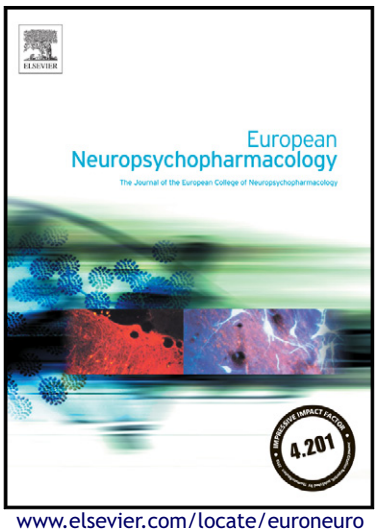


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# Clozapine use in childhood and adolescent schizophrenia: a nationwide population-based study

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**ABSTRACT**

Early onset schizophrenia (EOS) begins in childhood or adolescence. EOS is associated with poor treatment response and may benefit from timely use of clozapine. This study aimed to identify the predictors of clozapine use in EOS and characterize the clinical profile and outcome of clozapine-treated youths with schizophrenia. We conducted a nationwide population-based study using linked data from Danish medical registries. We examined all incident cases of EOS (i.e., cases diagnosed prior to their 18th birthday) between December 31st 1994 and December 31st 2006 and characterized their demographic, clinical and treatment profiles. We then used multivariable Cox proportional hazard models to identify predictors of clozapine treatment in this patient population. We identified 662 EOS cases (1.9% of all schizophrenia cases), of whom 108 (17.6%) had commenced clozapine by December 31$^{st}$ 2008. Patients had on average 3 antipsychotic trials prior to clozapine initiation. The mean interval between first antipsychotic treatment and clozapine initiation was 3.2 (2.9) years. Older age at diagnosis of schizophrenia [HR=1.2, 95% CI (1.05-1.4), p=0.01]), family history of schizophrenia [HR=2.1, 95%CI (1.1-3.04), p=0.02] and attempted suicide [HR=1.8, 95%CI (1.1-3.04), p=0.02] emerged as significant predictors of clozapine use. The majority of patients (n=96, 88.8%) prescribed clozapine appeared to have a favourable clinical response as indicated by continued prescription redemption and benefited in terms of improved occupational outcomes. Our findings support current recommendations for the timely use of clozapine in EOS.

**KEYWORDS:** schizophrenia, children, adolescents, clozapine, antipsychotic, Denmark

## INTRODUCTION

A significant proportion of individuals with schizophrenia present during childhood or adolescence. Childhood onset schizophrenia (COS), defined as schizophrenia diagnosed before the age of 13 years, is rare and affects about 1:40,000 children (Gochman et al. 2011). Adolescent onset schizophrenia (AOS) is more common as approximately 5% of cases present between the ages of 13-17 years (Cannon et al. 1999). The term early-onset schizophrenia (EOS) is commonly used when referring to both COS and AOS.

EOS is diagnosed using the same criteria as adult onset schizophrenia and lies on the same neurobiological continuum (Rapoport et al. 2005). Compared to the adult onset cases, EOS is associated with more pronounced developmental and premorbid deviance (Vourdas et al. 2003) and greater genetic loading evidenced by higher prevalence of family history of psychosis (Ahn et al. 2014), increased rates of genetic abnormalities, particularly copy number variations (Addington and Rapoport, 2009), and possibly more penetrant effects for common risk-conferring polymorphisms (Addington and Rapoport, 2009). Substance abuse, particularly use of cannabis in early adolescence, appears to be more prevalent in EOS (Kumra et al. 2005), may precipitate the earlier onset of psychosis (Schimmelmann et al. 2012; Large et al. 2011), and lead to greater symptom severity and poor treatment response (Kumra et al. 2005). The effect of these risk factors may be further exacerbated by urbanicity (Kuepper et al. 2011) and social adversity (Heinz et al. 2013).

EOS is also associated with unfavourable clinical and psychosocial outcome (Röpcke and Eggers, 2005; Remschmidt et al, 2007; Schimmelmann et al, 2007; Vyas et al, 2007). A further concern is increased suicidality, particularly in adolescent patients (Jarbin and Von Knorring, 2004; Falcone et al. 2010; Shoval et al. 2006; Sanchez-Gistau et al. 2013). Up to 32% of AOS patients may attempt suicide prior to their first admission (Falcone et al. 2010;

Shoval et al. 2006), up to 12% in the two years following the first admission (Sanchez-Gistau et al. 2013) and approximately 25% in the subsequent ten years (Jarbin and Von Knorring, 2004). Moreover, the 10-year prevalence of completed suicide in EOS following the first admission is reported to be as high as 5% (Jarbin and Von Knorring, 2004).

Antipsychotic medication is the mainstay treatment for EOS as is the case of adult onset cases. However, antipsychotic agents, regardless of pharmacological class, are only partially effective in EOS with acute response rates ranging from 34-50% (Sikich et al. 2008; Findling et al. 2010). The prevalence of poor treatment responders in EOS is therefore consistently high (Sikich et al. 2008; Findling et al. 2010). As clozapine has shown superior efficacy in treatment-resistant adult patients with schizophrenia, several clinical trials and observational studies have examined its efficacy and tolerability in EOS (Schneider et al. 2014). We have recently reviewed this literature (Schneider et al. 2014) which shows that clozapine is associated with significant symptomatic relief and sustained clinical improvement in EOS. These benefits need to be balanced against a wide-range of clozapine-induced adverse drugs reactions (ADRs) that necessitate close monitoring of patients' physical health. The most common ADRs in EOS are sedation and hypersalivation (reported in 90% of patients), followed by enuresis and constipation (up to 60%) ((Schneider et al. 2014).). Weight gain and metabolic changes are also relatively common (8-22%) but emergent diabetes is infrequent (<6%) (Schneider et al. 2014). Although haematological ADRs are potentially the most concerning, neutropenia occurs in a small minority of EOS patients (6-15%) and is usually transient while agranulocytosis is rare (<0.1%) (Schneider et al. 2014). There are no reports of fatalities in this age group. The average all-cause discontinuation rate of clozapine in EOS is very low (< 6%) (Schneider et al. 2014).

The most recent international guidelines recommend the use of clozapine in refractory EOS and provide a clear framework for ADR monitoring (McClellan et al, 2013; NICE, 2013). Despite this, the use of clozapine in EOS is generally thought to be both limited and delayed. For example, less that 0.4% of all clozapine prescriptions in the UK are for EOS patients (Cirulli, 2005) and nearly 40% of psychiatrists working in child and adolescent inpatient units have never prescribed clozapine (Cirulli, 2005). This suggests that clinical decision-making in connection to clozapine initiation in EOS is influenced by variables beyond clinical response or tolerability. However, systematic data addressing this issue are currently lacking. Accordingly, the purpose of this study was to identify the clinical features that predict clozapine treatment in EOS. We hypothesized that age at diagnosis, suicidality and cannabis abuse may emerge as significant predictors of clozapine treatment and that the influence of these factors may modified by sex, urbanicity, and social adversity.

**Experimental Procedures**

***Case Identification***

We used linked data from the Danish Psychiatric Central Research Register (DPCR) (Mors et al. 2011), the National Prescription Database (Kildemoes et al. 2011), the Danish Civil Registration System (CRS) (Pedersen et al. 2006) and the Integrated Database for Labour Market Research (IDA) (Munk-Jørgensen and Østergaard, 2011).

The DCPR covers the entire Danish population including immigrants and contains information on all admissions to inpatient psychiatric facilities since 1969 and all visits to specialty outpatient and emergency services since 1995 (Mors et al. 2011, Munk-Jørgensen and Østergaard, 2011). Diagnoses both for patients and their first-degree relatives followed the International Classification of Diseases, 8$^{th}$ revision (ICD-8) (WHO, 1967) till 1994 and the 10$^{th}$ revision (ICD-10) (WHO, 1992) thereafter. We used the DPCR to identify all patients with schizophrenia (ICD-8: 295.x9, excluding 295.75, and ICD-10: F20) diagnosed between December 31st 1994 and December 31st 2006. The same database was used to identify psychiatric diagnosis of the patients' first-degree relatives. From the initial pool of 34,467 patients we selected those with schizophrenia diagnosed prior to their 18$^{th}$ birthday. Age at diagnosis was based on the date of the first service contact during which a diagnosis of schizophrenia was recorded. Additional information extracted concerned number and duration of hospitalizations, cannabis abuse disorders, and suicide attempts (detailed definitions provided in the online data supplement).

We used the national prescription database to extract data regarding antipsychotic use (Kildemoes et al. 2011). The database includes all prescription based medicines collected from pharmacies during outpatient status. We collected data on all redeemed

prescriptions for any antipsychotic medication till 31st December 2008. Dosage was calculated using defined daily doses (DDD) (WHOCC, 2009) corrected for bed-days as the national prescription database does not contain information about medications used during hospitalizations.

The CRS contains continually-updated information on all Danish residents and was used to extract information about place of birth and residence. Information about patients' parental death and psychiatric diagnoses in first degree family members were obtained by linking data from the CRS and the DPCR. The IDA was used to extract patients' education and employment data.

The study was approved by the Danish Data Protection Agency, National Board of Health and Statistics Denmark (currently renamed Danish Health and Medicine Authority). Approval from the National Scientific Ethical Committee was not required because register-based data are anonymized.

***Predictors of Clozapine Initiation***

The date of antipsychotic treatment initiation was defined as the redemption date of the first prescription for any antipsychotic agent. The variables examined as potential predictors of clozapine initiation were selected based on the previous literature for their association with earlier onset and/or increased illness severity in EOS. We therefore considered sex, urbanicity at birth and the time of the diagnosis of schizophrenia, family adversity indexed by parental loss before patients' 18th birthday, family history of schizophrenia among 1st degree relatives, duration of untreated illness, age at the time of the diagnosis of schizophrenia, and cannabis abuse and attempted suicide prior to or within the first year of diagnosis. Detailed definitions are provided in the on line data supplement.

***Assessment of clinical and functional outcome***

As the national registries do not hold data on symptom levels, we could only assess treatment response using surrogate measures. We based our choice on previous Danish registry data that show that the average time to all-cause discontinuation of clozapine is approximately 9 months (Uggerby et al, 2011). We therefore defined treatment response as having redeemed prescriptions for clozapine for a minimum of six consecutive months following initiation. Periods shorter than this may reflect discontinuation due to ADRs during titration while discontinuation after 6 months is likely to be influenced by non-specific factors affecting long-term adherence including refusal of on-going haematological monitoring. Functional outcome was based on the patients' highest educational and employment level. Therefore information was collected only for those patients who were 20 years or older by 31st December 2008.

***Statistical Analysis***

We extracted data using SAS 9.2 (SAS Institute Inc, Cary, NC) and analysed using STATA 11 (Stata-Corp LP, College Station, Texas). We compared clozapine to non-clozapine treated patients and clozapine responders to non-responders on a range of demographic, clinical and outcome variables using appropriate parametric and non-parametric statistics.

The association between each individual predictor variable and time to clozapine initiation was first examined using separate univariate cox proportional hazard models. Variables that predicted time to clozapine initiation at the level of $p<0.10$ were then entered in a multivariable cox model. Multicollinearity between predictors was measured using Variance Inflation Factor (VIF). VIF values >5 denote multicollinearity.

**Results**

We identified 662 cases with childhood or adolescent schizophrenia. We excluded 48 patients who did not redeem any prescriptions for outpatient treatment. The final study population comprised 614 patients who were first diagnosed with schizophrenia at a mean age of 16.20 years. The socio-demographic, clinical treatment and functional characteristics of the sample are summarized in Table 1 and in supplemental Table S1 in the online data supplement. Clozapine was prescribed at least once to 108 patients (17.6% of the sample). The mean interval between onset of antipsychotic treatment and clozapine initiation was 3.2 (2.9) years. Prior to this, patients had had approximately 3 (range: 1-10) therapeutic trials with different antipsychotics, mostly (61.6%) second generation agents as shown in supplemental Table S2 in the online data supplement.

***Characteristics of EOS patients prescribed clozapine***

Compared to patients who never received clozapine, patients who had been prescribed clozapine at least once had higher rates of cannabis abuse, were more likely to have attempted suicide, were marginally older, less likely to have lived in the suburban/rural areas at the time of diagnosis with schizophrenia, and less likely to be employed at the age of 20 years (Table 1). No other differences were statistically significant (Table 1).

***Prediction of Clozapine initiation***

The results of the cox proportional hazard models are summarized in Table 3. Urbanicity either at birth (p=0.66) or at diagnosis (p=0.13), parental loss (p=0.98) and history of cannabis use (p=0.16) were not significant predictors of time to clozapine initiation. In contrast, older age at diagnosis [HR=1.25, 95%CI (1.06-1.48), p=.003], having attempted suicide [HR=1.98, 95% CI (1.23-3.20), p=.001], female sex [HR=0.69, 95%CI (0.46-1.04), p=0.05] and family history of schizophrenia [HR=1.89, 95%CI (0.98-3.66), p=0.05] were significant predictors and were entered into the multivariable cox proportional hazard

model. In this final model, older age at diagnosis [HR=1.24, 95% CI (1.05-1.48), p=0.01]), positive family history of schizophrenia [HR=2.19, 95%CI (1.13-3.04), p=0.02] and having attempted suicide [HR=1.85, 95%CI (1.13-3.04), p=0.02] remained significant (all VIF <1.06) while sex did not [HR=0.71, 95%CI (0.46-1.10), p=0.13]. Graph 1 illustrates the Kaplan-Meier curves for the three significant predictors.

***Characteristics of patients remaining on clozapine for more than 6 months***

Of the 108 clozapine treated patients, 96 (88.9%) redeemed clozapine prescriptions for at least six consecutive months and thus were considered responders. Those who discontinued clozapine earlier than 6 months had higher rates of attempted suicide; otherwise the two groups were statistically comparable (Table 3). Numerically there was a suggestion that clozapine responders may have shorter hospital stays and possibly better occupational outcomes at age 20 years. However, the sample may have been underpowered to detect differences between those who redeemed clozapine prescriptions for less as opposed to more than 6 months (Table 3).

**Discussion**

We found that approximately 1 in every 5 patients with EOS redeemed at least one clozapine prescription, on average within 3-4 years from illness onset. Clozapine initiation was associated with older age at diagnosis, a history of suicide attempts and positive family history of schizophrenia. Prior to commencing clozapine, patients had been prescribed on average 3 different antipsychotics, mostly second generation agents (Table S2, on line data supplement). The majority of clozapine treated patients (88.9%) can be considered as having a favourable response since they continued to redeem clozapine prescriptions for more than 6 months.

Our findings regarding antipsychotic exposure prior to clozapine in EOS are comparable to those in patients with adult onset schizophrenia. Nielsen and colleagues (2012) used the same registers to characterize patients with adult onset schizophrenia (mean age of onset 26.2 years) that were first prescribed clozapine between January 1$^{st}$ 1997 and December 31, 2005. They also found that clozapine was initiated after an average of 3 antipsychotic trials. The mean interval between the diagnosis of schizophrenia and clozapine initiation was 1-2 years which is shorter than in the EOS sample. Similar findings were also reported by Harrison et al (2010) based on data from adult patients commenced on clozapine between 1993 and 2007 in a large mental health clinic in Auckland, New Zealand (34). In the UK, the most recent study was conducted at the Maudsley Hospital in South London for patients commencing clozapine between 2006 and 2010 (Howes et al. 2014). The authors reported that clozapine initiation occurred after an average of 5 antipsychotic trials and suggested that this led to a delay in clozapine treatment of about 4 years (Howes et al. 2014). Our data therefore suggest that, within Denmark at least, time to clozapine initiation in EOS, follows similar patterns to those seen in adult onset cases and is

generally aligned with treatment recommendations to start clozapine after two unsuccessful therapeutic trials with different antipsychotics (McClellan et al. 2013; NICE, 2013).

Key predictors of clozapine treatment In adult onset schizophrenia include increased use of services, particularly inpatient facilities, increased number and dose of antipsychotic medications, younger age of onset and male sex (Harrisson et al. 2010; Howes er al. 2011; Nielsen et al. 2012). In contrast, number of hospitalizations, level of antipsychotic use and sex did not differentiate between clozapine and non-clozapine treated EOS patients. Neither did we find an excess of males in the clozapine treated EOS group although this is often reported in adult schizophrenia (Harrisson et al. 2010; Howes et al. 2011; Nielsen et al. 2012). Another important difference between adult and early onset schizophrenia with regards to clozapine treatment concerns the effect of suicidality. A history of suicide attempts emerged as a key predictor of clozapine treatment in EOS. Evidence from several lines of research suggests that clozapine may reduce suicidality and suicide related mortality in schizophrenia (reviewed by Meltzer, 2012) and this may have influenced clinical decision-making in this study. Our finding contrasts with a US study (Stroup et al. 2014) who found no association between suicide attempts/self-harm on clozapine initiation. Their sample consisted of 15,524 clozapine-treated patients with schizophrenia aged 18-64 years derived from national (45-state) Medicaid Analytic Extracts covering the years 2001-2005. It is not clear whether this reflects differences in clinical practice or in patients' access to care following suicidal attempts or in reporting procedures.

Also contrary to the adult literature, clozapine treatment in EOS was associated with older age at diagnosis. This is not due to age-related restrictions in the use of clozapine specific to Denmark. It is possible that clinicians offer clozapine to older adolescents as they

may consider them better able to understand the monitoring requirements and have better tolerability than younger adolescents or children. The association between clozapine initiation and positive family history of schizophrenia has not been examined in previous studies. The presentation of schizophrenia in children and adolescents is uncommon and making the diagnosis can be challenging (Gochman et al, 2011). In this context, the presence of family history for the disorder may reassure clinicians about the validity of their diagnosis and may empower them to consider clozapine earlier.

***Methodological Considerations***

The strengths and limitation of this study reflect its register-based design. Detailed clinical information is not available in the registers. Consequently it was not possible to comment on symptomatic response to clozapine or to ascertain whether all eligible patients had been prescribed clozapine. Prescription data were available only for outpatient treatment. It was not possible to ascertain whether some patients were offered clozapine during their hospital stay but refused or discontinued treatment very early due to ADRs or poor adherence with haematological monitoring. The major strength of the study is the availability of information from the complete Danish population which minimizes sampling and recall biases.

***Clinical Implications***

Our findings suggest that clinicians involved in the care of EOS patients are mindful of current guidelines for the use of clozapine in this age group and endeavour to align their practice accordingly. This is the first study to examine clozapine use in EOS using nationwide data. Our findings support the timely use of clozapine in EOS. The majority of EOS patients prescribed clozapine appeared to derive some benefit as they remained on this medication for longer than 6 months. We were not able to establish the degree of clinical improvement

but continued use of clozapine may lead to reduced hospitalizations and improved vocational outcome. It was not possible to ascertain to what degree all potentially eligible patients were offered clozapine. It would be important to address this issue in further studies in order to identify potential barriers to clozapine use in this age group.

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**Table 1. Study Population**

| | Non-Clozapine Treatment Group (N=506) | Clozapine Treatment Group (N=108) | *P* |
|---|---|---|---|
| ***Sociodemographic variables*** | | | |
| **Sex** (n % male) | 258 (50.99) | (48) 44.44 | 0.22 |
| **Urbanicity at diagnosis, n (%)** | | | |
| Living in the capital | 86 (17.03) | 20 (18.87) | **0.05** |
| Living in suburb of capital | 113 (22.38) | 14 (13.21) | |
| Living in provincial city | 34 (6.73) | 9 (8.49) | |
| Living in provincial town | 128 (25.25) | 39 (36.79) | |
| Living in rural area | 144 (28.51) | 24 (22.64) | |
| **Urbanicity at birth, n (%)** | | | |
| Living in the capital | 93 (21.08) | 20 (21.28) | 0.89 |
| Living in suburb of capital | 88 (19.95) | 19 (20.21) | |
| Living in provincial city | 37 (8.39) | 8 (8.51) | |
| Living in provincial town | 109 (24.72) | 27 (28.72) | |
| Living in rural area | 114 (25.85) | 20 (21.28) | |
| **Parental loss, n (%)** | 39 (7.71) | 7 (6.48) | 0.66 |
| **Positive family history for schizophrenia, n (%)** | 31 (6.42) | 12 (11.88) | 0.06 |
| ***Clinical variables*** | | | |
| **Age at schizophrenia diagnosis** (years) | 16.10 (1.64) | 16.63 (1.03) | **.001** |
| **History of attempted suicide**, n (%) | 70 (13.83) | 24 (22.22) | **.03** |
| **Cannabis abuse**, n (%) | 23 (4.55%) | 11 (10.19) | **.02** |
| ***Treatment variables*** | | | |
| **Duration of untreated illness** (days) | 335.33 (566.86) | 417.92 (668.54) | 0.31 |
| **Number of hospitalisations** (per year) | 1.04 (1.71) | 1.17 (1.17) | 0.47 |
| **Duration of hospitalisations** (days per year) | 80.01 (192.78) | 103.91 (200.25) | 0.27 |
| **Defined Daily Dose of Antipsychotics (**per year)* | 2.31 (38.74) | 3.91 (57.40) | 0.74 |
| **Number of antipsychotics prescribed prior to clozapine** | --- | 3.37 (2.26) | --- |
| **Interval between first antipsychotic prescription and clozapine initiation (years)** | --- | 3.2 (2.9) | --- |
| **Clozapine initiation prior to age 18 years**, n (%) | --- | 33 (30.56) | --- |
| **Clozapine treatment for > 6 months**, n (%) | --- | 96 (88.88) | --- |
| **Functional Outcome variables** | | | |
| **Highest Educational Status, n (%)**** | | | |
| Primary School | 423 (92.20) | 101 (97.87) | 0.28 |
| High-School | 19 (4.36) | 0 (0.00) | |
| Vocational Education | 12 (2.75) | 2 (2.13) | |
| Higher Education, short-track | 2 (0.46) | 0 (0.00) | |
| Higher Education, medium and long-track | 1 (0.23) | 0 (0.00) | |
| **Highest Working Status, n (%)**** | | | |
| Inside workforce | 101 (22.10) | 11 (10.68) | **0.03** |
| Outside workforce | 354 (77.46) | 92 (89.32) | |
| Unemployed | 2 (0.44) | 0 (0.00) | |

Continuous variables are shown as mean (standard deviation) and categorical variables as number ( %) within group; * Defined daily Dose was corrected for bed-days per year; **Based on a sample of 457 non-clozapine and 103 clozapine treated patients who were at least 20 years old in 2008; significant uncorrected p value in bold typeface

**Table 2. Univariate and adjusted hazard ratios from cox proportional hazard models predicting time to clozapine initiation**

| | Univariate Models | | Multivariate Model | |
|---|---|---|---|---|
| | ***HR (95% CI)*** | ***p*** | ***HR (95% CI)*** | ***P*** |
| **Sex** | 0.69 (0.46- 1.04) | 0.05 | 0.71 (0.46-1.10) | 0.13 |
| **Age at diagnosis of schizophrenia** | 1.25 (1.06-1.48) | .003 | 1.24 (1.05-1.48) | **0.01** |
| **Family history of schizophrenia** | 1.89 (0.98-3.66) | 0.05 | 2.19 (1.13- 3.04) | **0.02** |
| **Urbanicity at birth** | .98 (0.85-1.13) | 0.81 | --- | --- |
| **Urbanicity at diagnosis** | 1.04 (0.90-1.20) | 0.57 | --- | --- |
| **Parental loss** | 1.00 (0.46-2.17) | 0.99 | --- | --- |
| **Premorbid cannabis use** | 1.60 (0.80-3.18) | 0.21 | --- | --- |
| **Suicide attempts** | 1.98 (1.23-3.20) | 0.001 | 1.85 (1.13-3.04) | **0.02** |

**Table 3. Comparison of patient that remained on clozapine for more than 6 months versus those who discontinued earlier**

| | Discontinuation group (N=12) | Continued treatment group (N=96) | *p* |
|---|---|---|---|
| ***Demographic variables*** | | | |
| Sex (male, n %) | 5 (41.66) | 43 (44.79) | 0.83 |
| ***Clinical Variables*** | | | |
| Age at Diagnosis | 16.71 (0.98) | 16.62 (1.04) | 0.76 |
| History of attempted suicide | 5 (41.65) | 19 (19.79) | **0.03** |
| Cannabis use | 1 (8.33) | 10 (10.41) | 0.41 |
| **Treatment Variables** | | | |
| Total Number Hospitalizations | 18.67 (11.28) | 20.58 (18.72) | 0.73 |
| Duration of Hospitalizations (days) | 604.5 (939.81) | 442.06 (378.36) | 0.24 |
| **Functional Outcome Variables** | | | |
| Education (high school or higher, n %) | 0 (0) | 2.44% | 0.61 |
| Working Status (within workforce, n %) | 2 (16.67) | 9 (9.37) | 0.47 |

Continuous variables are shown as mean (standard deviation) and categorical variables as number (%) within group



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Conflict of Interest

None of the authors has any conflicting interests to declare

**Contributors**

CS, EP, TW, CG, and DD were involved in data extraction, data analysis and contributed to the manuscript. SF and PBP oversaw the study design and data analysis. SF wrote the manuscript and all other authors contributed material and comments.