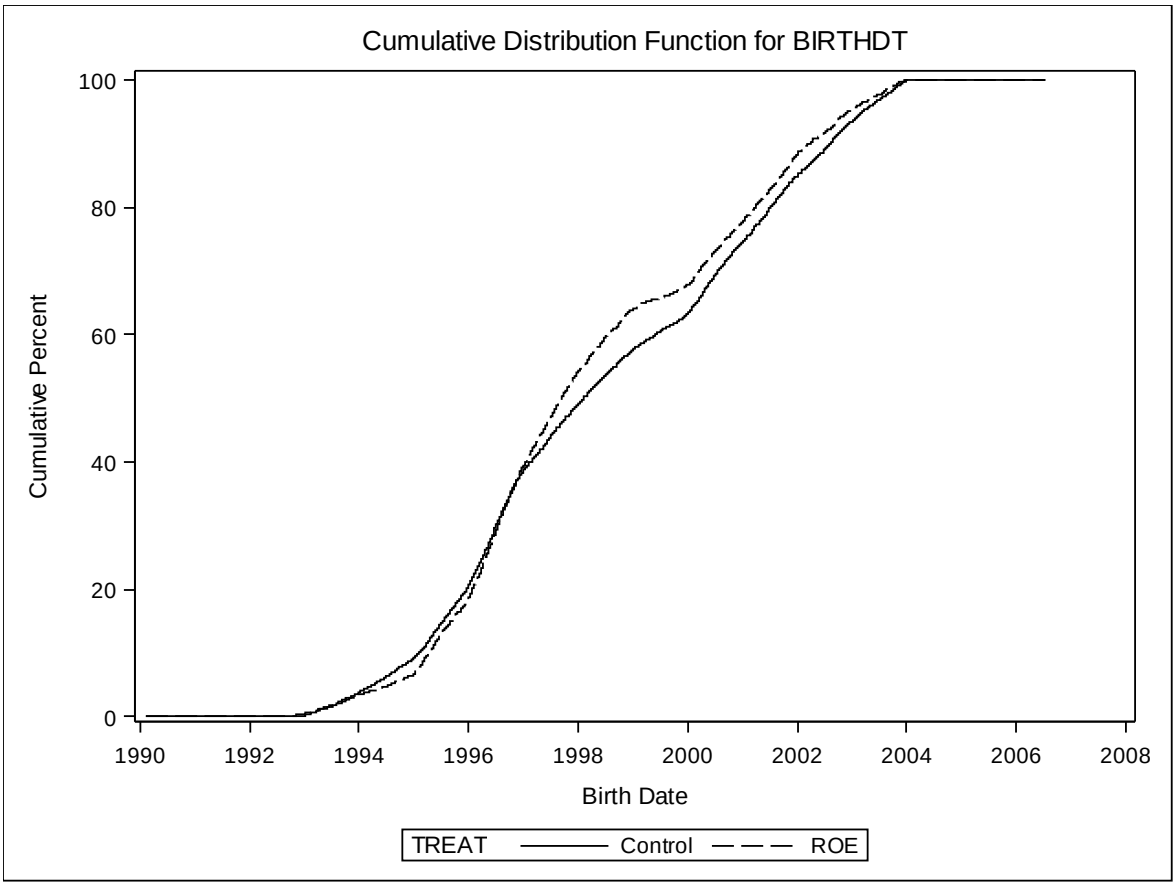


Matched Sample

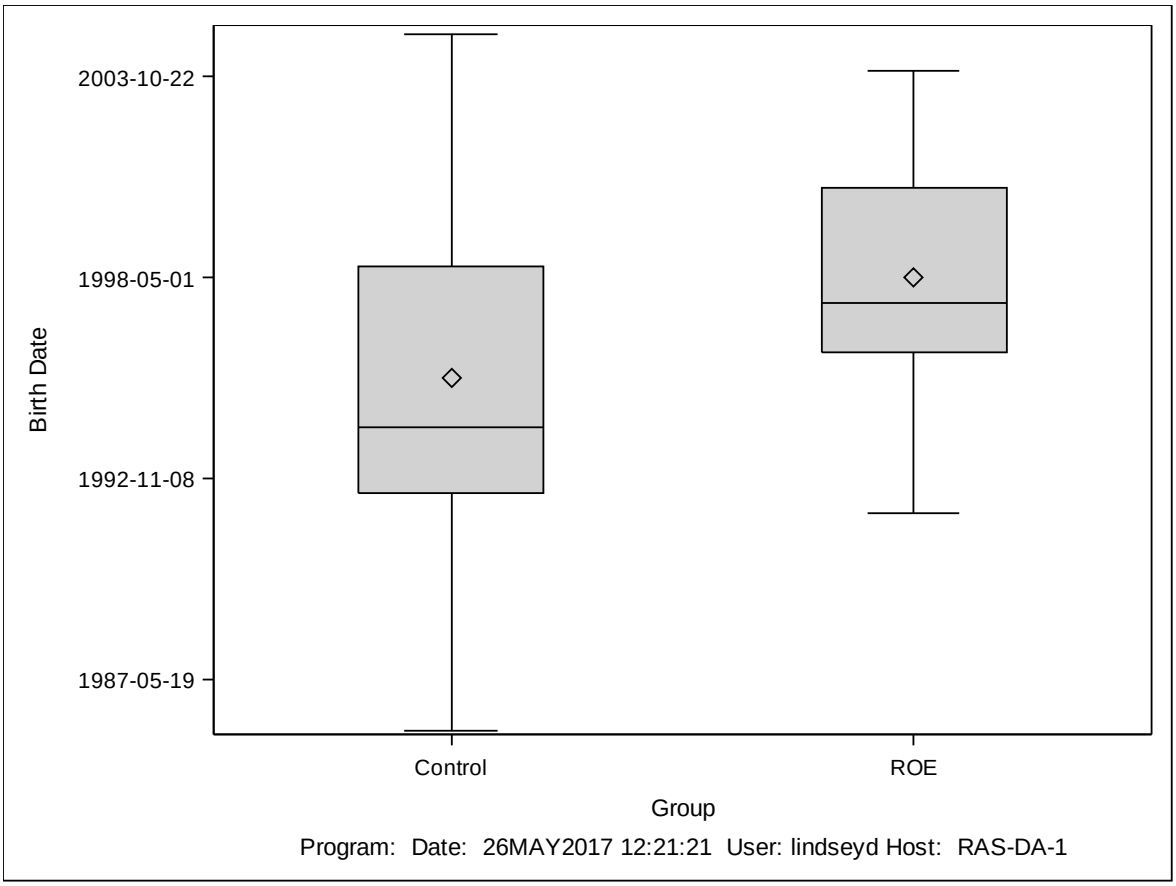
Group 2. Birthdate



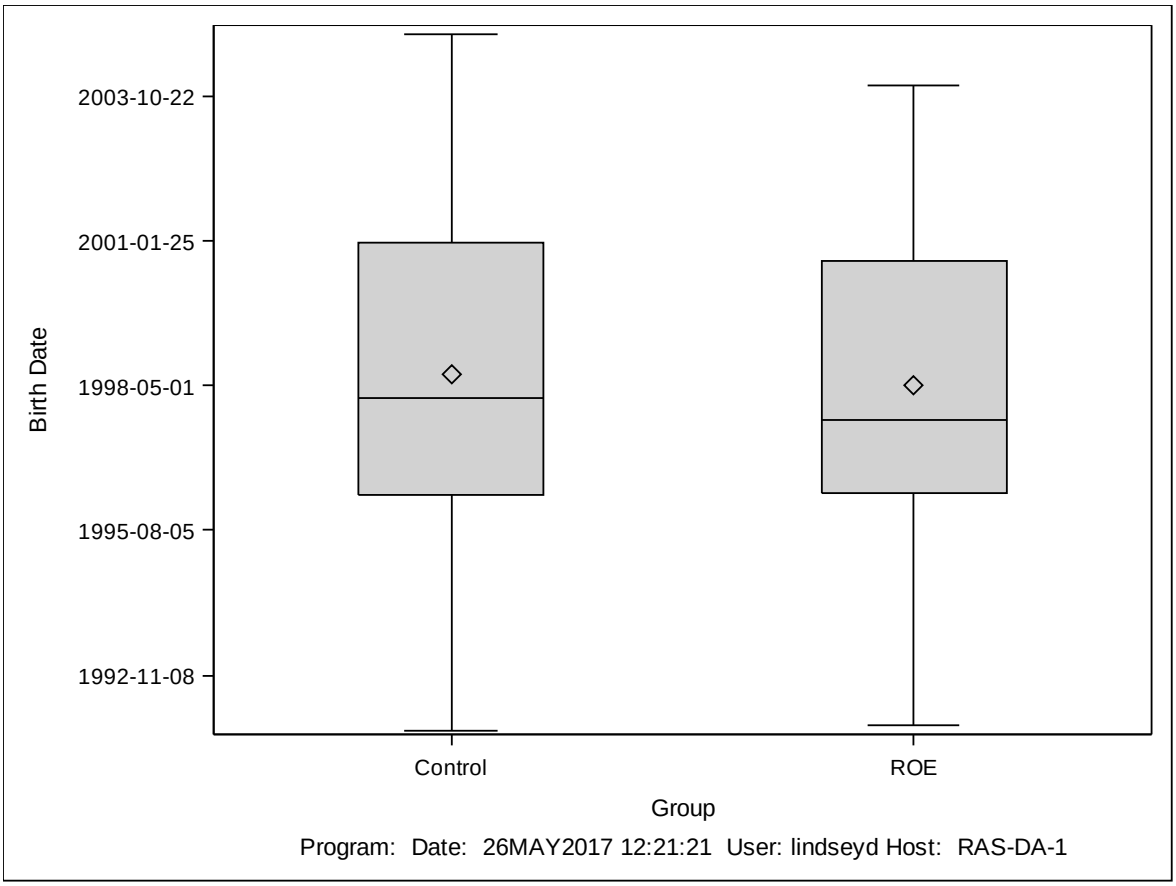
Original Sample



Matched Sample

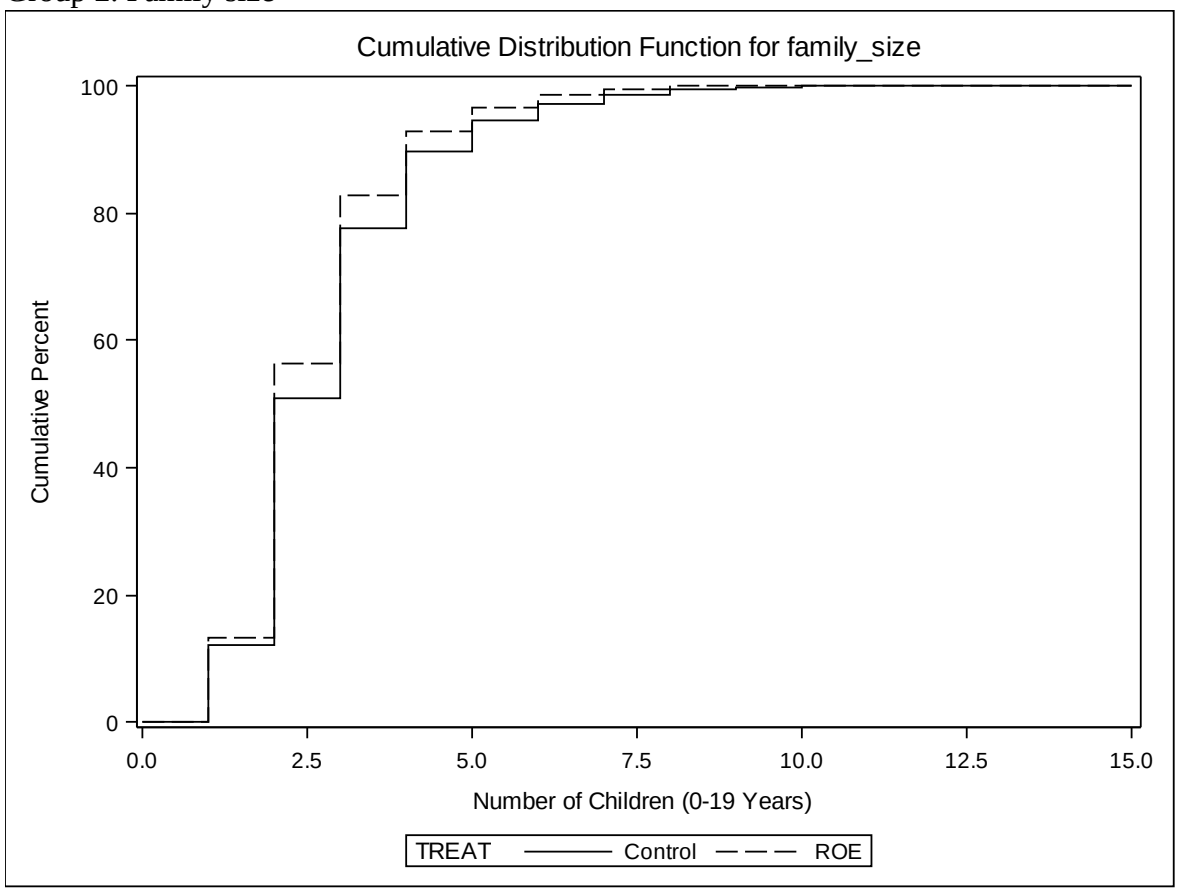


Original Sample

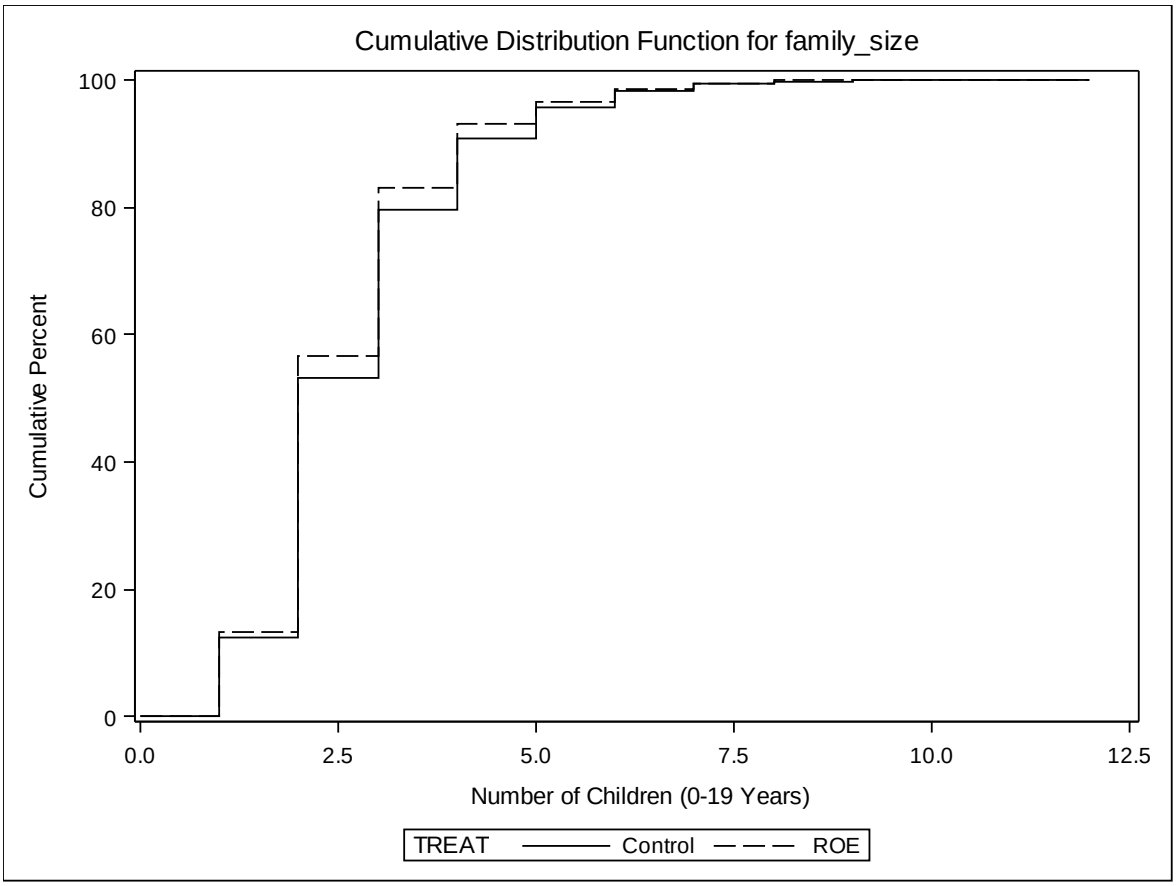


Matched Sample

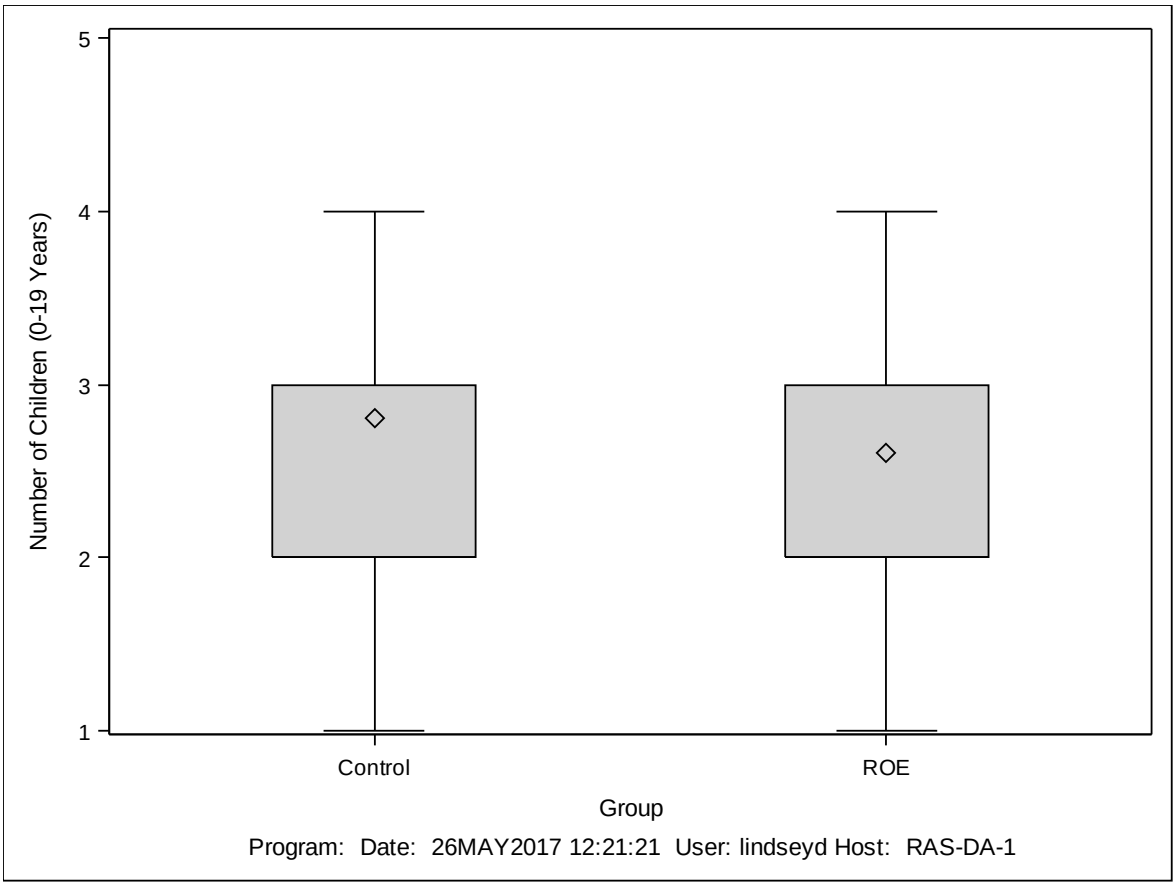
Group 2. Family size



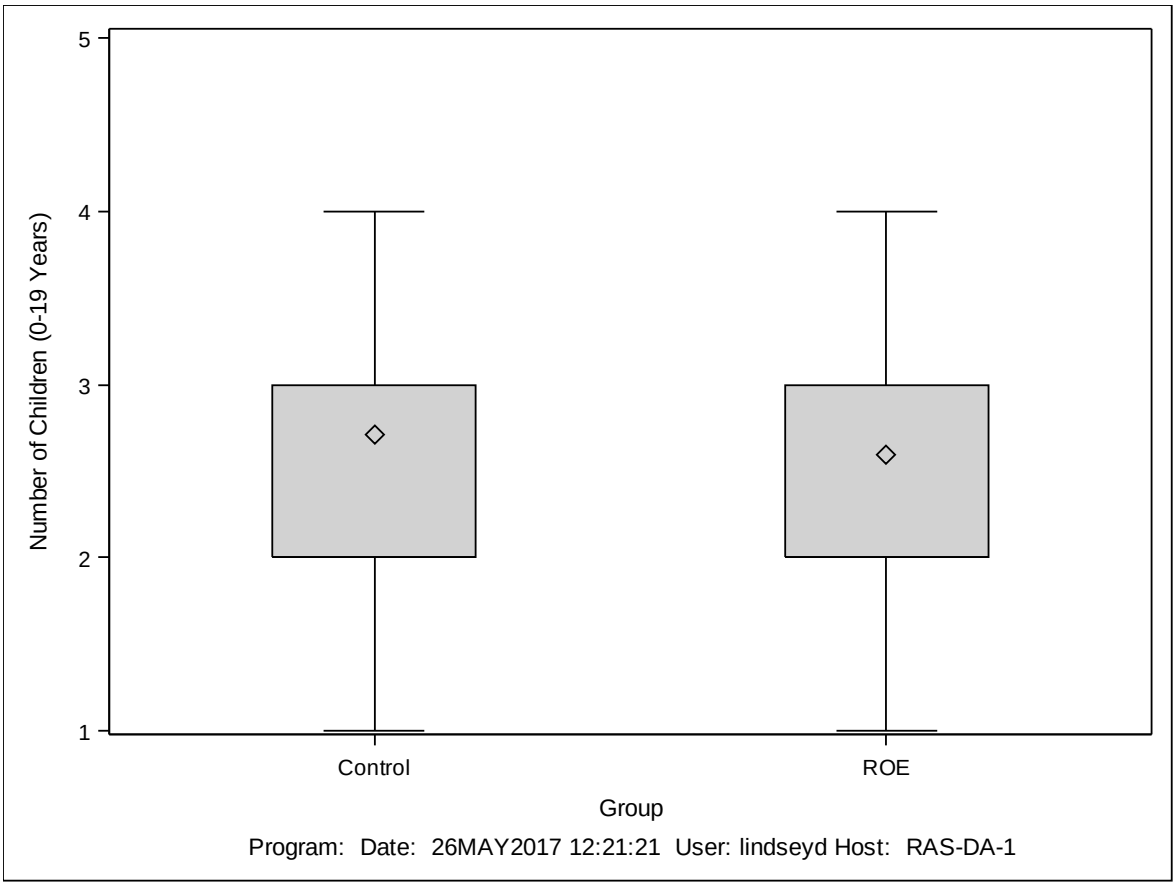
Original Sample



Matched Sample

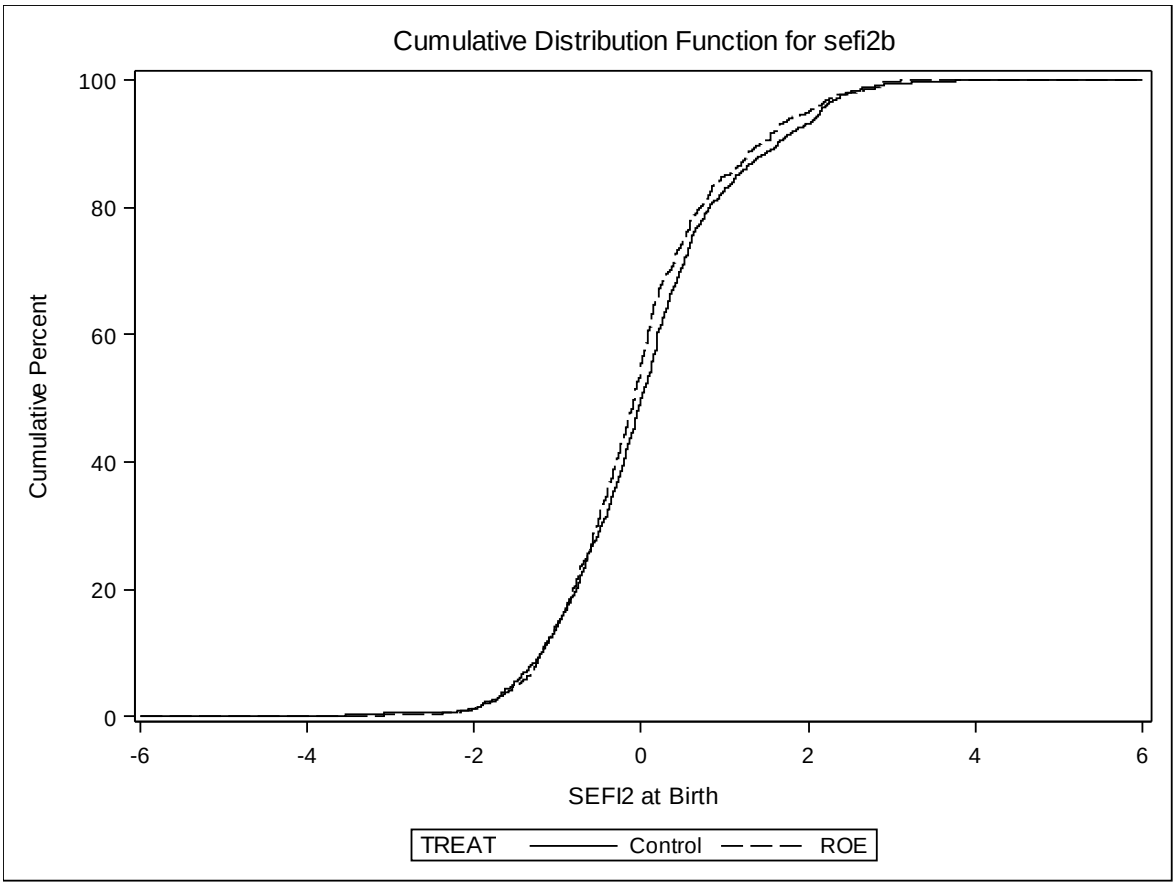


Original Sample

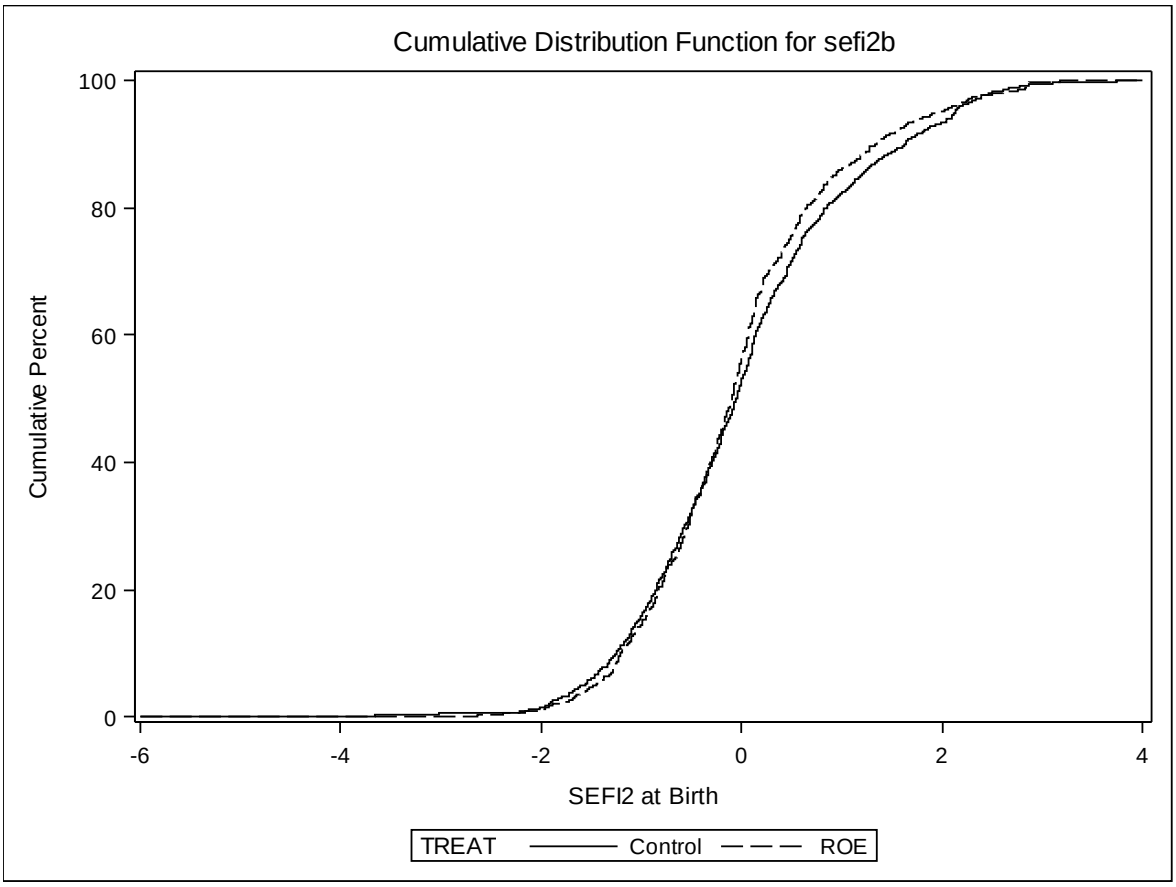


Matched Sample

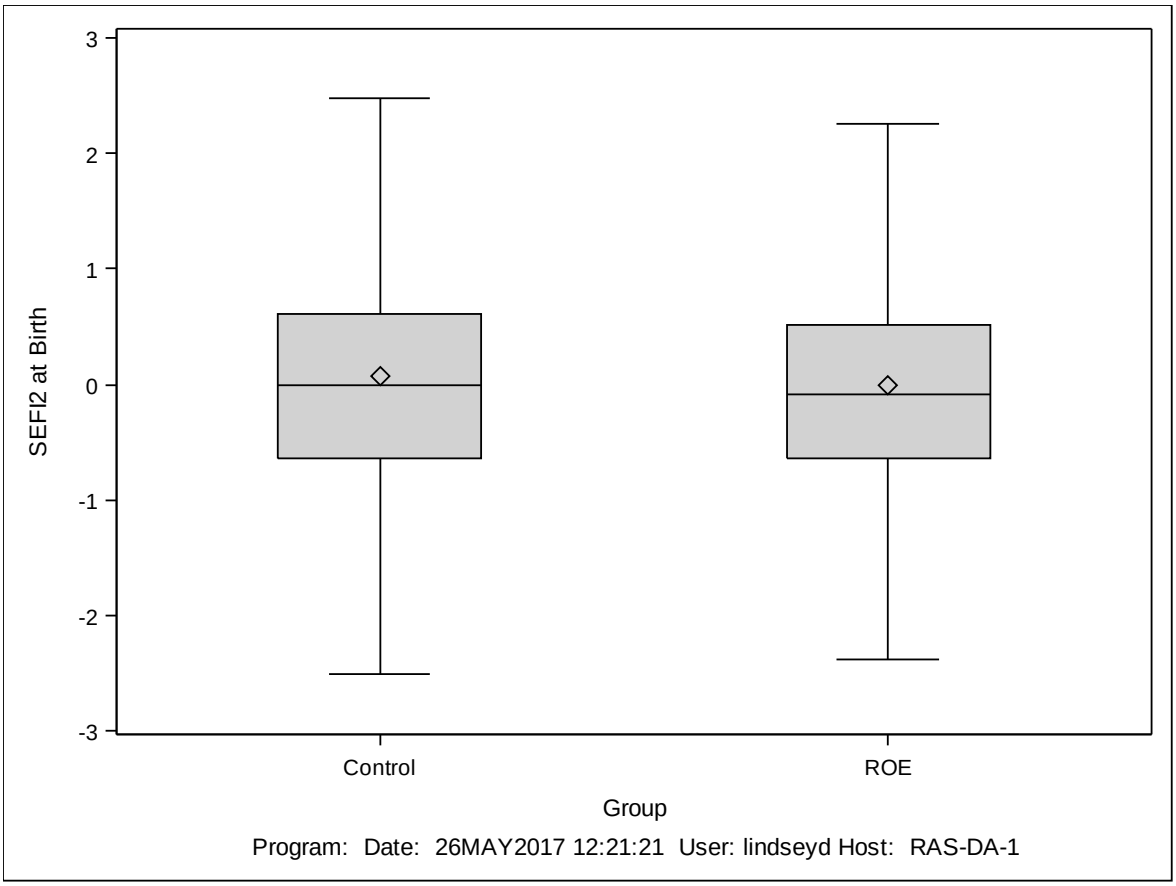
Group 2. SEFI-2 at birth


Cumulative Distribution Function for sefi2b
Cumulative Percent
100
80
60
40
20
0
-6
-4
-2
0
2
4
6
SEFI2 at Birth
TREAT
Control
ROE

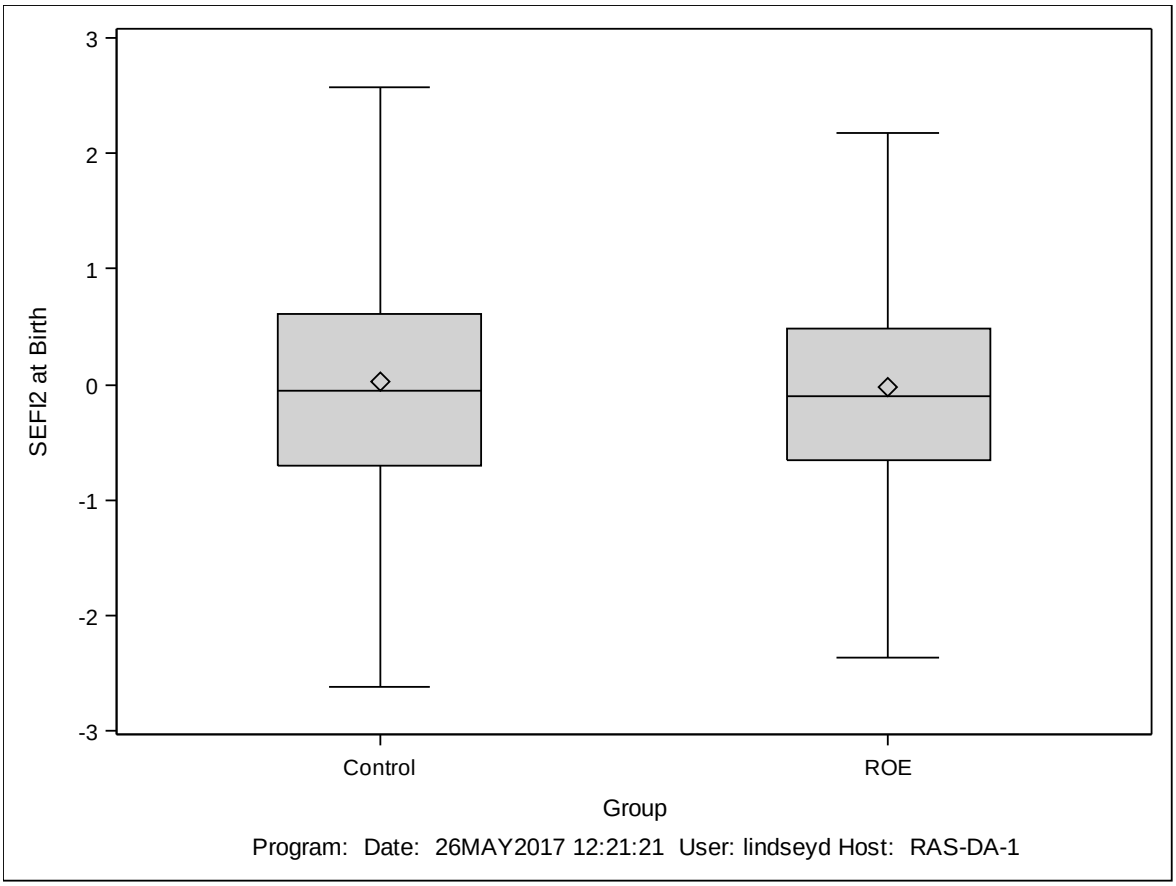
Original Sample



Matched Sample

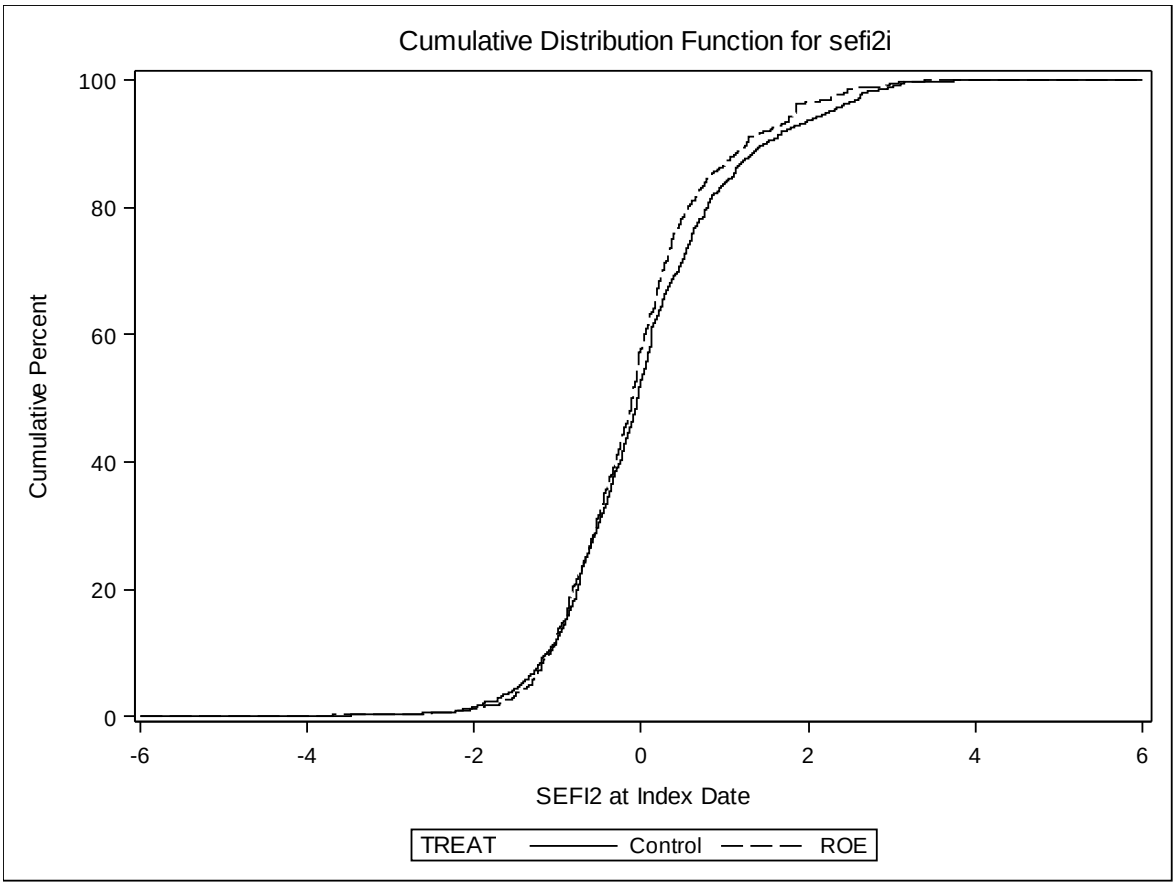


Original Sample

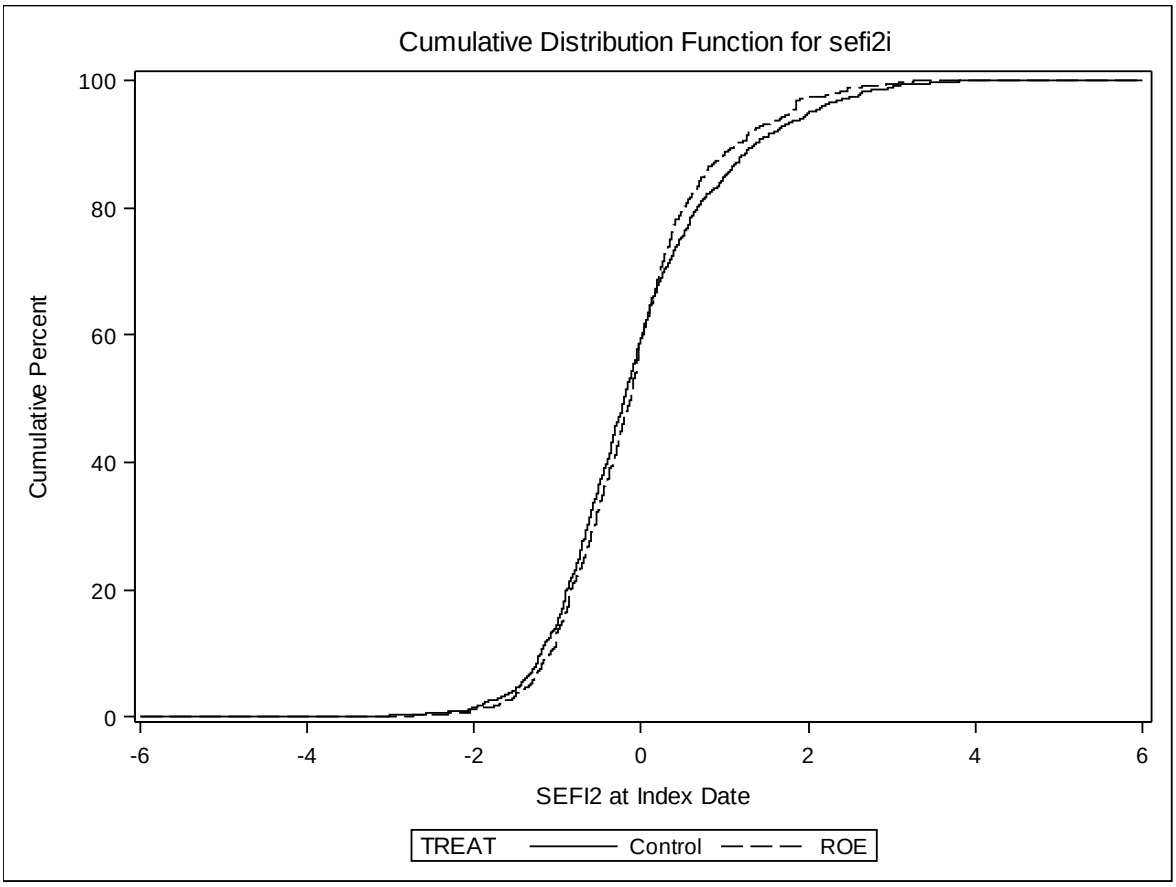


Matched Sample

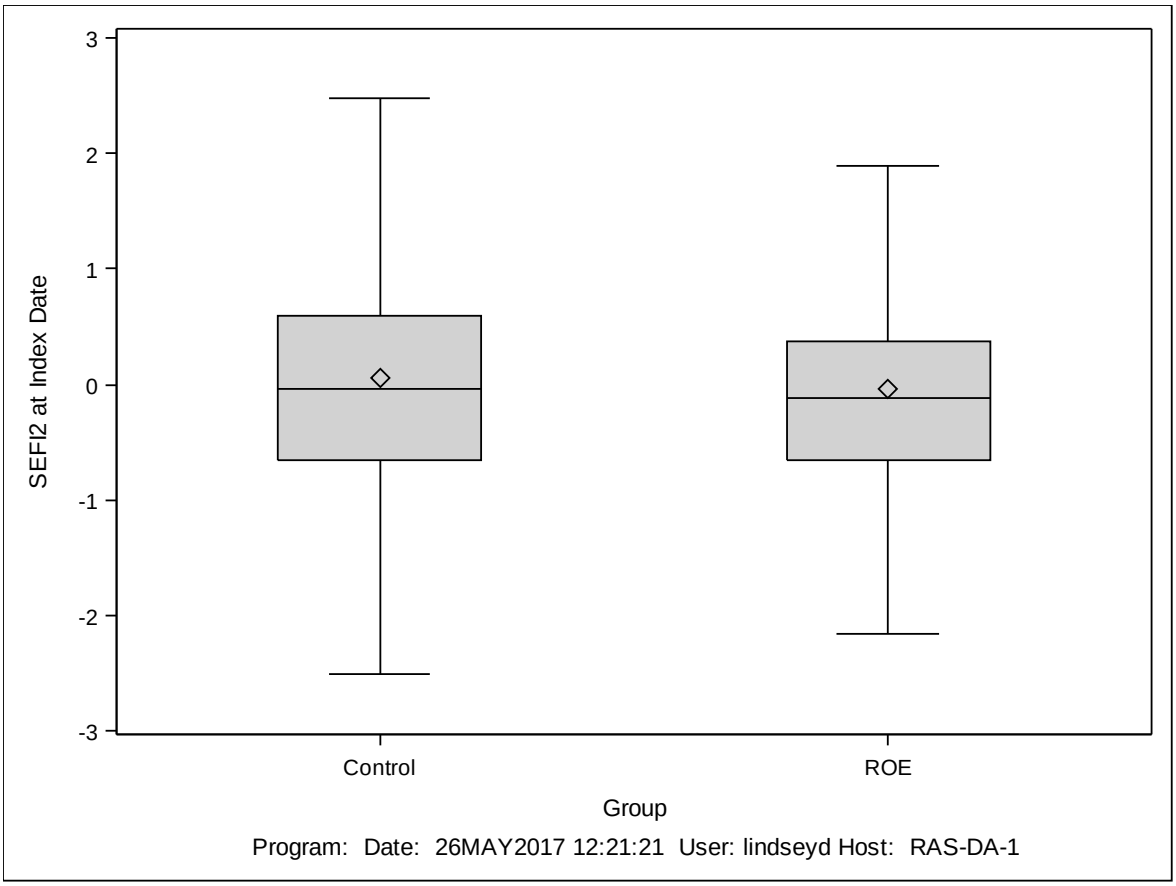
Group 2. SEFI-2 at propensity score index date


Cumulative Distribution Function for sefi2i
Cumulative Percent
100
80
60
40
20
0
-6
-4
-2
0
2
4
6
SEFI2 at Index Date
TREAT
Control
ROE

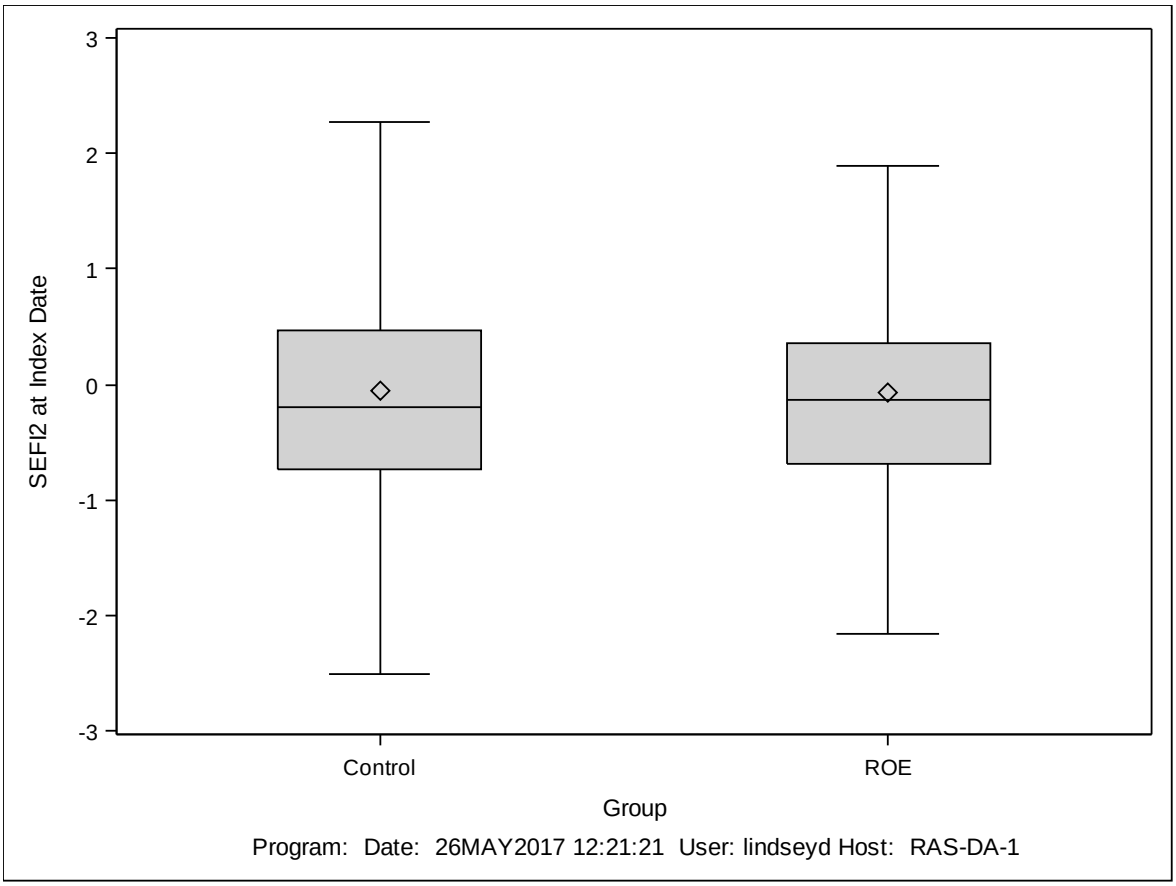
Original Sample



Matched Sample

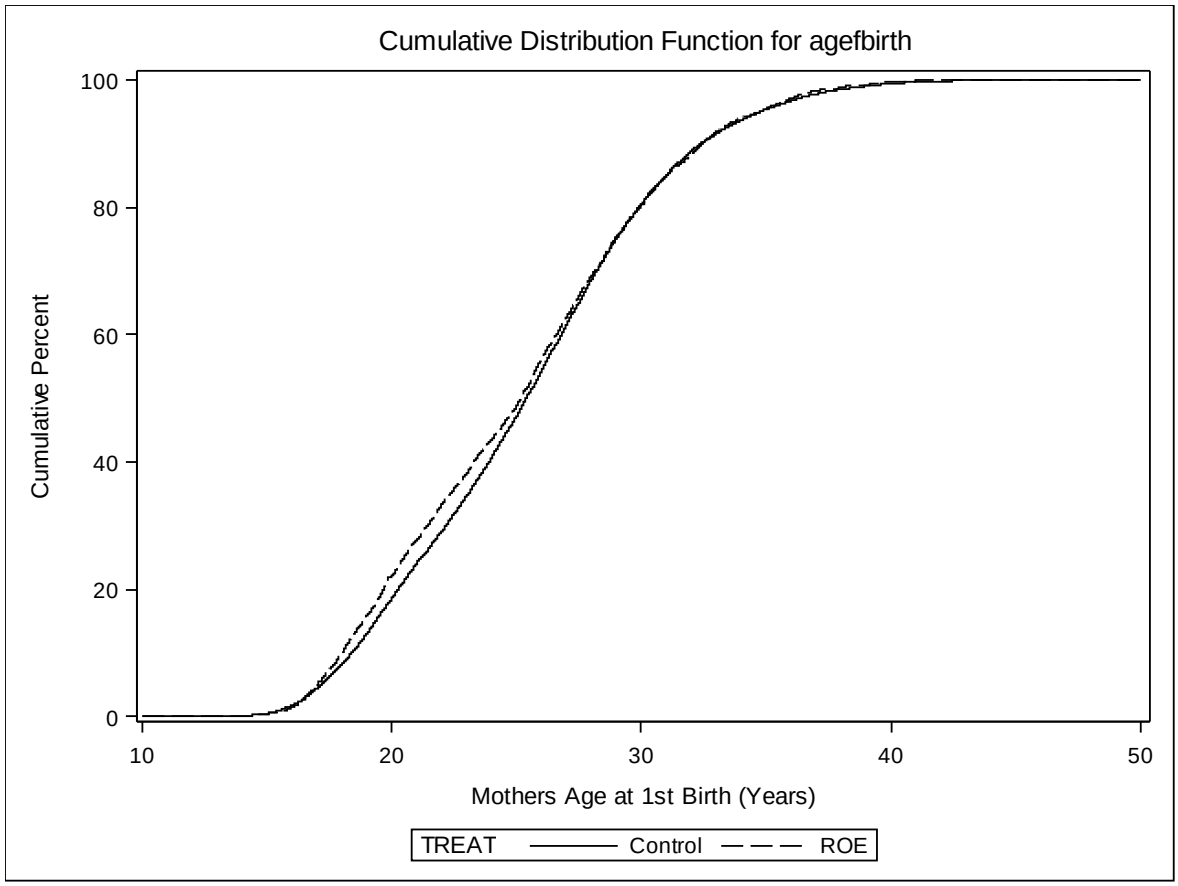


Original Sample

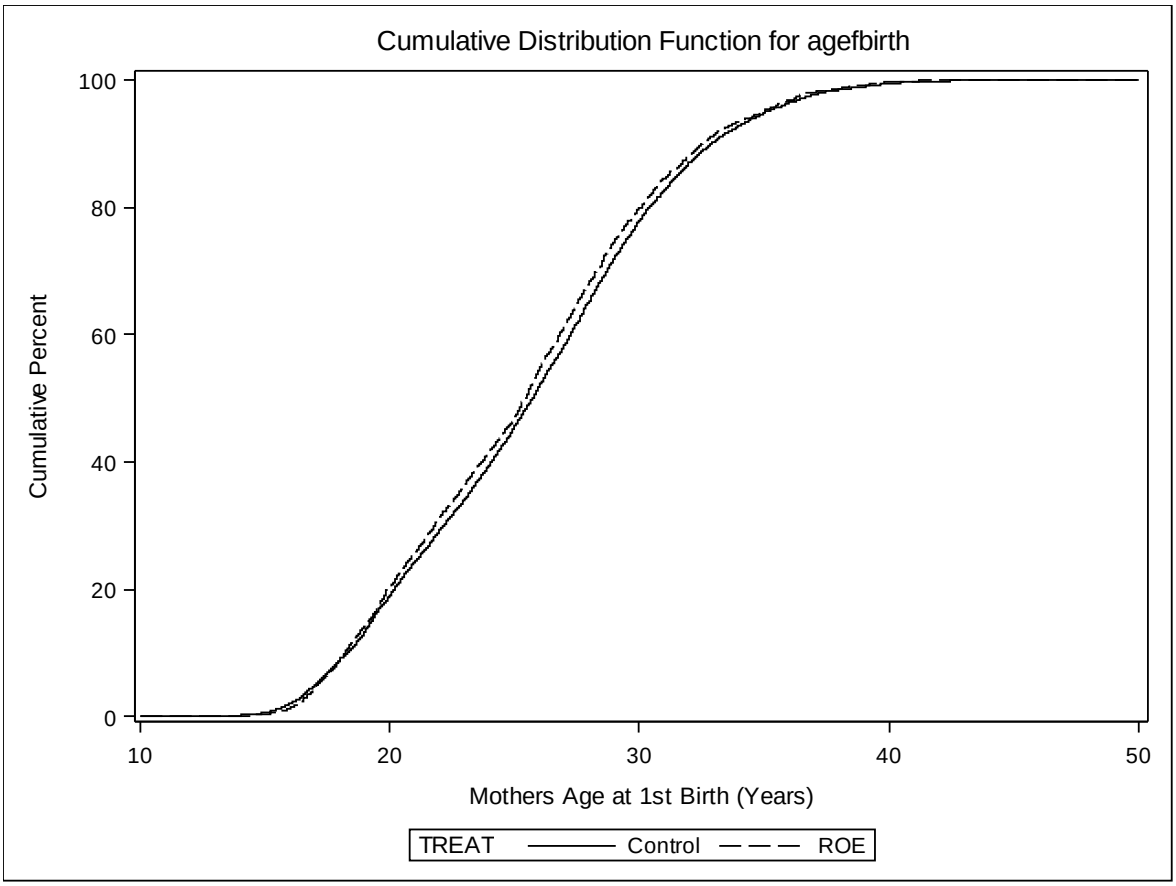


Matched Sample

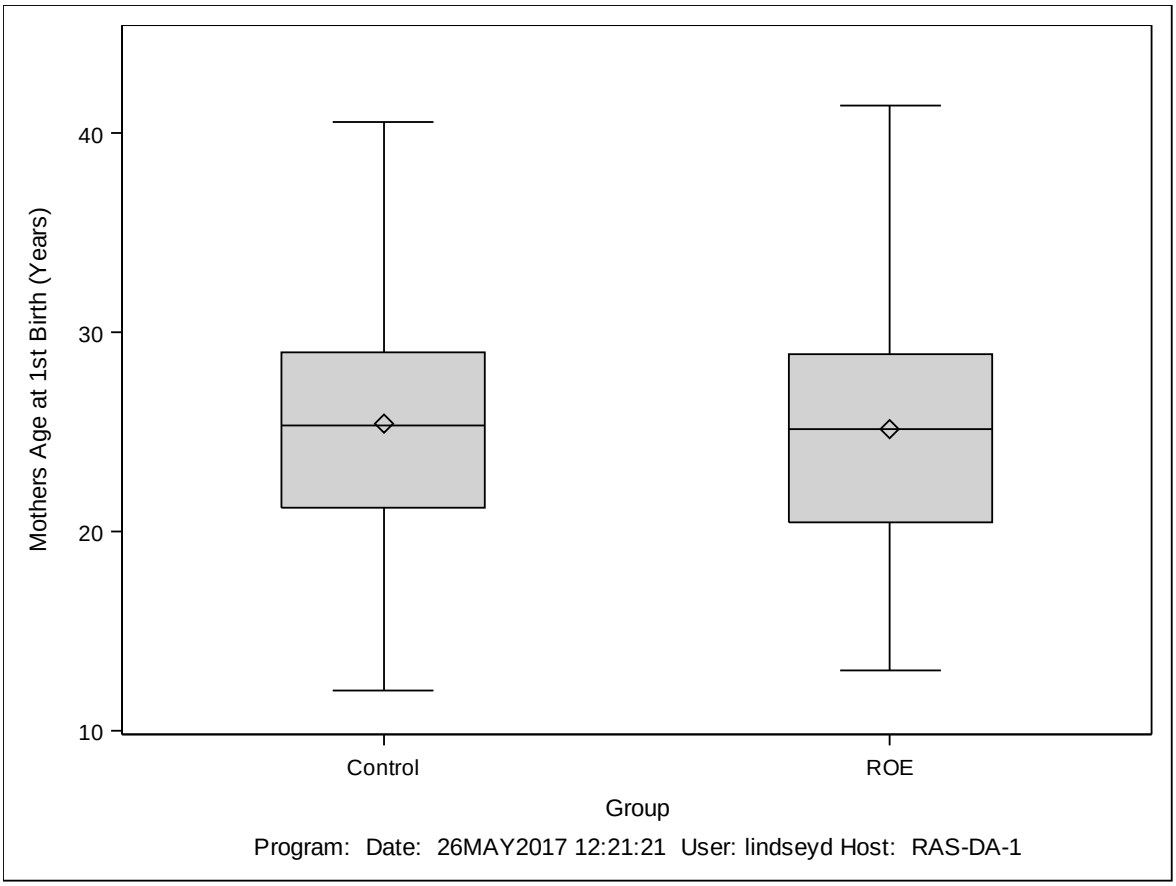
Group 2. Mother's age at date of first child's birth



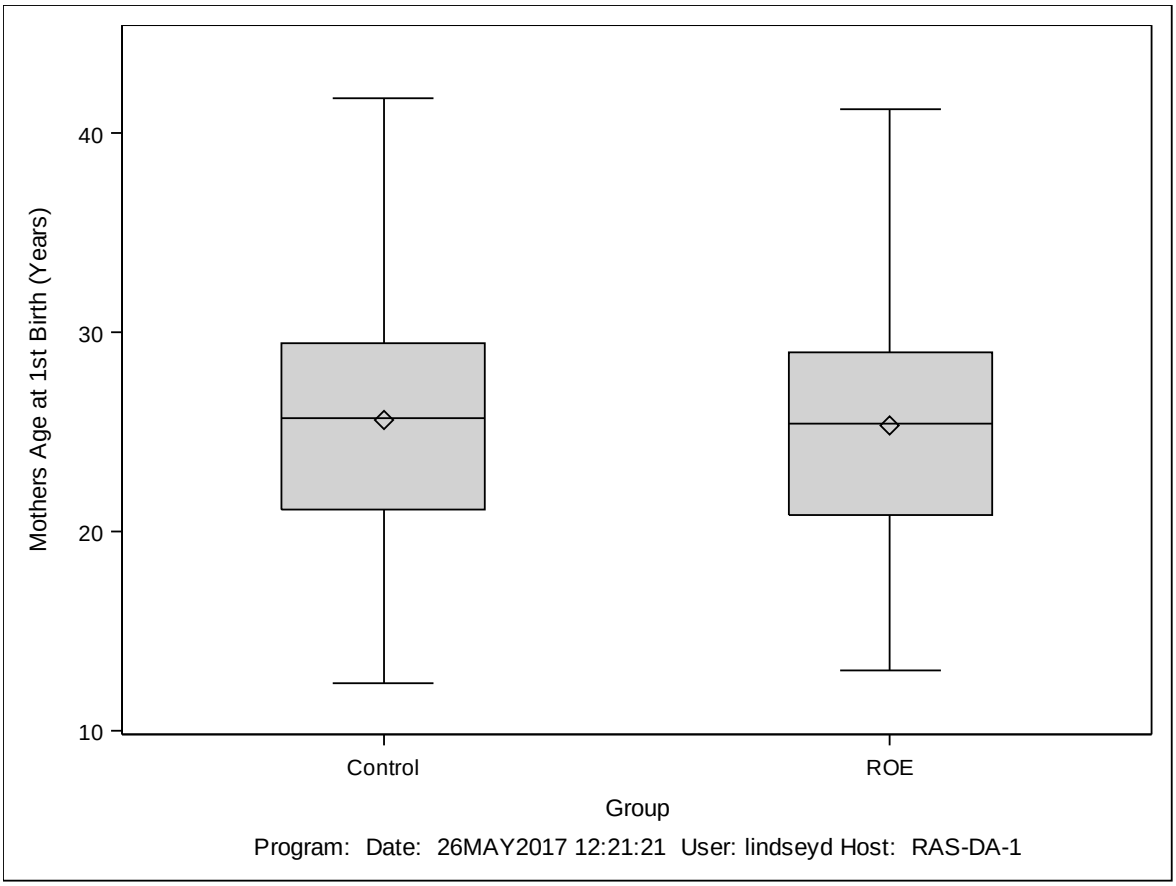
Original Sample



Matched Sample

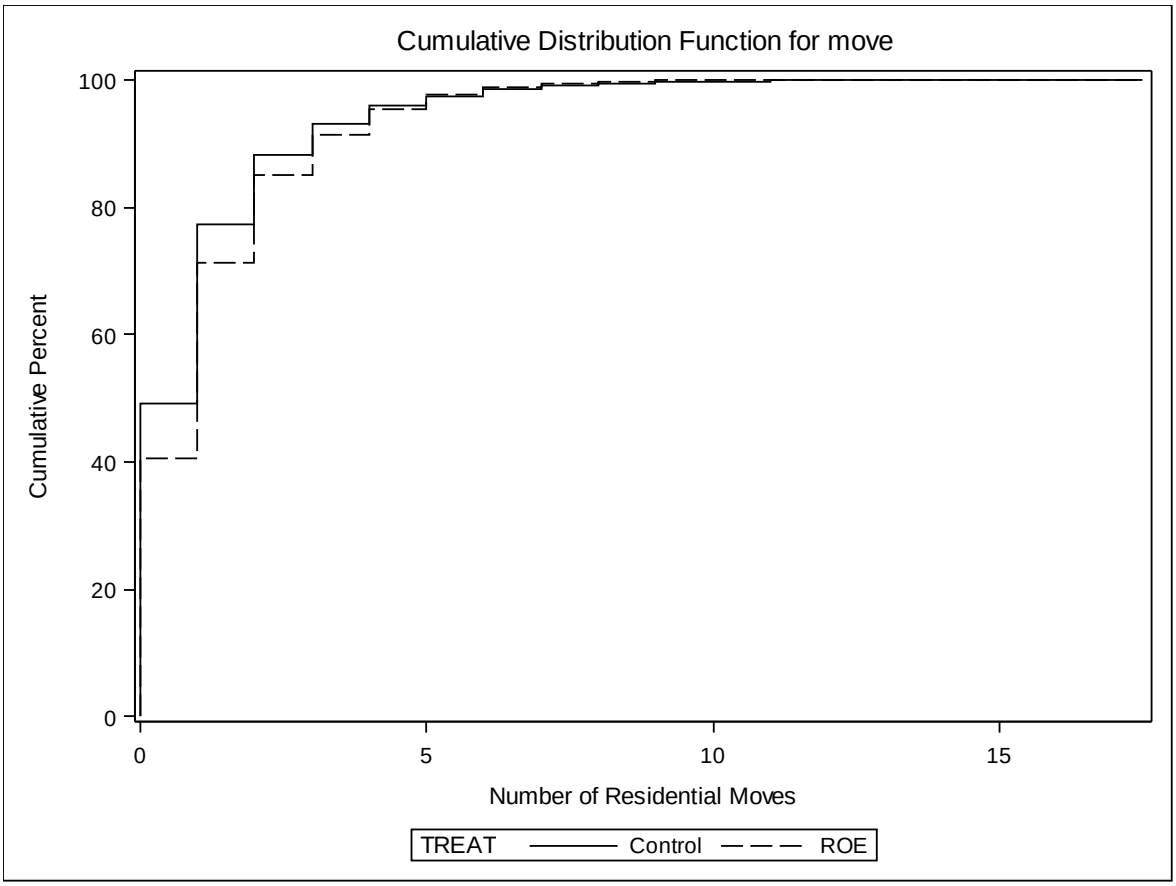


Original Sample

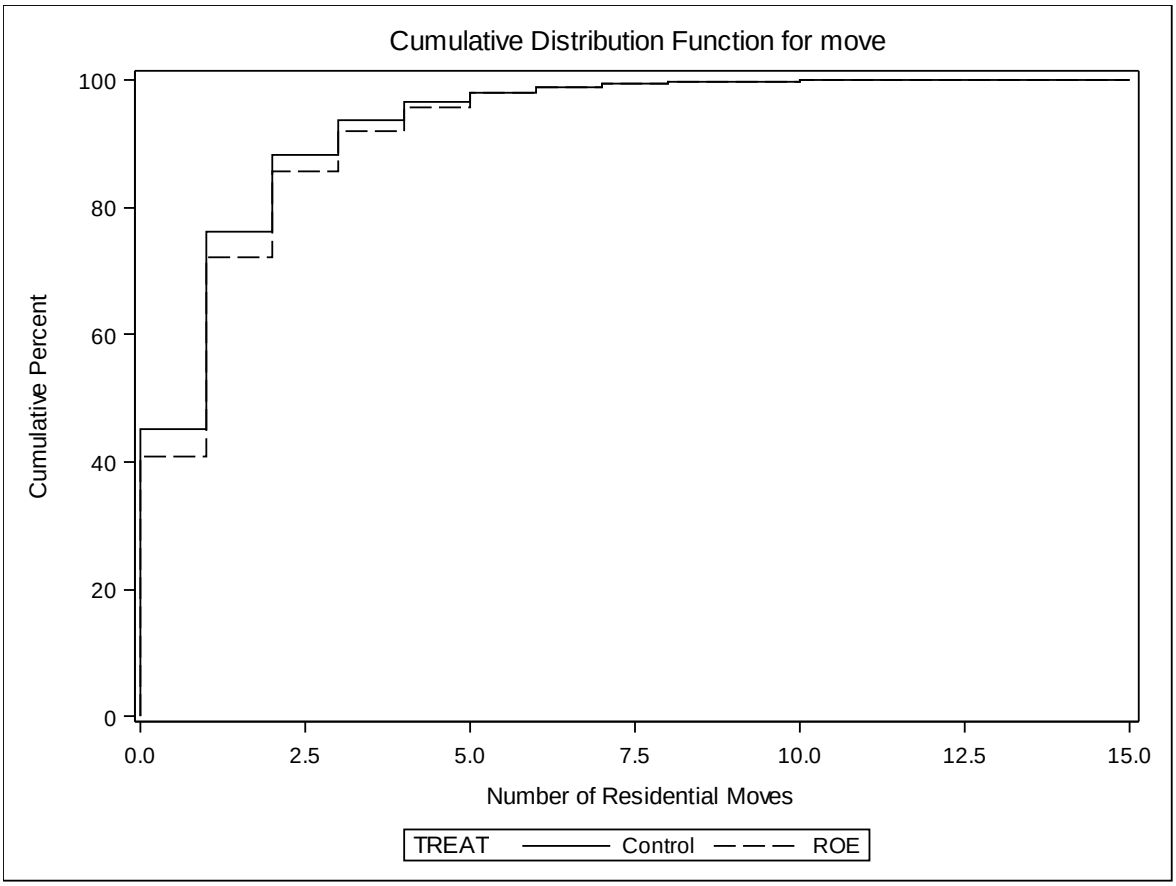


Matched Sample

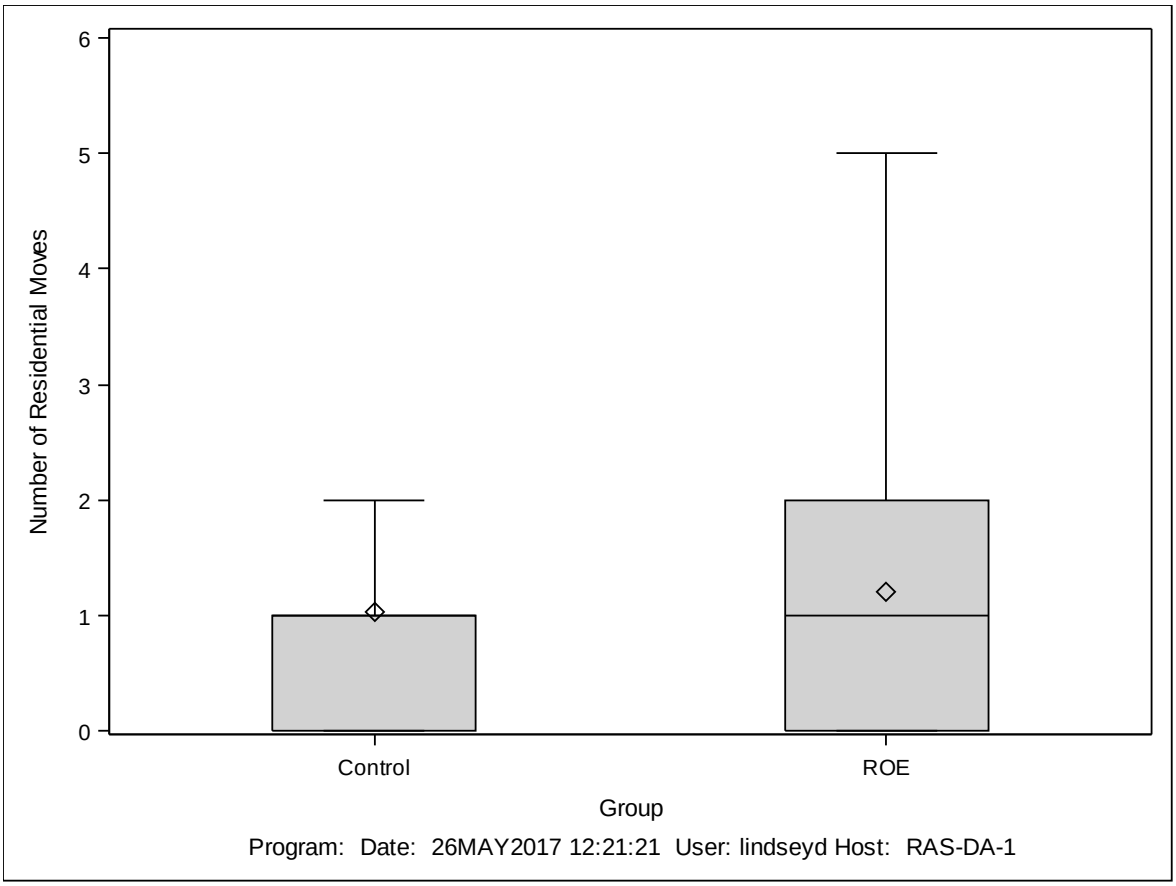
Group 2. Residential mobility



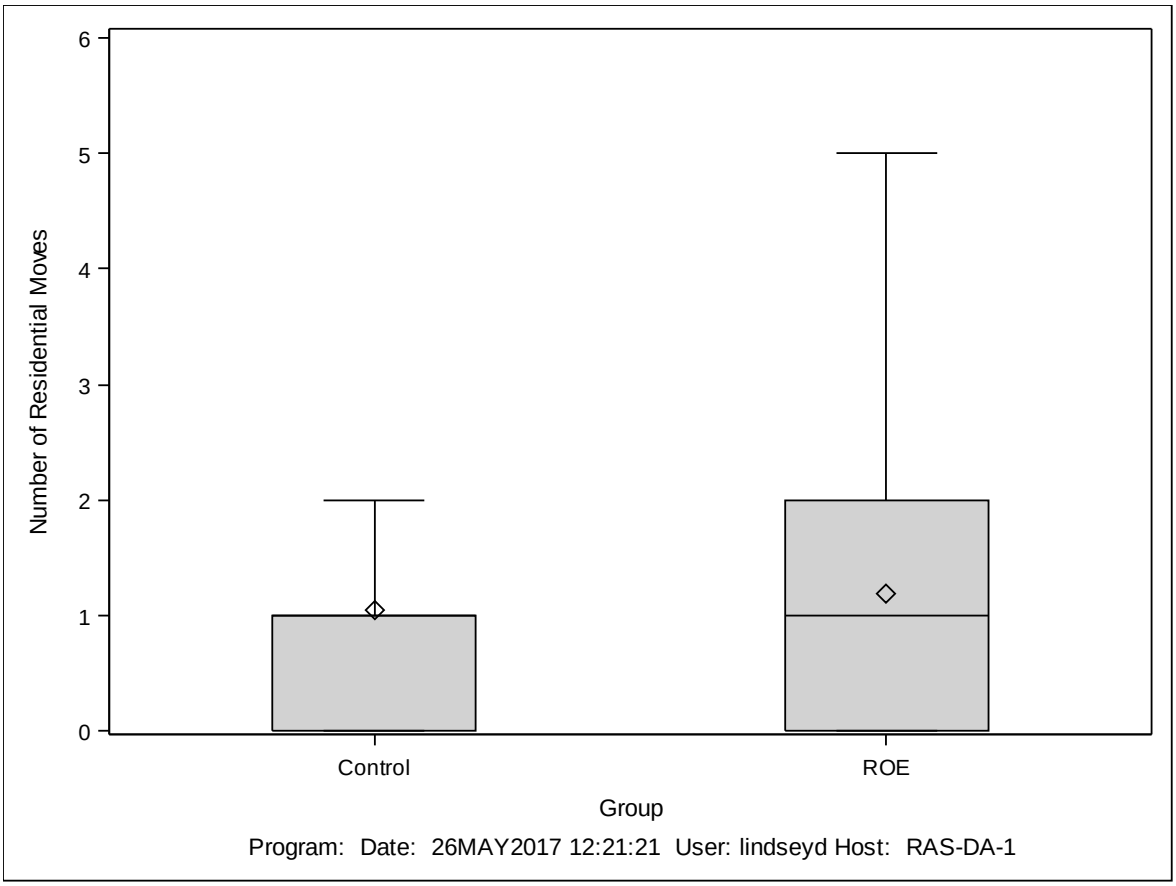
Original Sample



Matched Sample

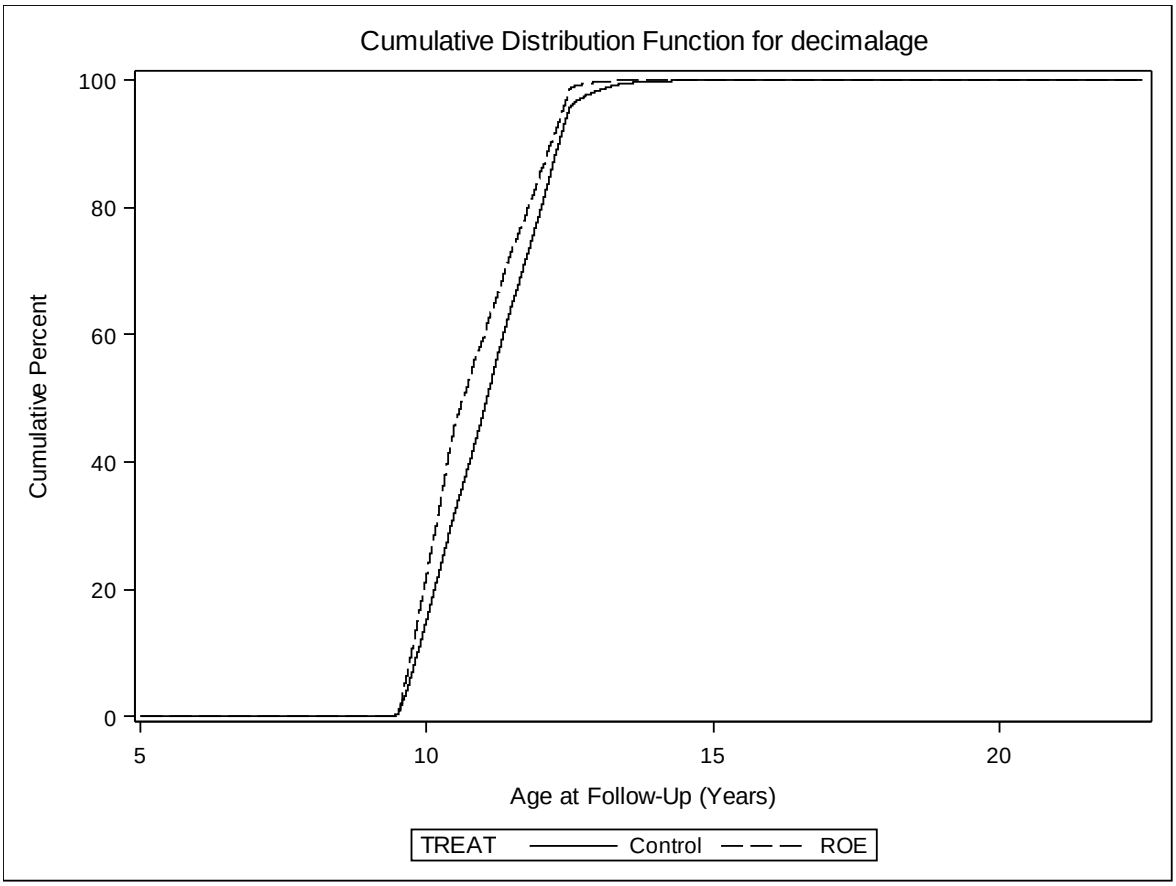


Original Sample

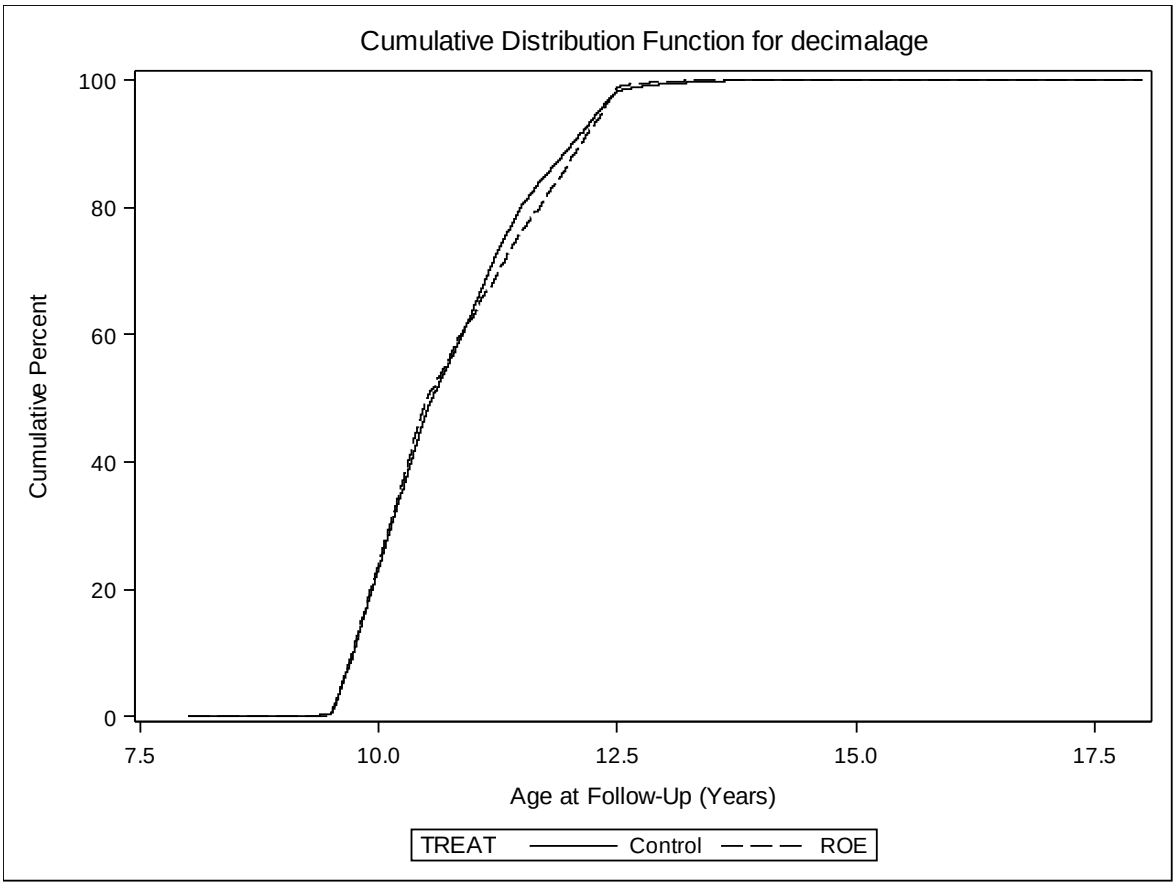


Matched Sample

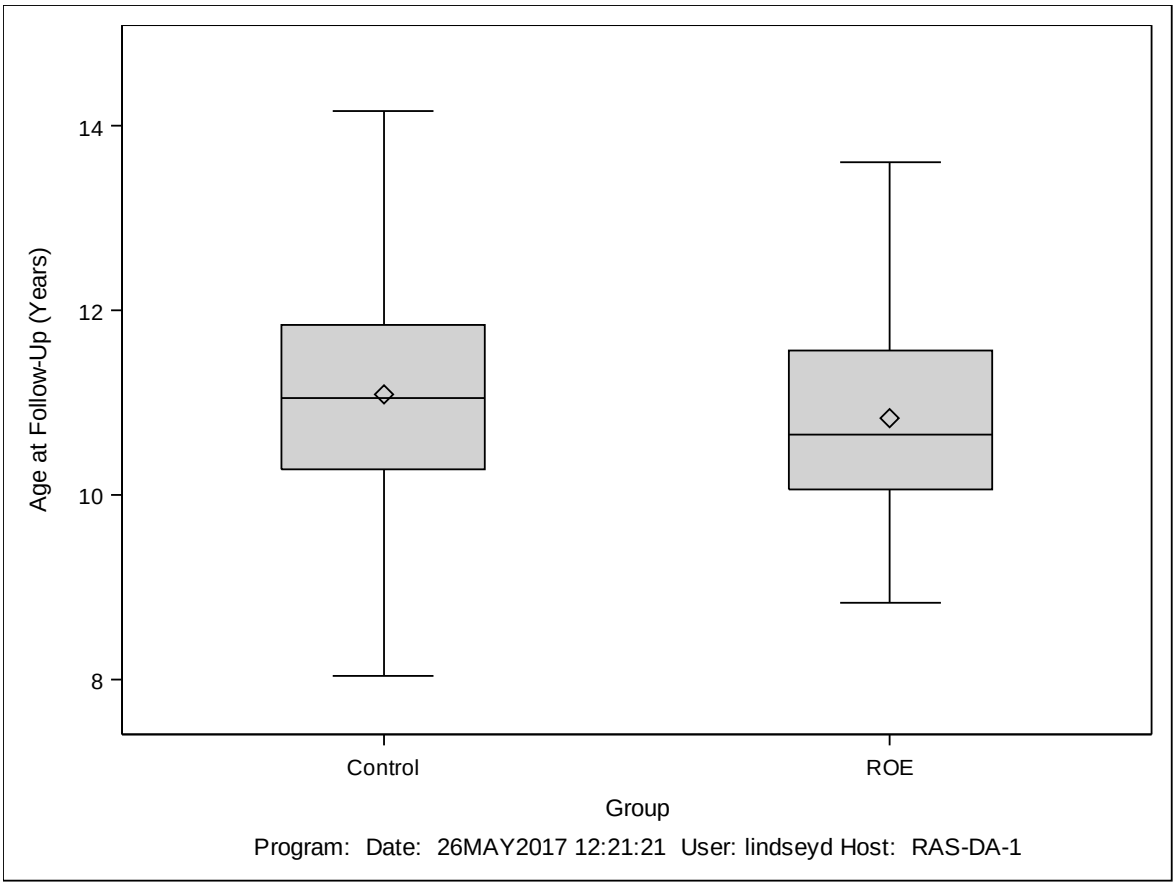
Group 2. Age at follow-up



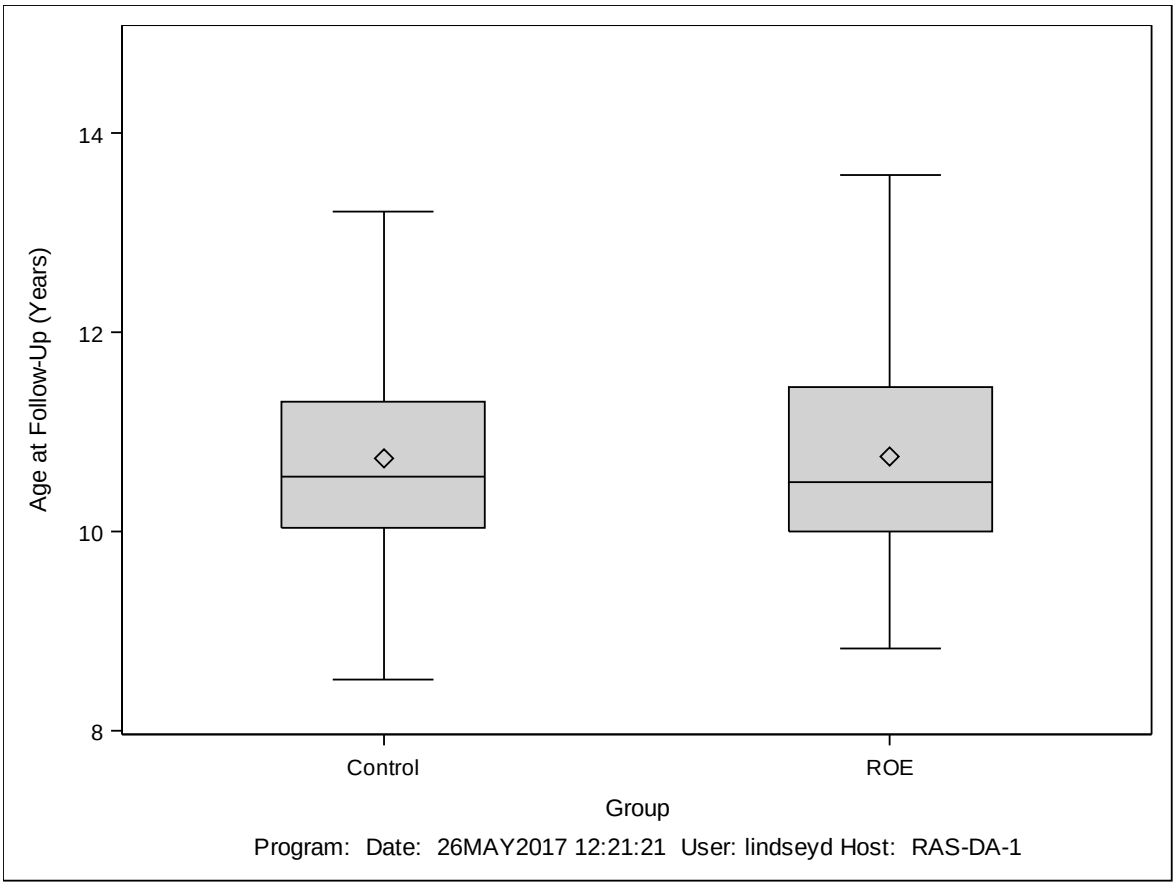
Original Sample



Matched Sample

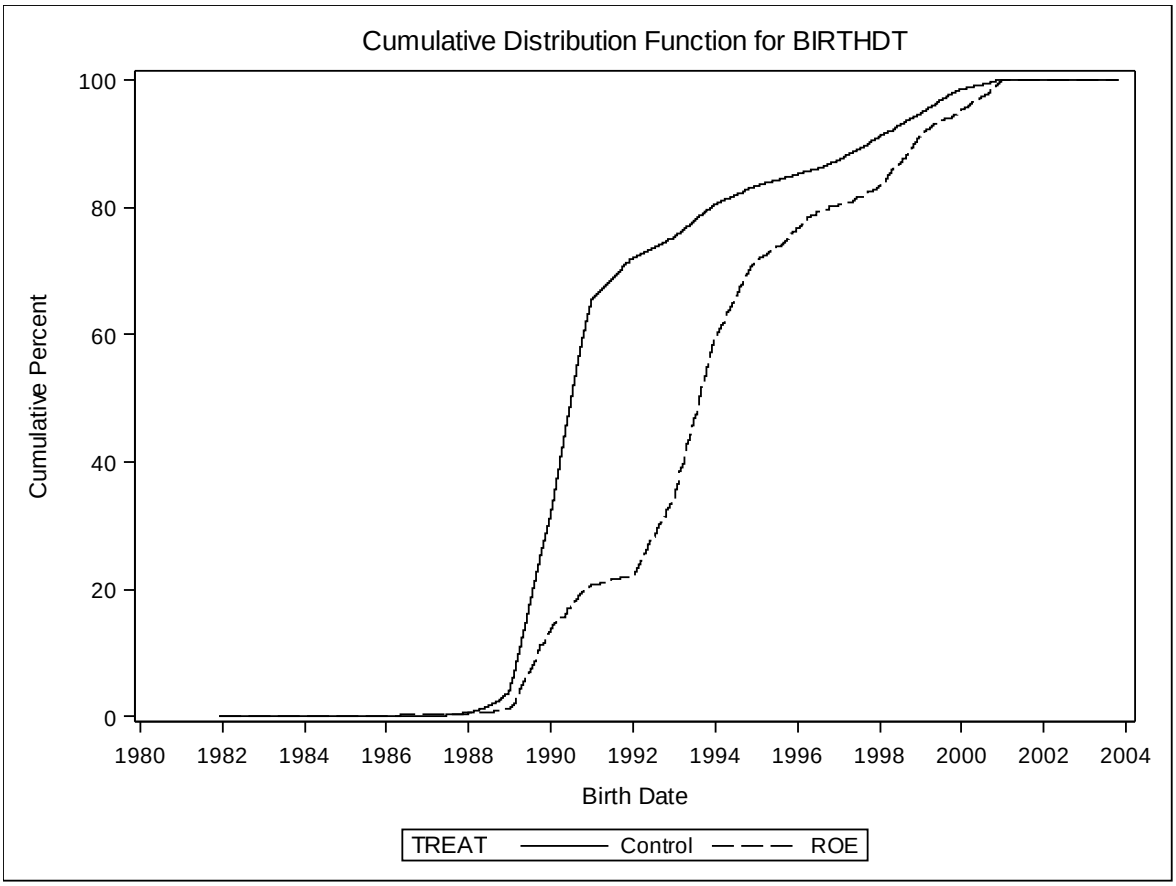


Original Sample

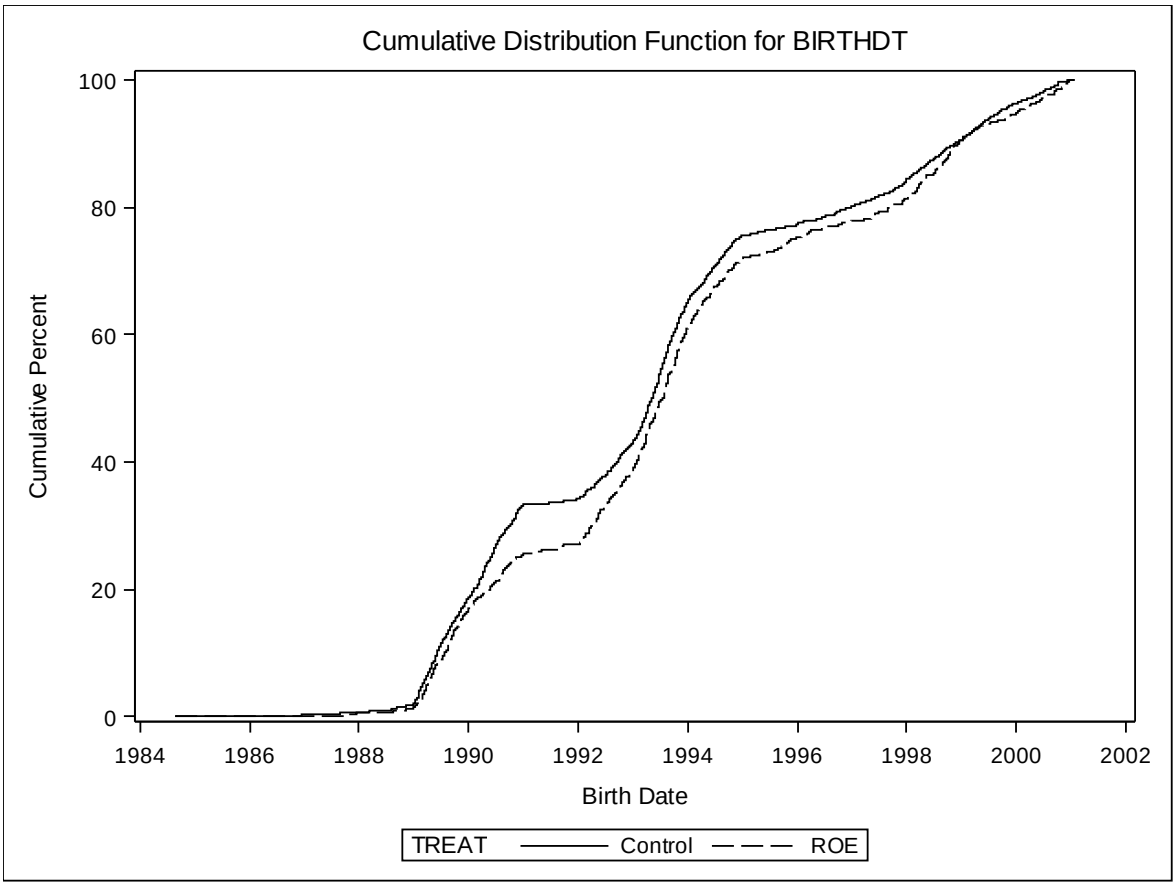


Matched Sample

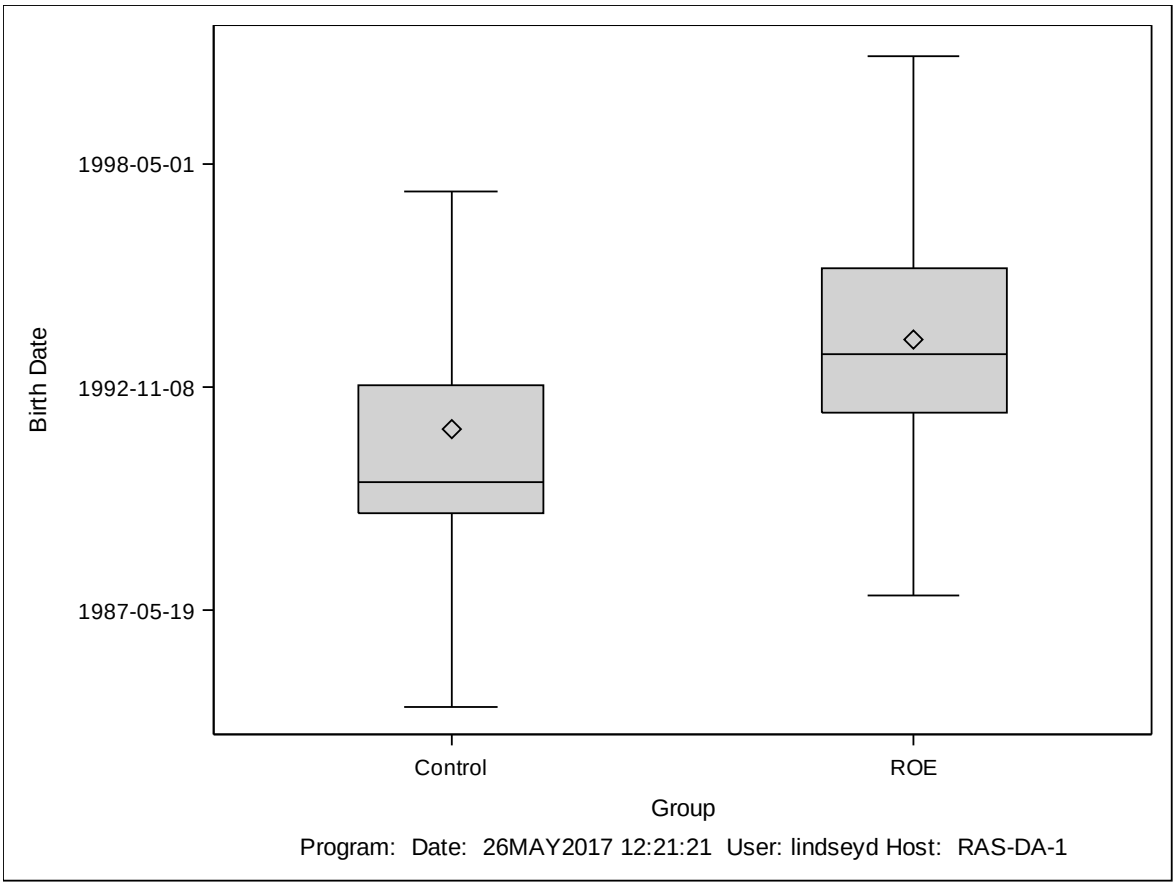
Group 3. Birthdate



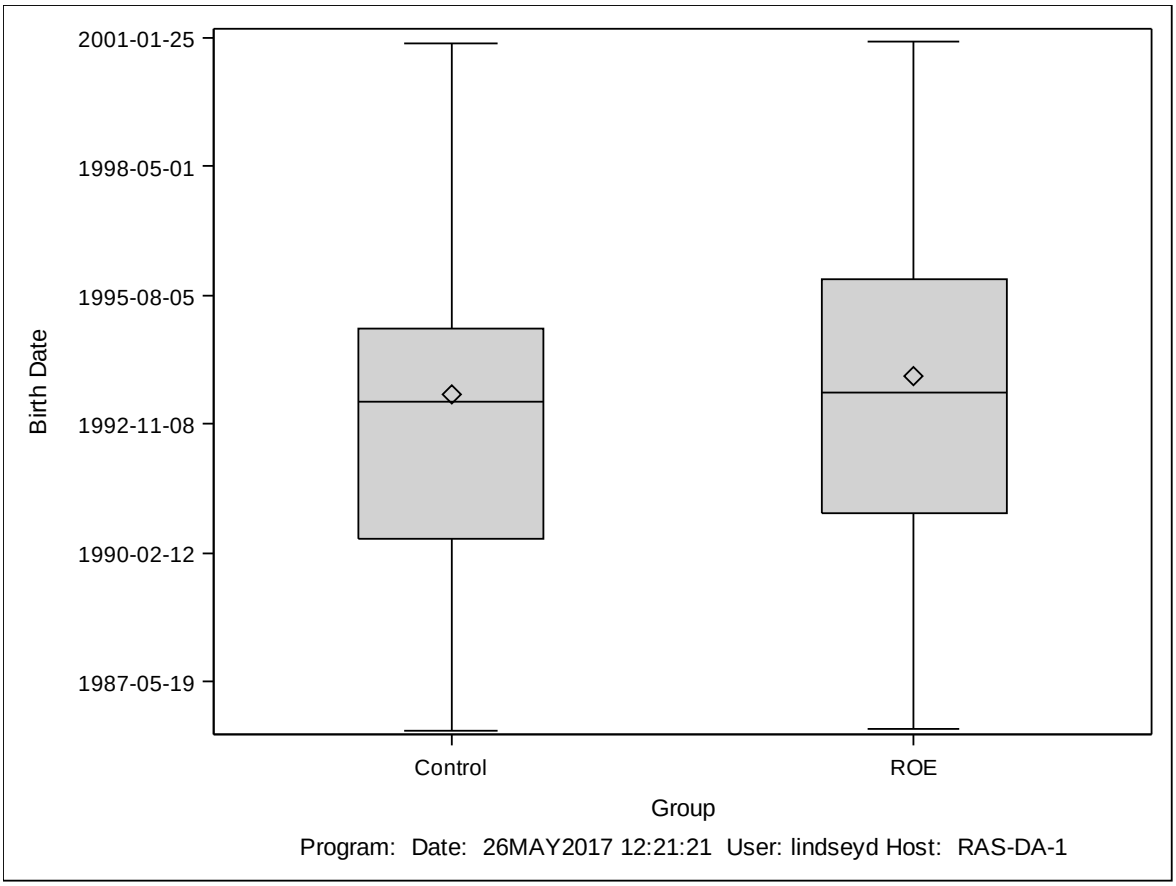
Original Sample



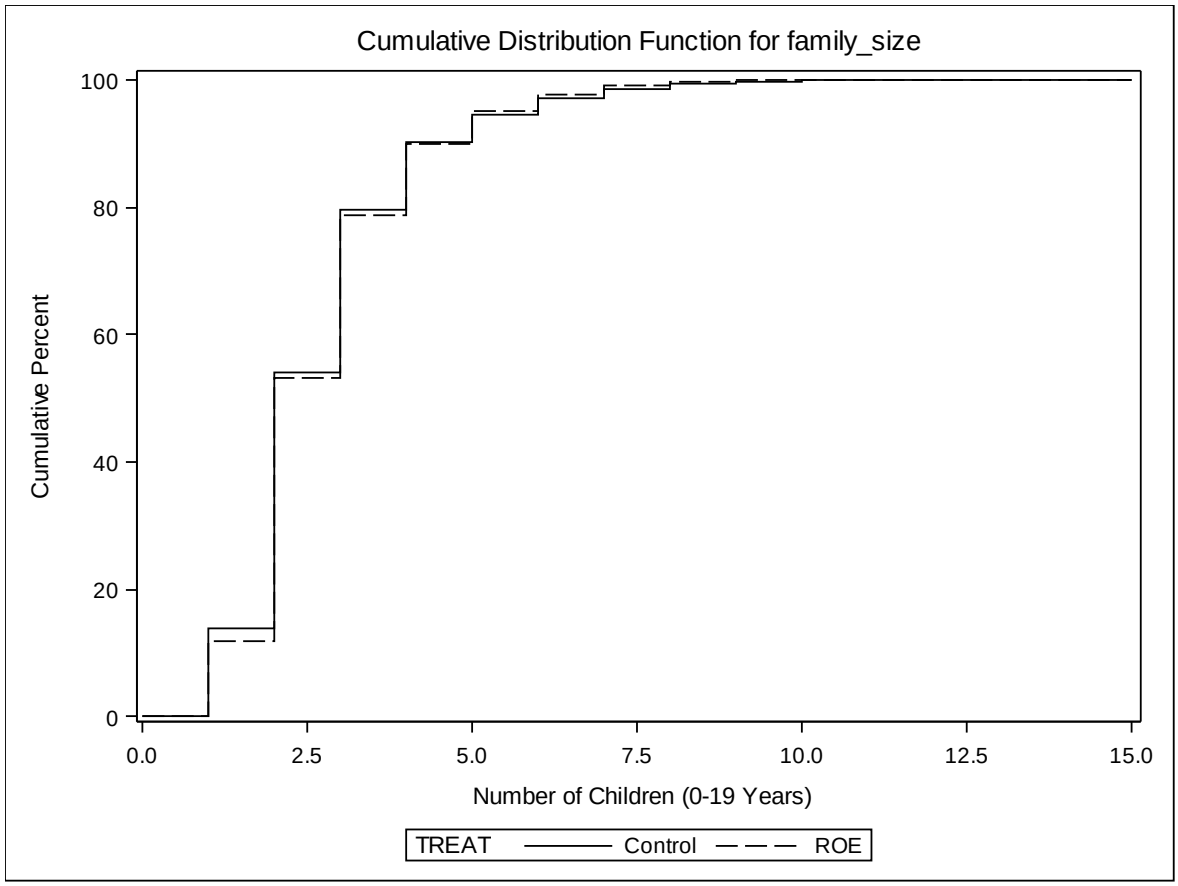
Matched Sample



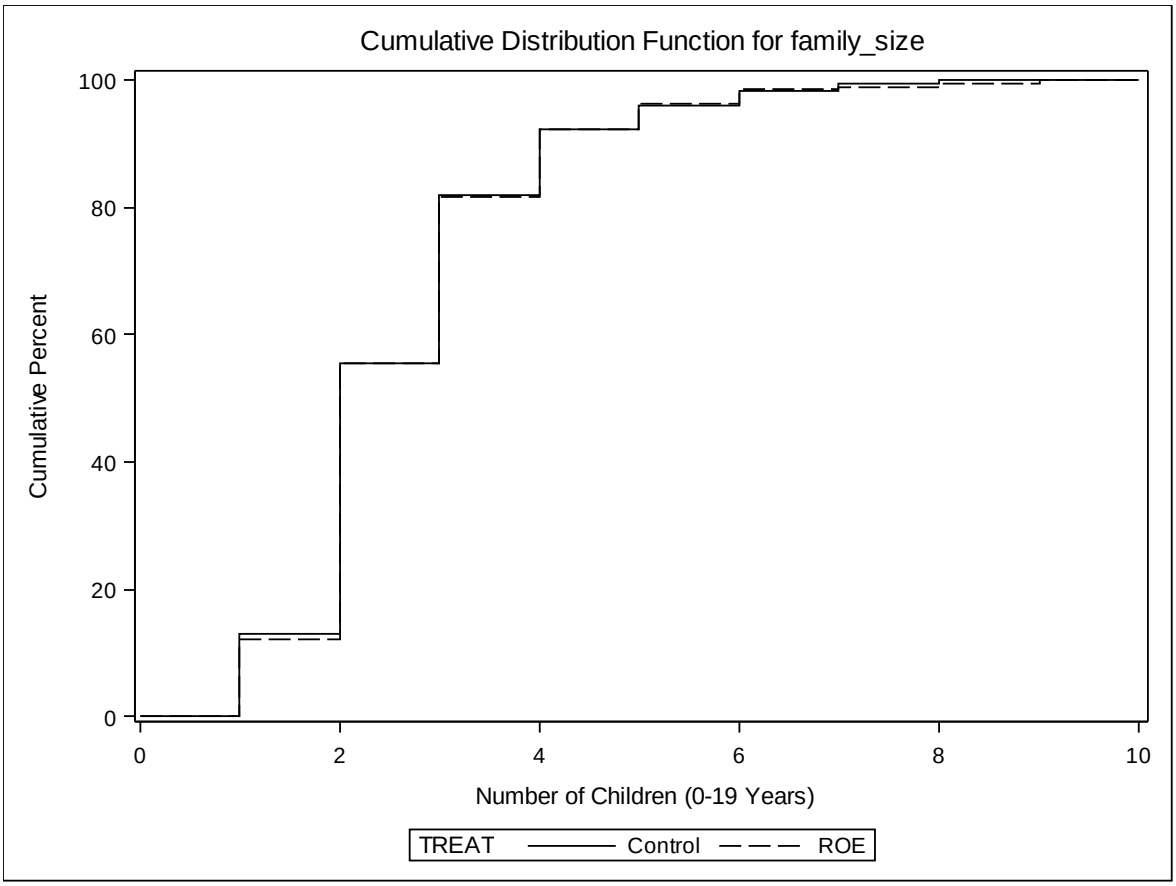
Original Sample



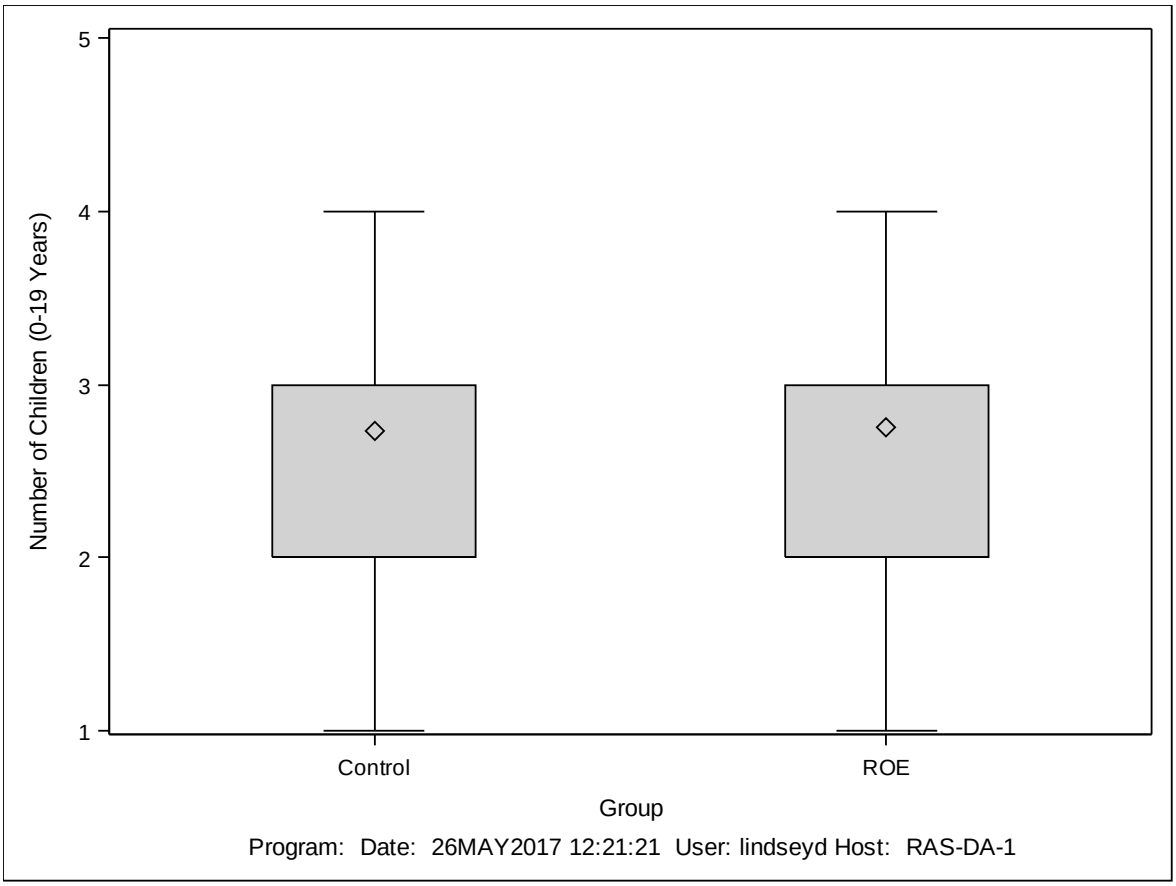
Matched Sample



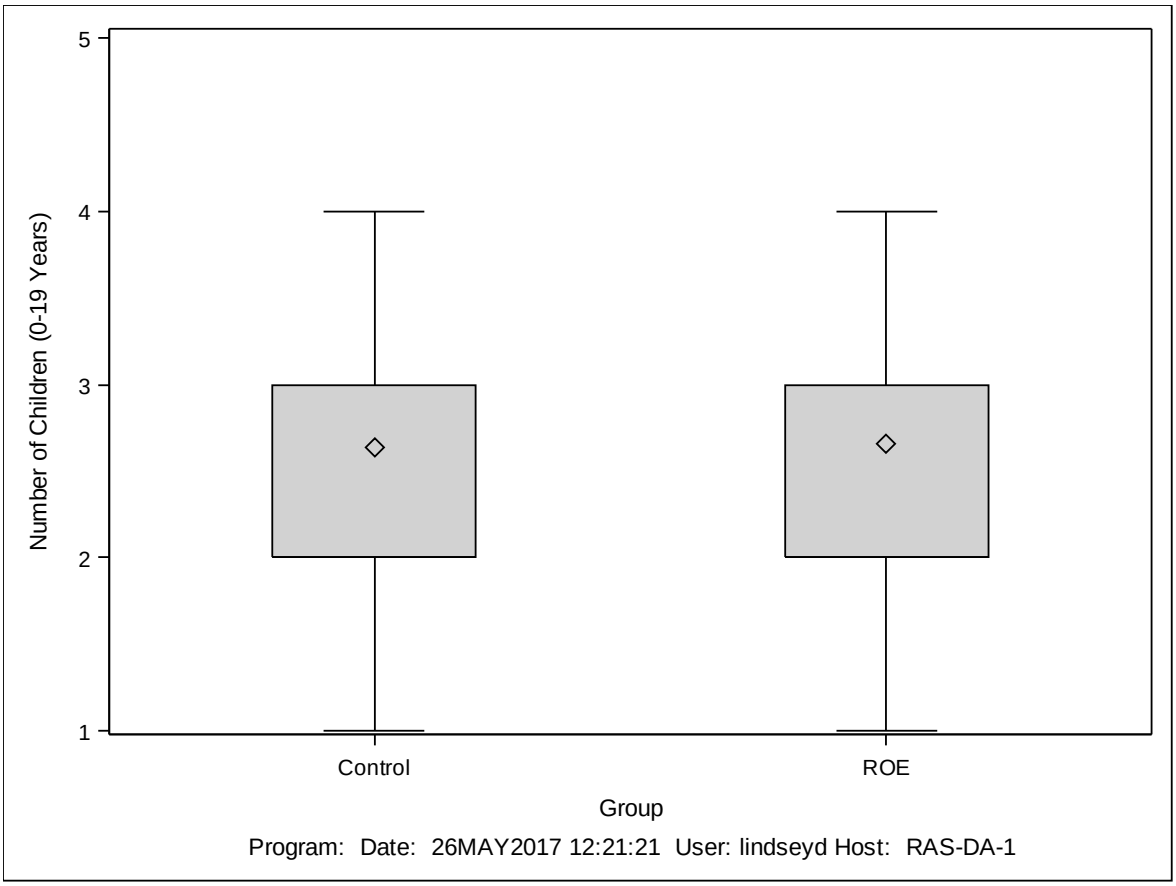
Original Sample



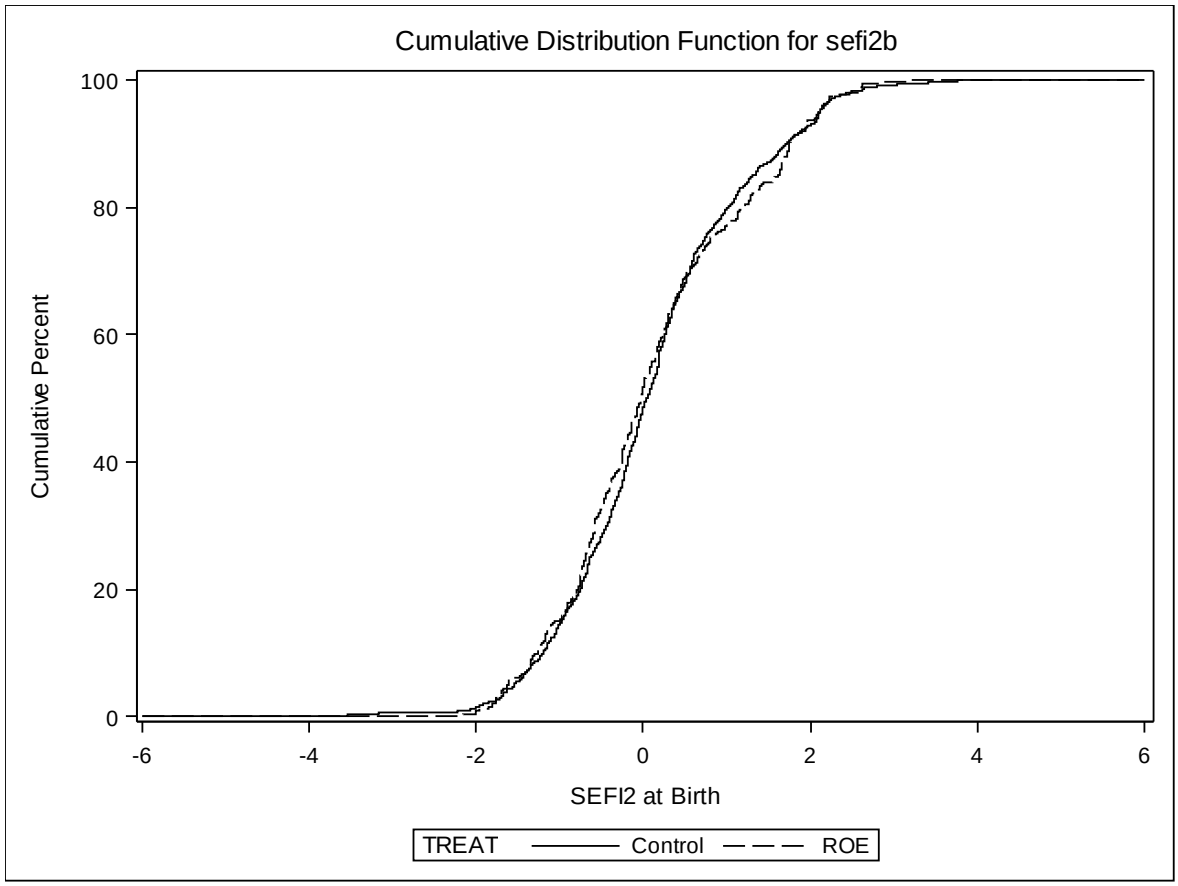
Matched Sample



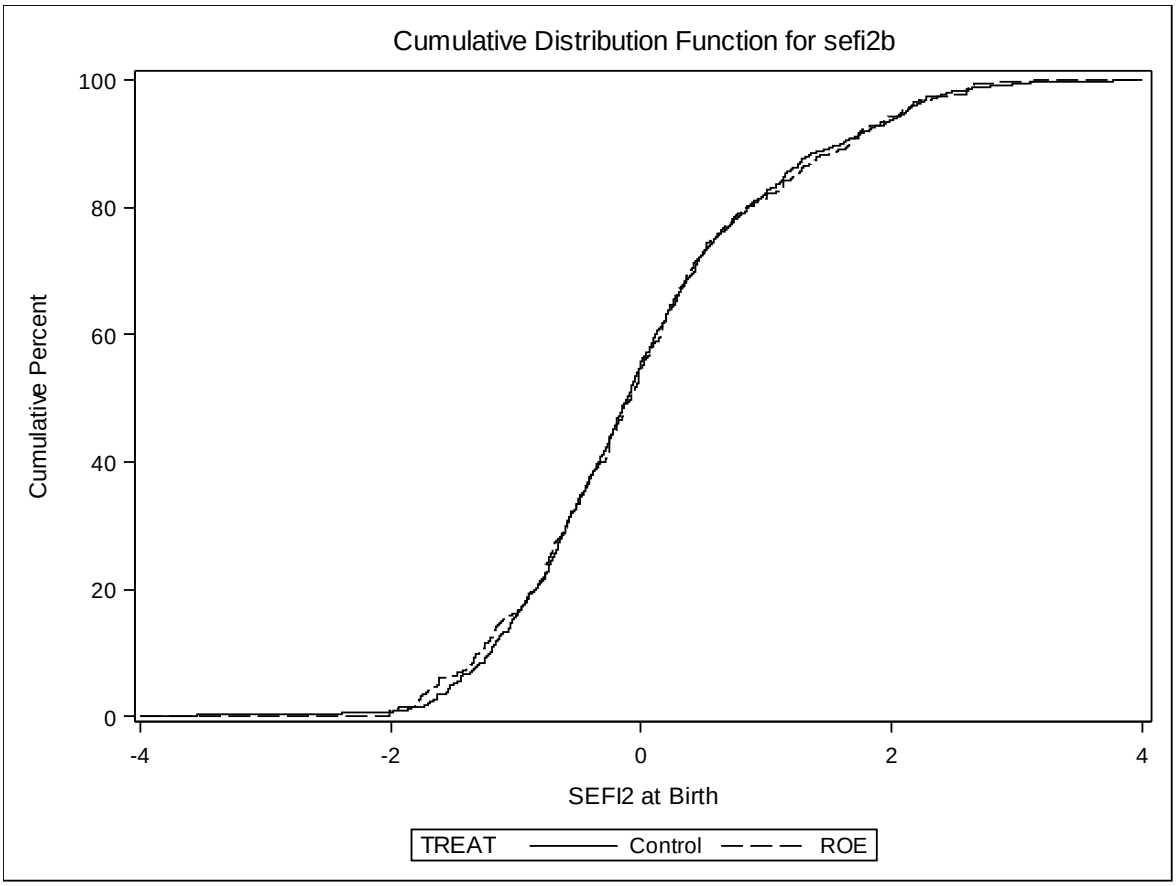
Original Sample



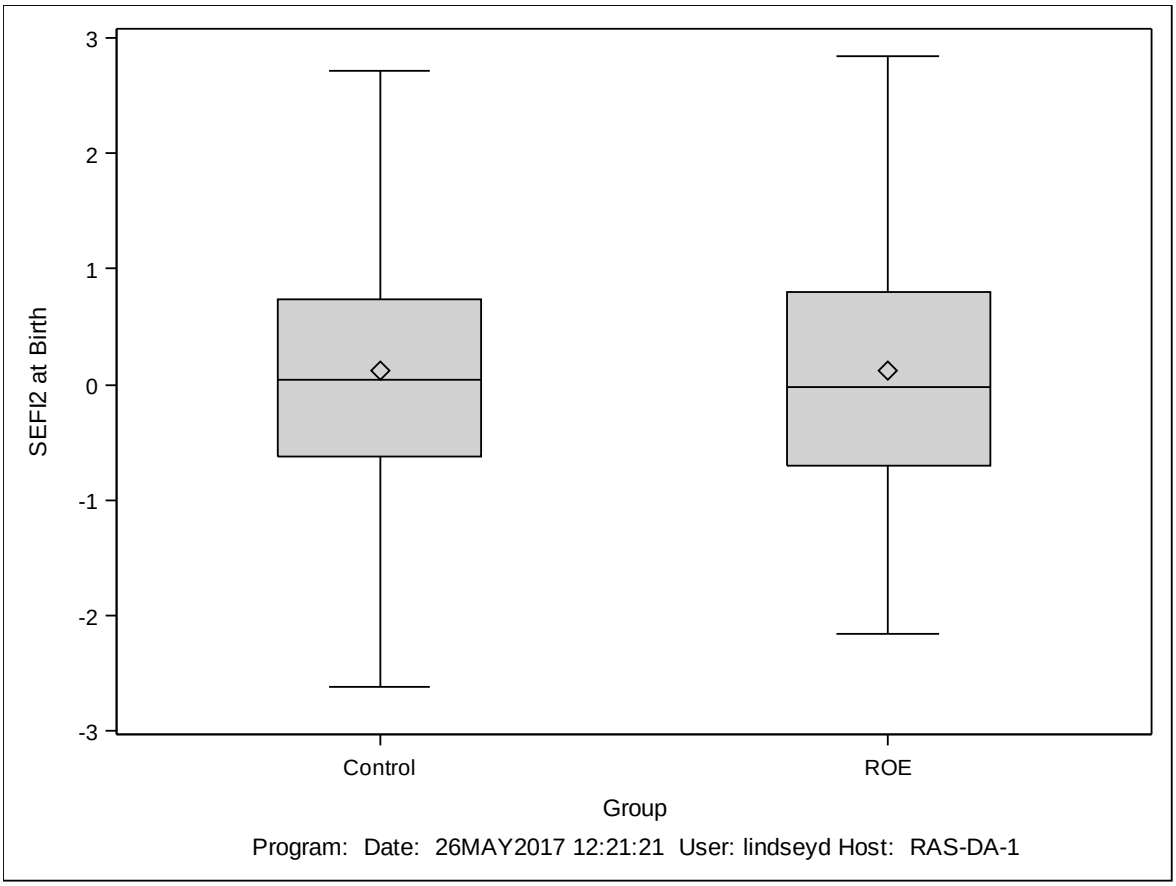
Matched Sample



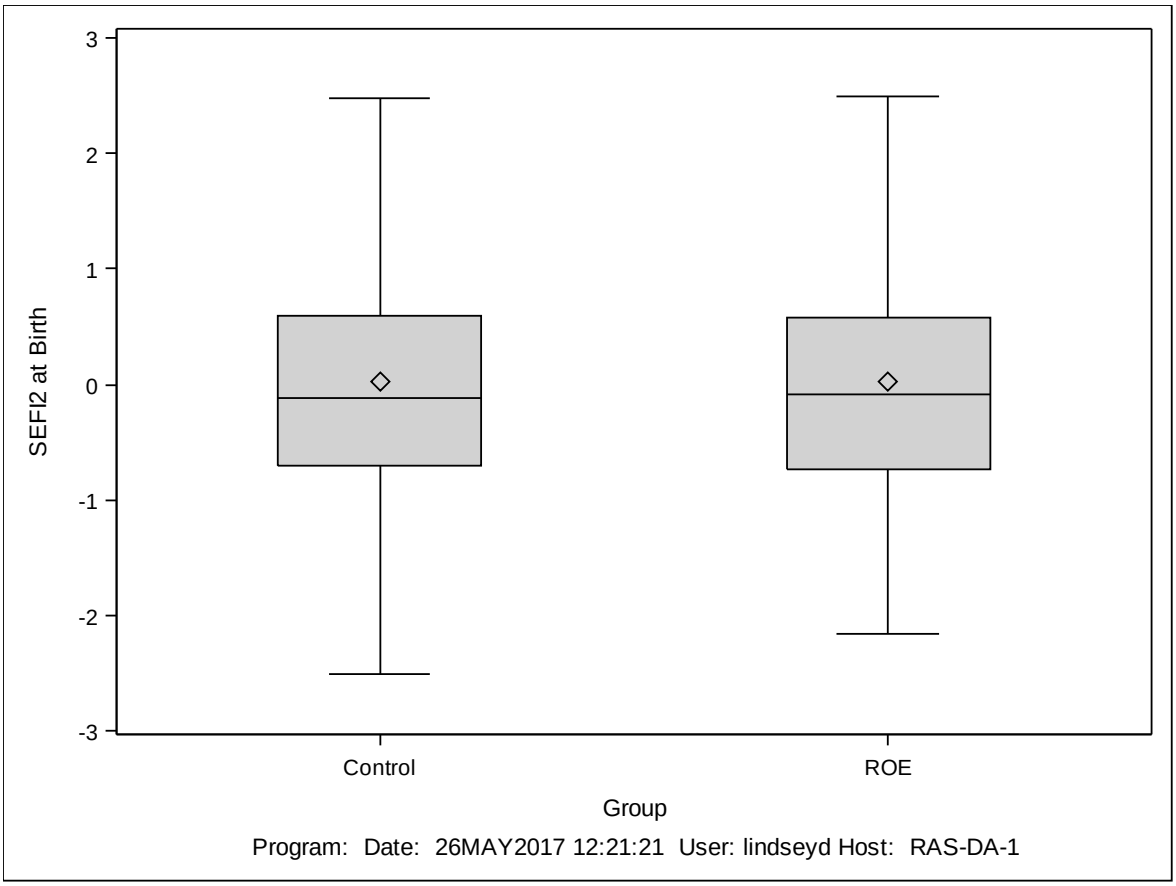
Original Sample



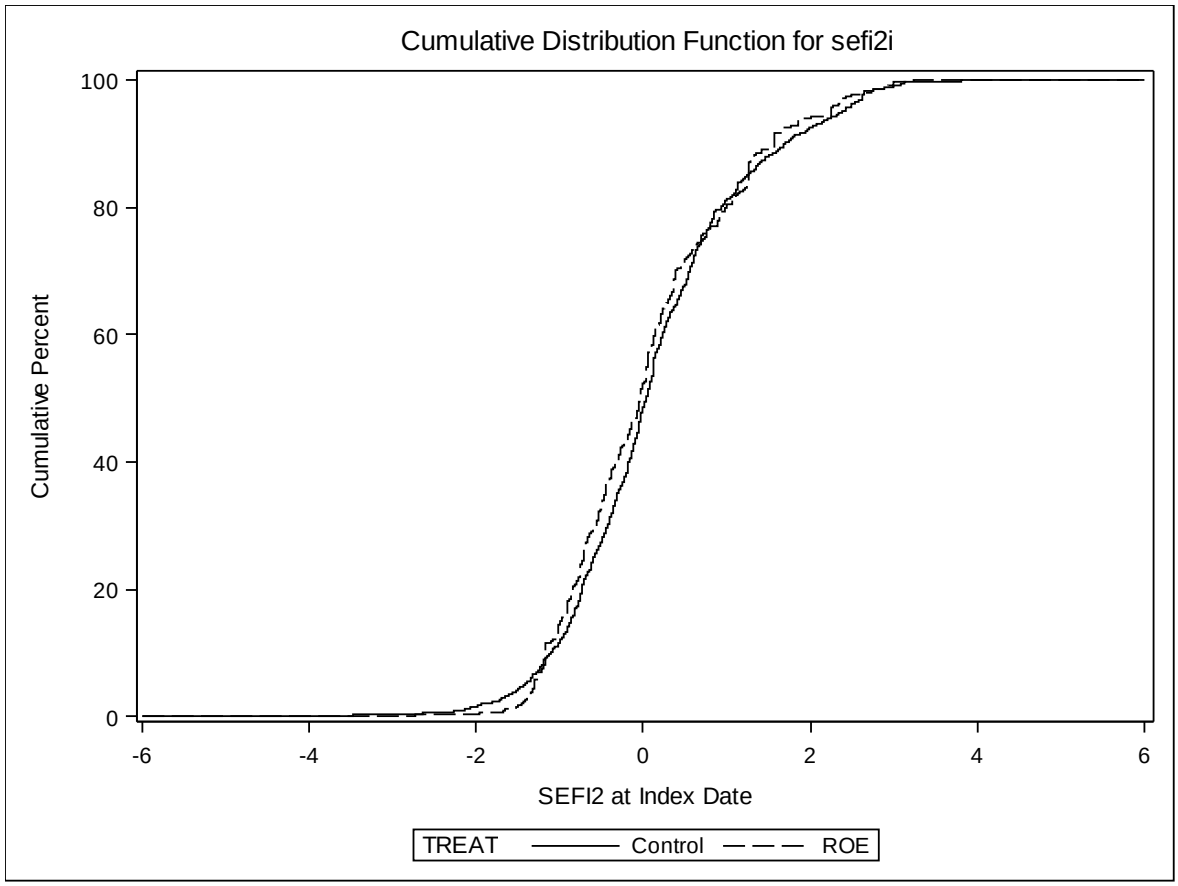
Matched Sample



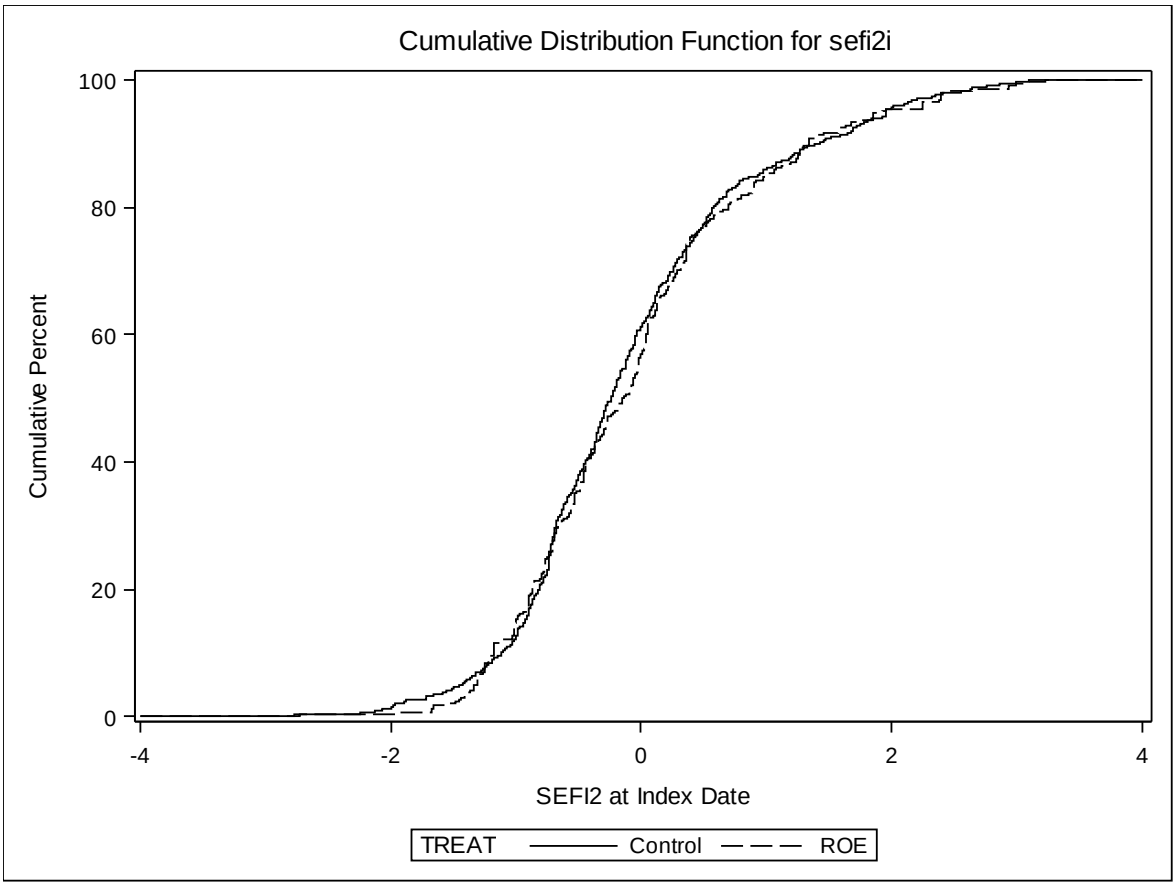
Original Sample



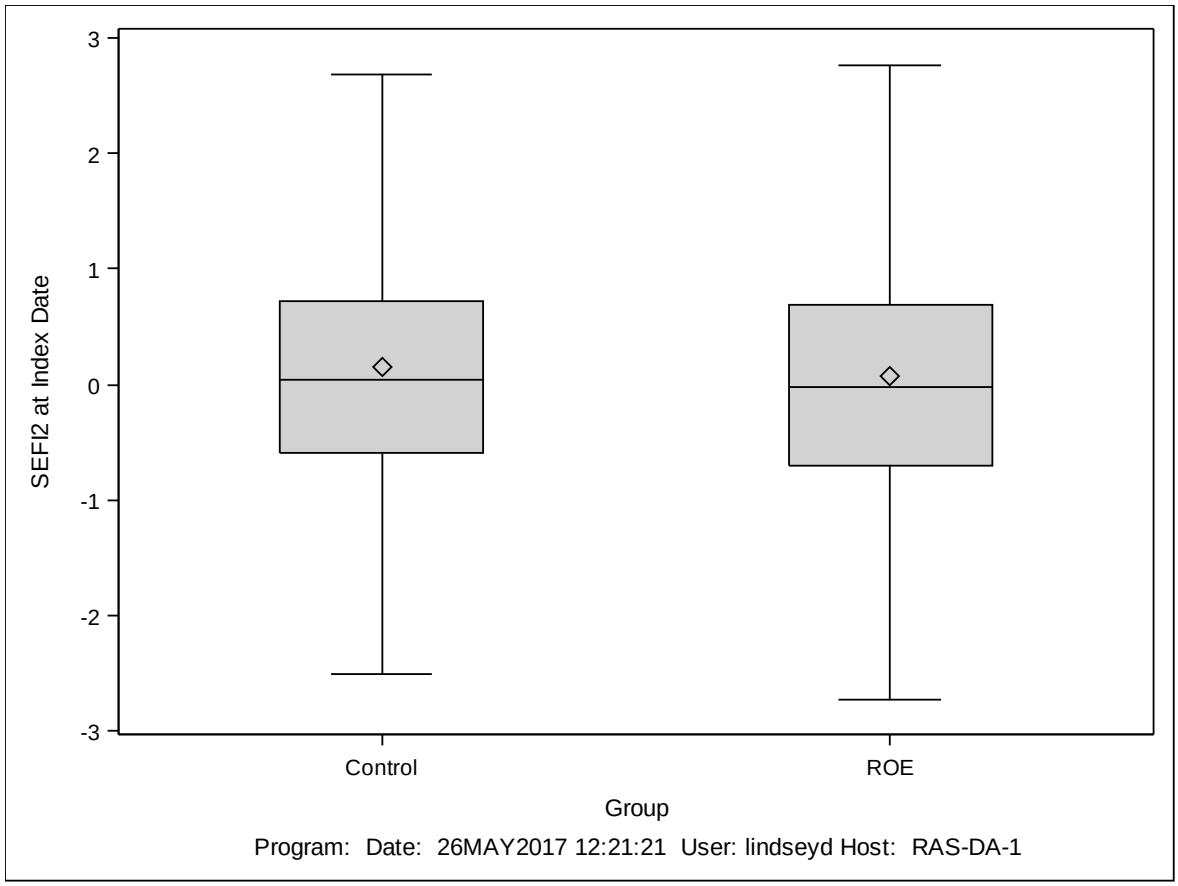
Matched Sample



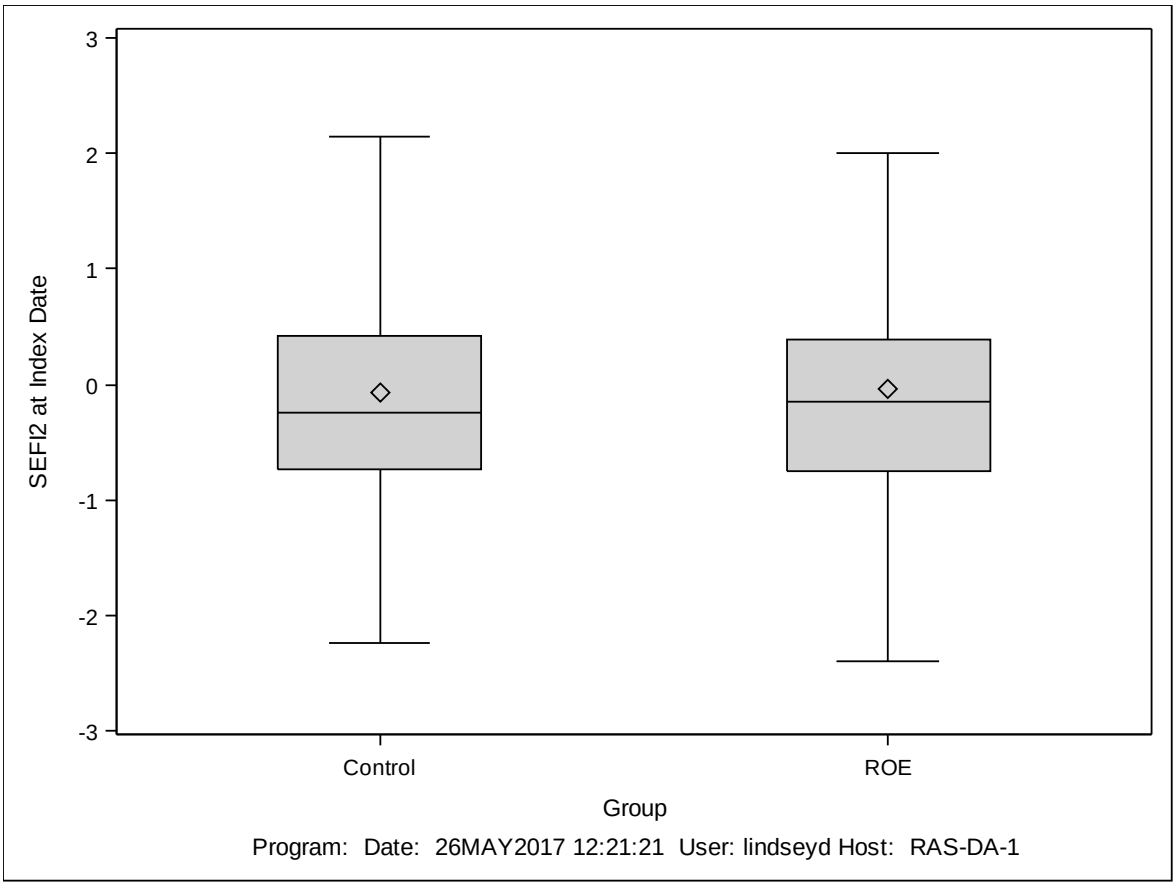
Original Sample



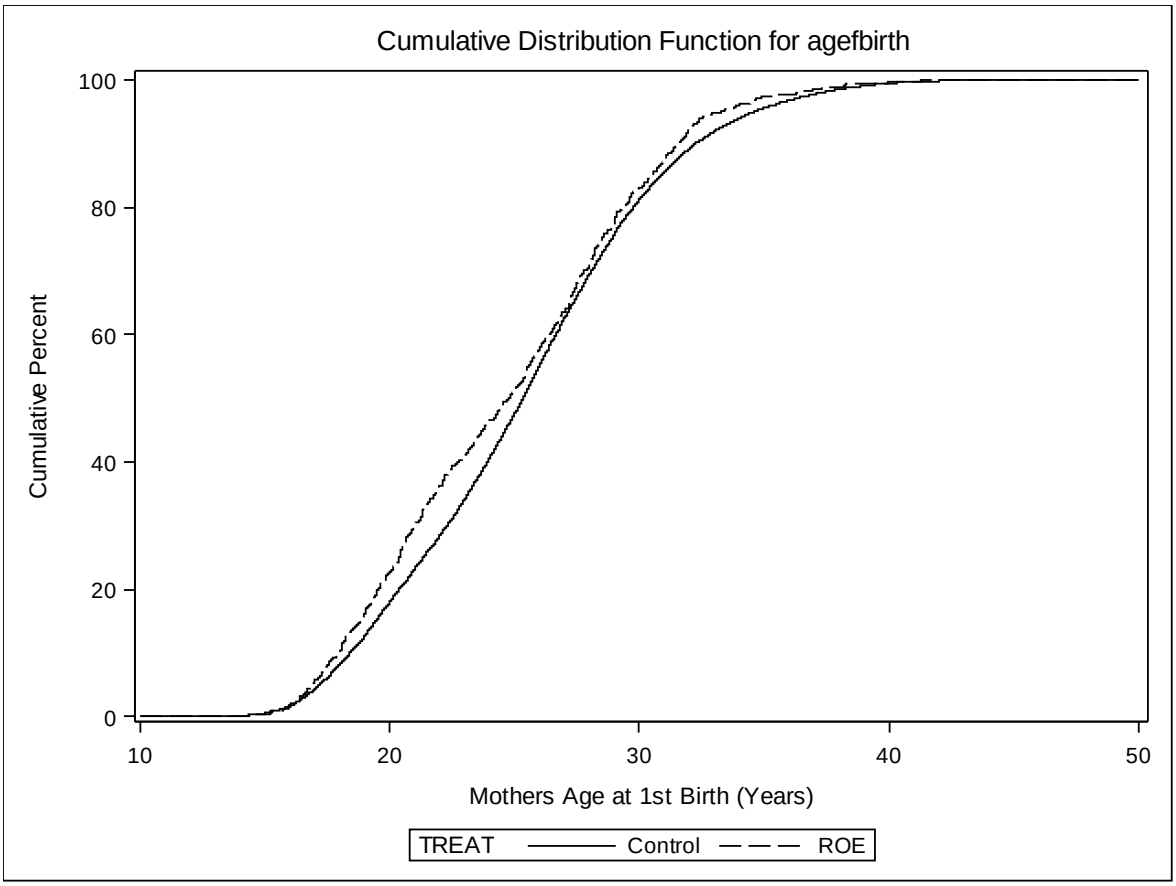
Matched Sample



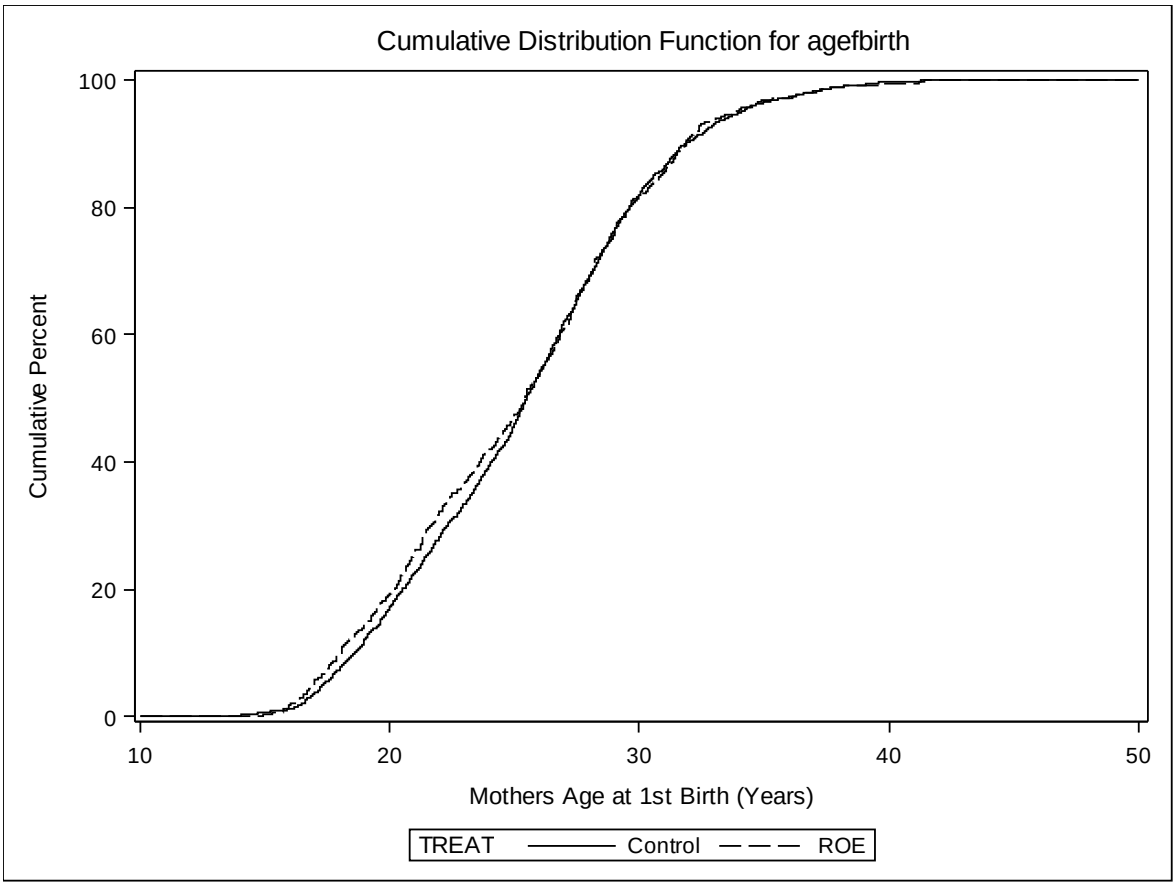
Original Sample



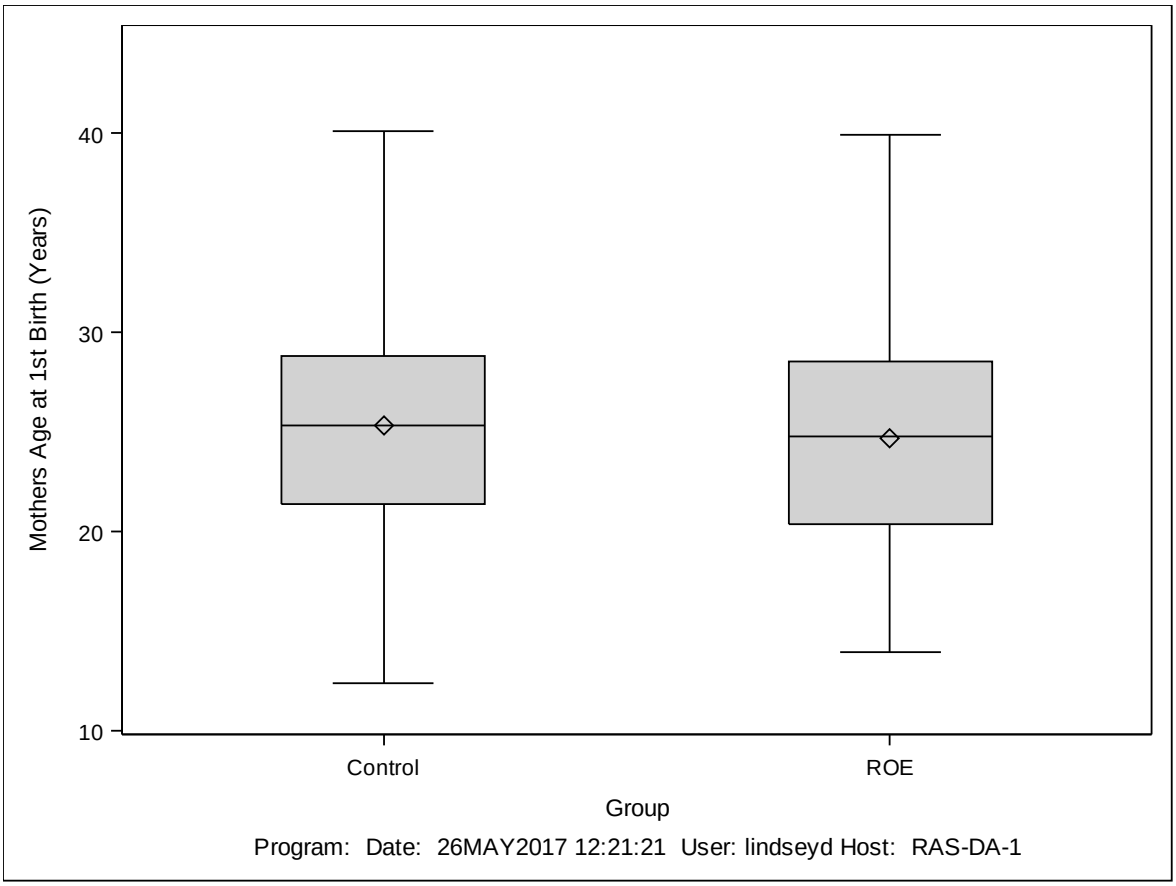
Matched Sample



Original Sample



Matched Sample



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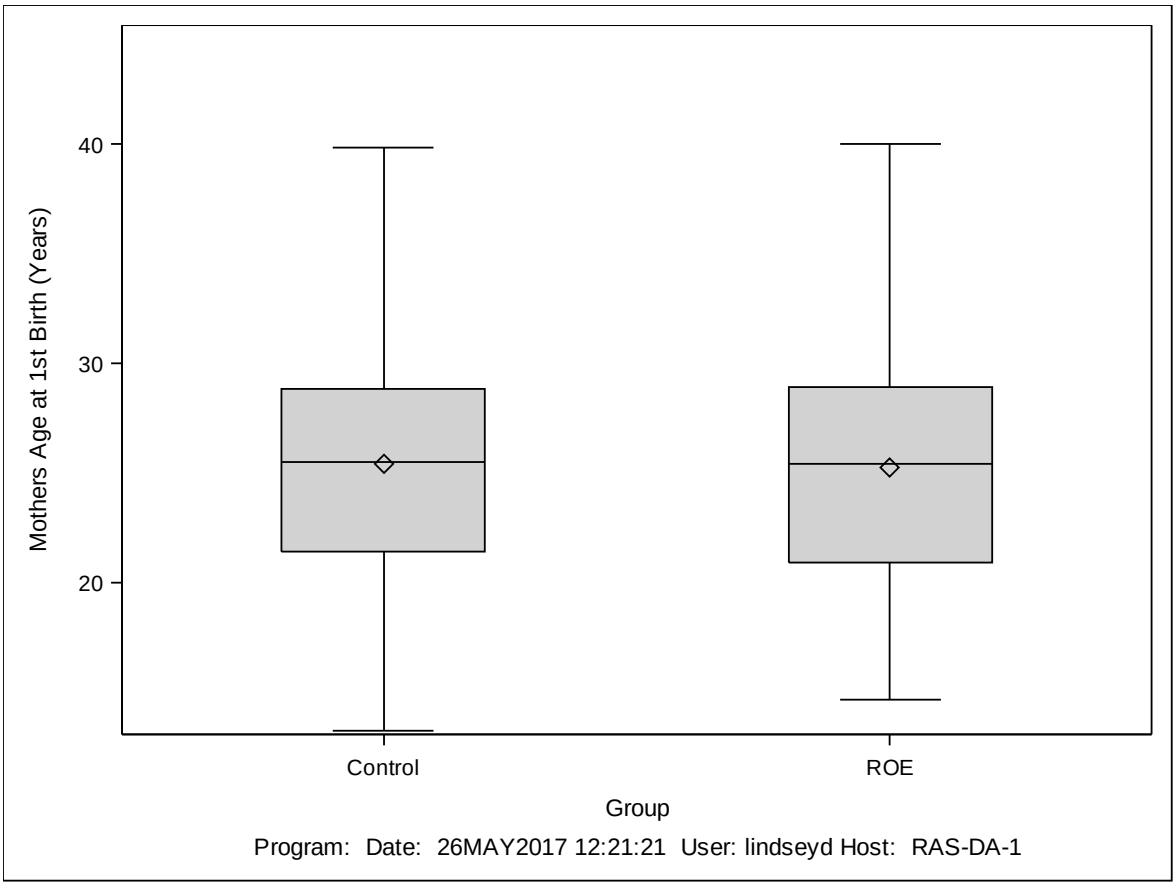

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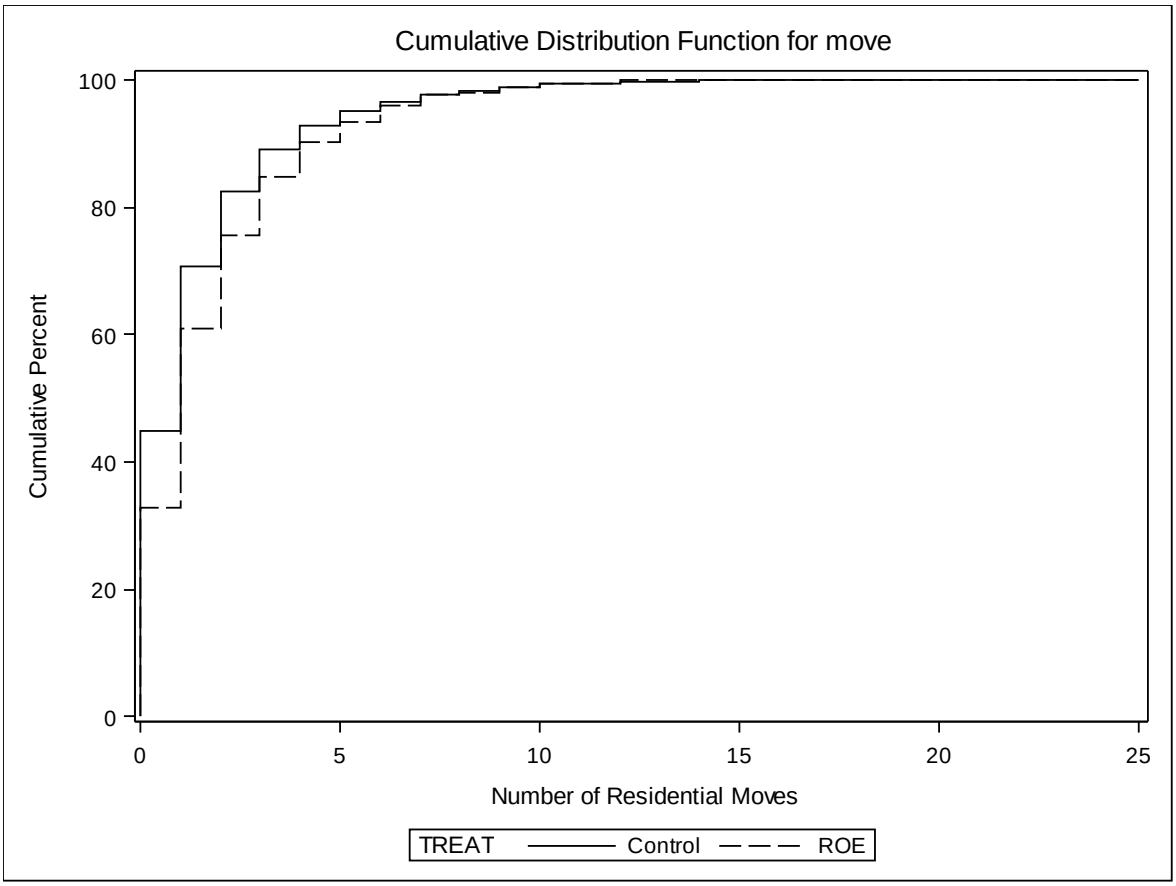

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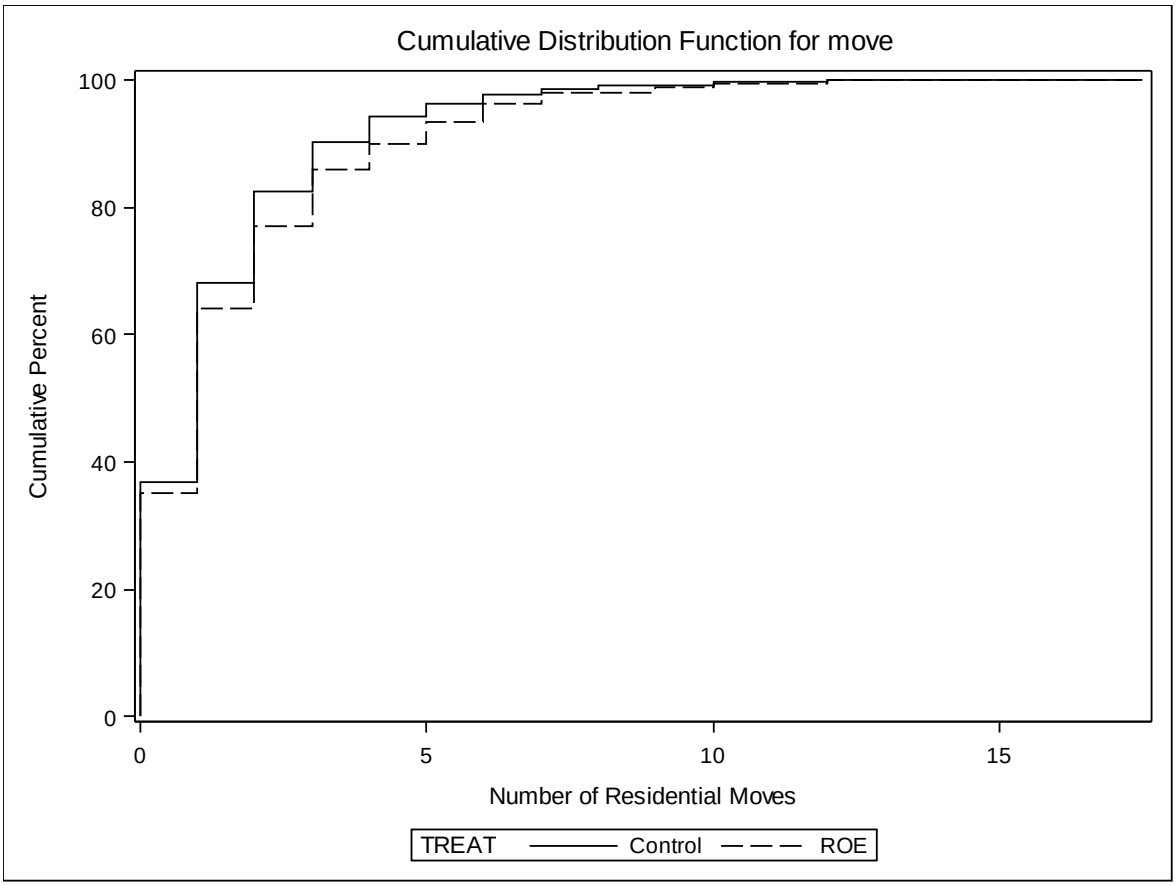

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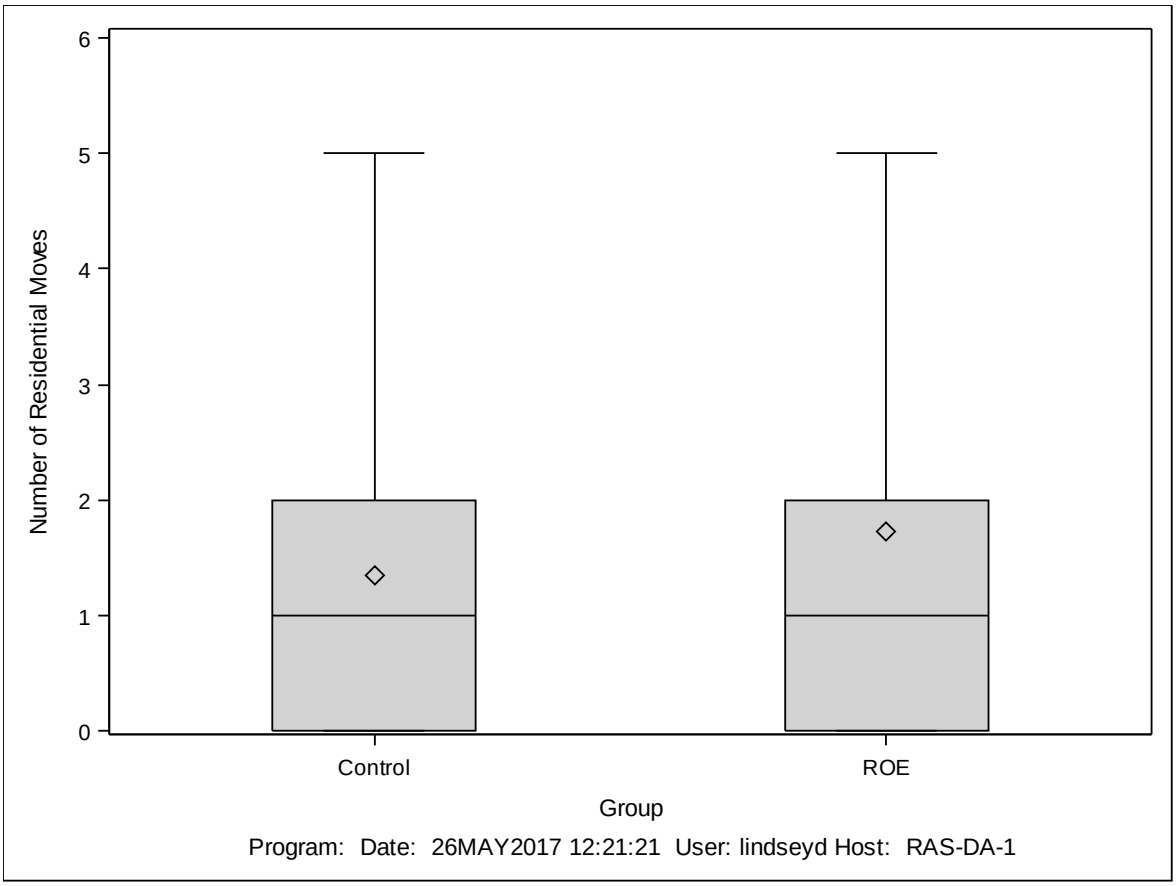

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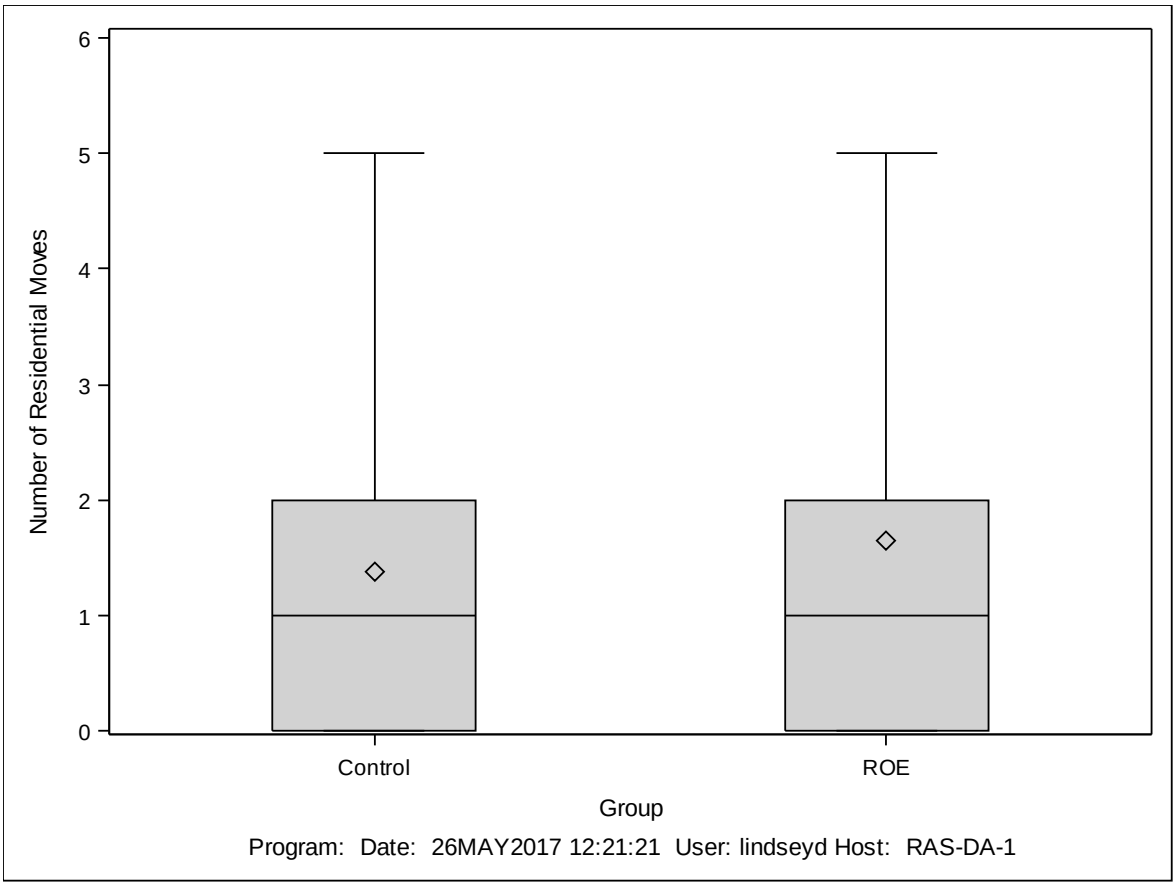

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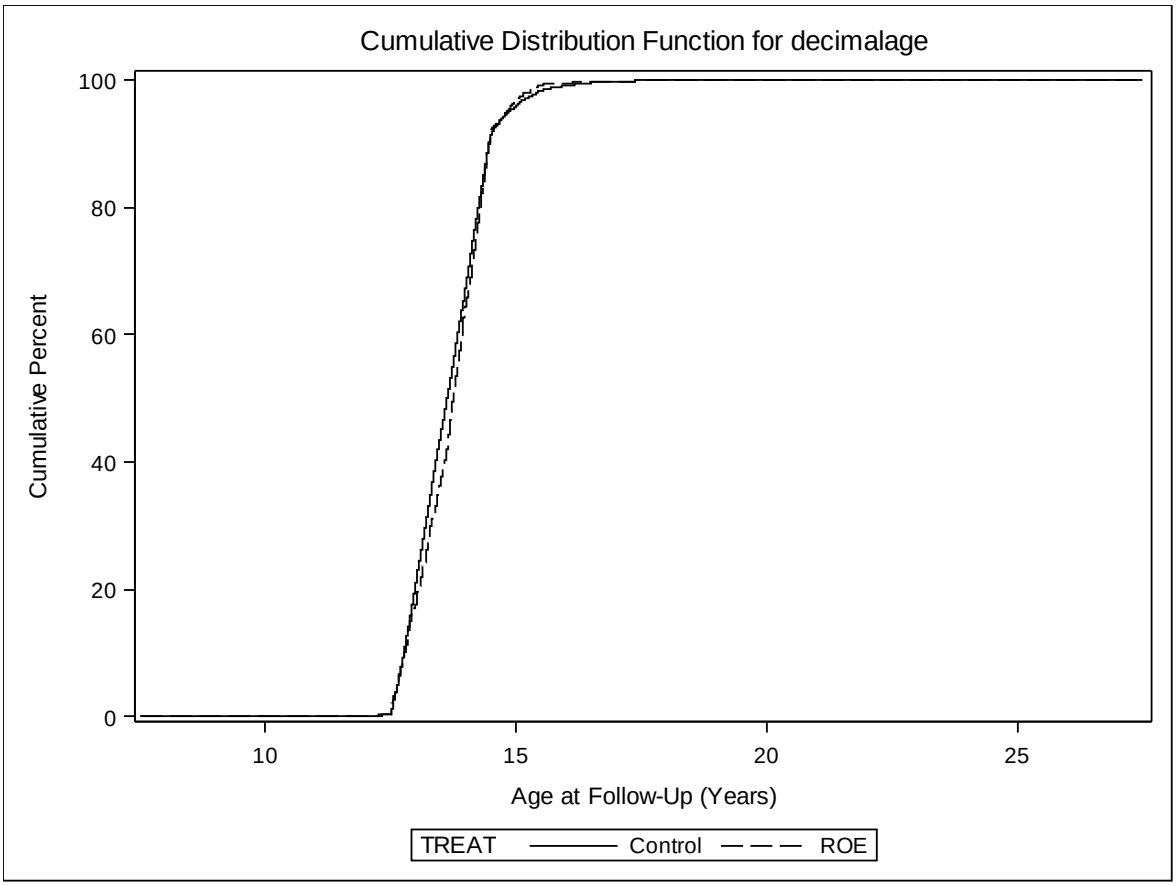

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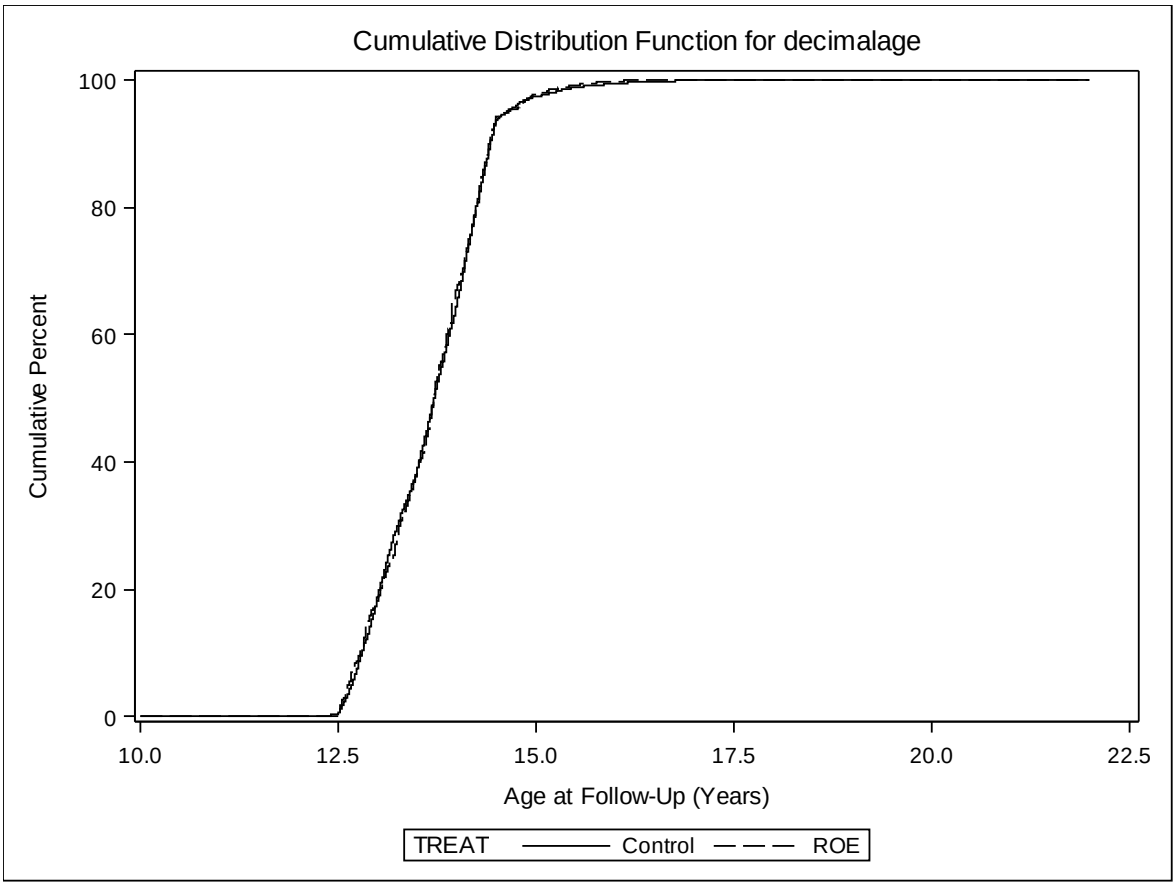

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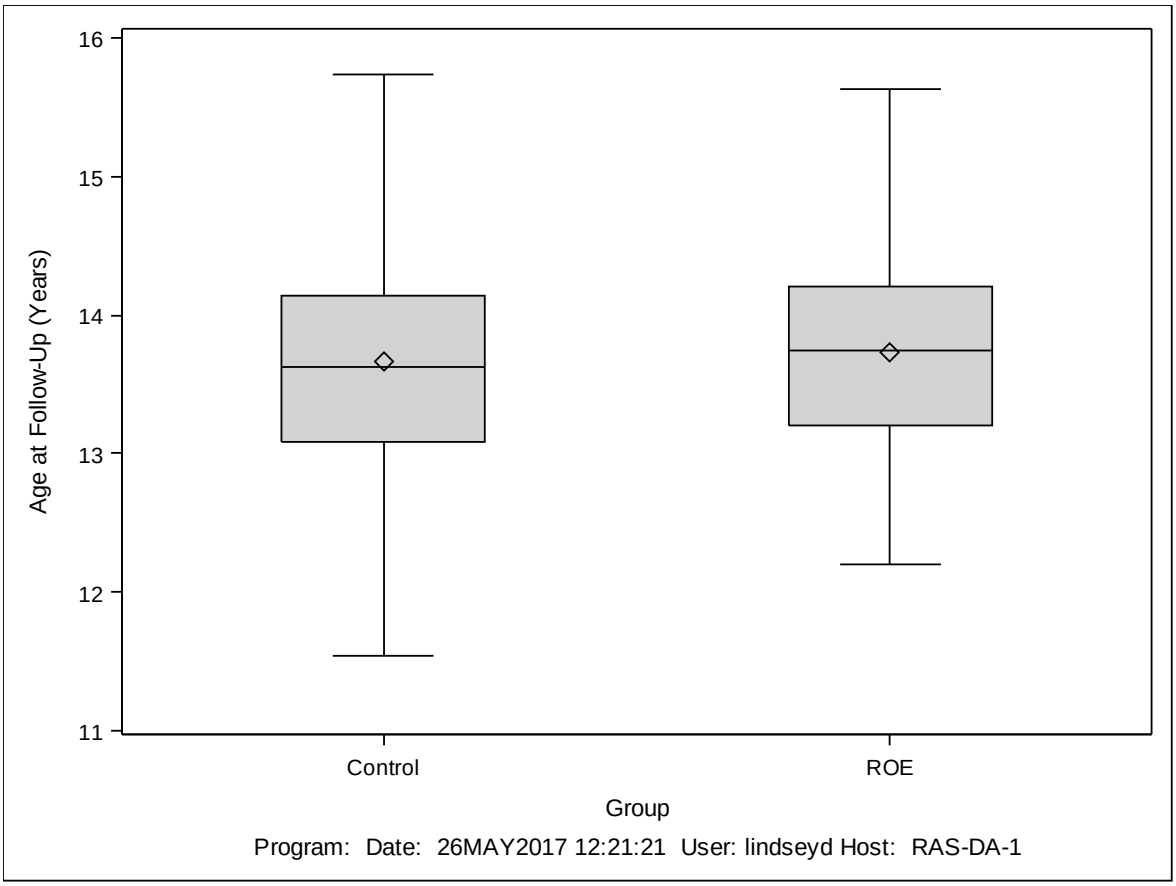

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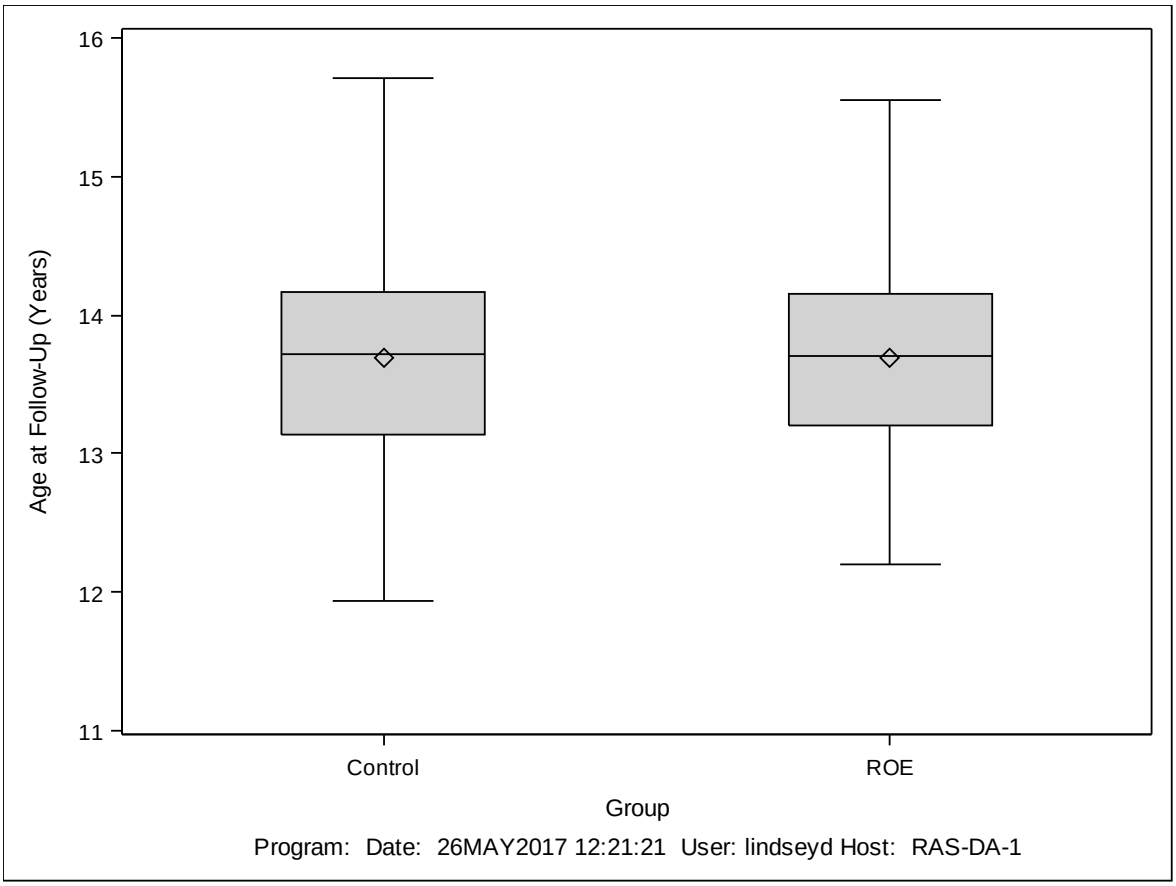

Matched Sample