Title

Long-term exposure to methylmercury and psychiatric symptoms in residents of Minamata, Japan

Authors

Takashi Yorifuji[a, b], Toshihide Tsuda[c], Sachiko Inoue[a], Soshi Takao[a], and Masazumi Harada[d]

Affiliations

[a]Department of Epidemiology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama, 700-8558, Japan

[b]Department of Environmental Health, Harvard School of Public Health, 401 Park Drive, 3-112-12 East, Boston, MA 02215, USA

[c]Department of Environmental Epidemiology, Okayama University Graduate School of Environmental Science, 3-1-1 Tsushima-naka, Kita-ku, Okayama, 700-8530, Japan

[d]Department of Social Welfare Studies, Kumamoto Gakuen University, 2-5-1 Ooe, Kumamoto, 862-8680, Japan

Address correspondence to:

Takashi Yorifuji, MD, PhD

Department of Epidemiology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences

2-5-1 Shikata-cho, Kita-ku, Okayama, 700-8558, Japan

Tel: +81(JP)-86-235-7174

Fax: +81(JP)-86-235-7178

E-mail: yorichan@md.okayama-u.ac.jp

Abstract

Introduction: It is well-known that prenatal or postnatal exposure to methylmercury can produce neurological signs in adults and children, exemplified by a case of large-scale poisoning in Minamata, Japan, in the 1950s. However, evidence regarding whether pre- or postnatal exposure to methylmercury causes psychiatric symptoms (e.g., impairment of intelligence and mood and behavioral dysfunction) is still limited—excluding cases of fetal Minamata disease patients.

Methods: We evaluated the effects of pre- or postnatal exposure to methylmercury on psychiatric symptoms using data derived from a 1971 population-based survey in Minamata and neighboring communities. We adopted residential areas as an exposure indicator and psychiatric symptoms as the outcome. Then, we estimated the adjusted prevalence odds ratio (POR) and confidence interval (CI) of psychiatric symptoms in relation to residential area.

Results: There were 904 participants in Minamata (high exposure area), 1,700 in Goshonoura (middle exposure area), and 913 in Ariake (low exposure area). Compared to the Ariake area, participants in the Minamata area manifested psychiatric symptoms more frequently: PORs for impairment of intelligence and mood and behavioral dysfunction were 5.2 (95% CI: 3.7–7.3) and 4.4 (95% CI: 2.9–6.7), respectively. Furthermore, participants with psychiatric symptoms in the Minamata area more frequently had neurological signs. Peaks in prevalence of psychiatric symptoms occurred around age 20 and in older age adults in the area. These findings did not change when we excluded those who had been officially certified as Minamata disease patients by that time.

Conclusions: The present study suggests a relationship between pre- or postnatal exposure to methylmercury and psychiatric symptoms among the general population in

Minamata even after excluding officially certified patients.

Keywords

Environmental pollution, Epidemiological studies, Methylmercury compounds, Minamata disease, Prenatal exposure delayed effects, Psychiatric disorders

Abbreviations

CI: confidence interval

POR: prevalence odds ratio

1. Introduction

It is well-known that prenatal or postnatal exposure to methylmercury can cause neurological dysfunction in adults and children (U.S.EPA. 1997). In a large-scale poisoning caused by methylmercury in Minamata, Japan, patients manifested neurological signs, including ataxia, paresthesia, constriction of the visual field, dysarthria, and hearing difficulties (Harada 1995; Yorifuji et al. 2008). However, evidence regarding whether pre- or postnatal exposure to methylmercury causes psychiatric symptoms (e.g., impairment of intelligence or mood and behavioral dysfunction) is still limited (Wigle et al. 2008), excluding cases of fetal Minamata disease patients (described below) (Harada 1978).

In Minamata, the patients who were postnatally affected by methylmercury were termed “acquired Minamata disease patients”. One case-series study targeting acquired Minamata disease patients demonstrated a higher prevalence of psychiatric symptoms (impairment of intelligence and mood and behavioral dysfunction) than found in non-patients (Inoue 1963). However, none of the epidemiological studies have quantitatively examined the prevalence of psychiatric symptoms among the general population who had postnatal exposure to methylmercury. Indeed, the effect of methylmercury on psychiatric symptoms in adults has been seldom recognized in reviews (Clarkson et al. 2003; U.S.EPA. 1997).

In Minamata, a considerable number of children with conditions resembling cerebral palsy, so-called “fetal Minamata disease patients”, were born in the affected areas (Harada 1978). They were exposed to methylmercury in utero, and it is well-known that they manifested psychiatric symptoms such as impairment of intelligence and mood and behavioral dysfunction as well as neurological signs and motor disturbance (Harada 1964). However, it is still unknown whether residents who

experienced a more moderate exposure in utero manifested psychiatric symptoms. One study reported a higher prevalence of impairment of intelligence among adolescents born in the exposed area compared to the non-exposed area from 1955 to 1958 (period of high exposure), after excluding fetal Minamata disease patients (Harada and Tajiri 2009). Another previous study demonstrated that methylmercury concentrations in umbilical cords in fetal Minamata disease patients as well as in a group of residents with impairment of intelligence were higher than in a healthy group (Harada et al. 1999). However, studies of this type are scarce.

In the present study, we evaluated the effects of pre- or postnatal exposure to methylmercury on psychiatric symptoms using data derived from the 1971 population-based survey in Minamata and neighboring communities (Tatetsu et al. 1972; Yorifuji et al. 2008).

2. Materials and Methods

2.1. Study Site and Participants

A brief history of Minamata disease is in order. Severe neurological disorders among people living in Minamata (in the southwestern part of Kumamoto Prefecture, Japan) were first officially recognized in 1956 (Figure 1) (Harada 1995). After the first patient was officially identified in 1956, numerous cases were reported, and the first patient with disease was determined to have had it in 1942 (Nishigaki and Harada 1975). Methylmercury had been produced as a byproduct of acetaldehyde production since 1932 and was discharged into Minamata Bay (a small part of the Shiranui Sea) from a local chemical factory. In 1958, the factory rebuilt its wastewater drainage channel, diverting wastewater directly into the Minamata River (Harada 1995). As a result, methylmercury contamination spread throughout the entire Shiranui Sea (Figure 1)

(Ninomiya et al. 2005; Ninomiya et al. 1995; Yorifuji et al. 2008). Acetaldehyde production peaked in 1960 (Yorifuji et al. 2009). Then, acetaldehyde production decreased gradually, and the discharge of wastewater was stopped in 1968. Although residents voluntarily and temporarily stopped fishing in small Minamata Bay in the late 1950s, fishing in the Shiranui Sea never been stopped (Tsuda et al. 2009). Therefore, residents around the Shiranui Sea consumed contaminated fish for more than 10 years after first recognition of the disease, and for more than 25 years after the first case in 1942.

In 1971, three years after the discharge of wastewater was stopped, a population-based study of neurological signs was conducted by doctors at the Department of Neuropsychiatry at Kumamoto University School of Medicine. This was the largest cross-sectional study ever and has been described in detail elsewhere (Tatetsu et al. 1972; Yorifuji et al. 2008). Thus, we describe it only briefly here. One of the present authors (M.H.) was a member of that investigation. Neurological signs characteristic of methylmercury exposure were mainly examined in residents in the Minamata, Goshonoura, and Ariake areas (Figure 1). The Minamata area consists of three villages along Minamata Bay, and most residents there had been eating contaminated fish on a daily basis. The Goshonoura area is on the other side of the Shiranui Sea. Residents there also consumed contaminated fish; however, the distance from the factory was about 20 km. The Ariake area does not face the Shiranui Sea. It was investigated as a reference area in 1971. The combined population of the villages in each of the three areas, Minamata, Goshonoura, and Ariake, was 1,120, 1,845, and 1,165 people, respectively. In the Minamata area, 83% (934) of the total population in the study area agreed to participate in the 1971 investigation. In the Goshonoura area, 93% (1,724) of the total population in the study area participated, and in the Ariake area,

79% (915) of the total population in the study area participated. We excluded residents who had past history of cerebrovascular disease (n=18 in the Minamata area, n=12 in the Goshonoura area, and n=8 in the Ariake area), organic brain disorder (n=6 in the Goshonoura area and n=2 in the Ariake area), and congenital anomaly (n=3 in the Minamata area, n=7 in the Goshonoura area, and n=1 in the Ariake area). Consequently, the final numbers of study participants were 904 in the Minamata area, 1,700 in the Goshonoura area and 913 in the Ariake area.

2.2. Measurement of Exposure

We adopted residential area as an exposure indicator. In 1960, researchers from the Kumamoto Prefecture Institute for Health Research investigated total mercury content in hair samples of 1,694 residents living on the Coast of the Shiranui Sea, including the Minamata and Goshonoura areas (Doi and Matsushima 1996; Matsushima and Mizoguchi 1996; Ninomiya et al. 2005). As reported by Ninomiya et al. (2005), in Minamata, the median level of mercury was 30.0 μg/g, with an interquartile range of 39.8 μg/g. In Goshonoura, the median was 21.5 μg/g, with an interquartile range of 24.0 μg/g. In Kumamoto City, the most distant city from Minamata, (see Figure 1), the median was 2.1 μg/g, with an interquartile range of 1.3 μg/g. We have no hair mercury content information from our study area of Ariake. Because the Ariake Sea is connected to the Shiranui Sea by straits, fishermen in the Ariake area sometimes fished in the Shiranui Sea (Yorifuji et al. 2008). Therefore, subjects in the Ariake area may not be a truly unexposed population. However, because like Kumamoto it is on the Ariake Sea rather than the Shiranui Sea, we assume that Ariake had a similar low exposure to methylmercury. Indeed, it was reported that mercury concentration in cats' organs on the Coast of the Ariake Sea was quite low compared to that of Minamata or other areas

around Shiranui Sea in 1960 (Kitamura et al. 1960). It was also reported that, even in early 1970s, mercury content in fish in the Shiranui Sea was higher than that in Ariake Sea (Fujiki and Tajima 1973). Consequently, we considered persons living in the Minamata area as having had high exposure, those living in the Goshonoura area as having had medium exposure, and those living in the Ariake area as having had low exposure to methylmercury.

2.3. Measurement of Outcome and Covariates

In the present study, we targeted psychiatric symptoms as the health outcome examined in the investigation in 1971. The investigation was conducted from August 12, 1971 to September 22, 1971. Although a total of 249 doctors participated in the investigation, 36 doctors were mainly responsible for examining the residents. They examined the residents of the study areas as a team and visited each study area in order. Thus, the doctors examined participants across different areas. Each of these examining doctors had at least 3 years of clinical experience and was given special training in the examination methods before the investigation. Each doctor examined an average of 10–20 residents a day, and each patient was examined by just one doctor. Informed consent was obtained orally.

The primary outcome of the 1971 investigation was the presence of neurological signs characteristic of methylmercury exposure in residents, with a higher prevalence of these neurological signs reported in the Minamata area than in the reference area of Ariake (Yorifuji et al. 2008). At the time of the examination, neurological disorders as well as the following psychiatric symptoms were investigated: impairment of intelligence, mood and behavioral dysfunction, dementia, neurotic tendencies, depressive disorder, bipolar disorder, and other emotional disturbances such

as schizophrenic tendencies. Impairment of intelligence was diagnosed based on participants' thinking, understanding, reasoning, calculating ability, and memory capacity as well as their knowledge (Inoue 1963). For example, the doctors diagnosed the participants as having impairment of intelligence when they had the following symptoms: lack of initiative, slow movement or speech, memory disturbance, reduced thinking, impaired ability to concentrate, reading disorder, loss of judgment, or etc (Inoue 1963). Mood and behavioral dysfunction was diagnosed according to whether the participants were, for example, apathetic, hypobulic, perseverative, euphoric, impatient, shy, difficult to approach, or irritable (Inoue 1963). They did not examine participants using psychological batteries or constant form for the interview and they diagnosed psychiatric symptoms clinically; they thus might not have detected milder psychiatric abnormalities.

In addition, the examining doctors collected demographic characteristics including age, sex, and occupation (full-time, part-time, or non-fisherman).

2.4. Statistical Analyses

We first calculated prevalence proportions of psychiatric symptoms by residential area. We then conducted statistical tests for linear trend, treating the three groups as an ordinal variable (1 to 3), and calculated p-values to test whether an estimated line deviated from a horizontal line (Selvin 2011). When no participant in the group had symptom, we treated the group having proportion of zero in the calculation, thus we did not disregard it. Subsequently, we estimated the adjusted prevalence odds ratios (PORs) of psychiatric symptoms in relation to residential area using a logistic regression model, adjusting for age (continuous), sex (binary), and occupation (category). When we estimated PORs, we only selected psychiatric symptoms which

had more than 10 cases in each residential area to avoid unstable statistical models. We conducted the same analysis stratifying by dichotomized age category (0–38 years of age and 39 years of age or older). We divided the age categories between 38 and 39 so that each stratum had the same number of participants. Furthermore, the factory started producing acetaldehyde in 1932, 39 years before the survey (George 2001). Therefore, the younger group was exposed to methylmercury pre- and postnatally; the older group was exposed only postnatally.

Next, we calculated prevalence proportions of neurological signs characteristic of methylmercury poisoning, separated according to psychiatric symptom status (impairment of intelligence and mood and behavioral dysfunction) only in the Minamata area. The selected neurological signs were bilateral sensory disturbance, perioral sensory loss, ataxia, dysarthria, tremors, and pathologic reflexes. These signs were observed more frequently in the Minamata area than in the Ariake area in a previous study (Yorifuji et al. 2008). Bilateral sensory disturbance included glove- and stocking-type sensory loss and bilateral diffuse sensory loss.

Finally, to evaluate the potential non-linear relationships between age and psychiatric symptoms in the Minamata area, we drew scatter plots and then modeled each indicator as natural splines of age (4 degrees of freedom). Considering the fetal Minamata disease patients, we hypothesized that there was at least one peak in young generation; therefore we employed the 4 degrees of freedom a priori (Hastie and Tibshirani 1999). However, our results did not change substantially depending on the number of degrees of freedom (6 or 8 degree of freedom), hence we show the results obtained from the 4 degrees of freedom. Because the number of participants who were older than age 80 was small, we treated them as participants who were 80 years of age. As a sensitivity analysis, we conducted the same analysis excluding participants who

were officially certified as Minamata disease patients by that time (August, 1971).

All analyses were conducted by PASW version 18.0J (SPSS Japan Inc.), and p-values less than 0.05 (two-sided) were considered significant. Non-linear relationships were examined by the package “splines” in the statistical software R version 2.10.1. All confidence intervals (CIs) were calculated at the 95% level.

3. Results

Demographic characteristics of participants are shown in Table 1. The mean age and sex ratio were similar in all three areas. Fewer families in the Minamata area were supported by fishing. All of the officially certified patients by that time (n = 54) lived in the Minamata area. Among them, 11 had been diagnosed with fetal Minamata disease.

The prevalences of impairment of intelligence, mood and behavioral dysfunction, and neurotic tendencies were the highest in Minamata (high exposure area). The prevalence of dementia was the highest in Ariake (low exposure area; Table 2).

In Table 3, we show the results of logistic regression models of the main analyses for selected psychiatric symptoms (those with cases > 10). Compared with persons in the Ariake area, persons in the Minamata area manifested higher PORs for impairment of intelligence (POR = 5.2, 95% CI: 3.7–7.3) and mood and behavioral dysfunction (POR = 4.4, 95% CI: 2.9–6.7). In the Goshonoura area (medium exposure), the prevalence were lower for both outcomes. Prevalence of dementia was lower in the Goshonoura and Minamata areas; however, the result was not significant in the Minamata area. When we stratified by age, the older group in the Minamata area manifested higher PORs for impairment of intelligence and mood and behavioral dysfunction than did the younger group, although the younger group still manifested

elevated PORs compared to the Ariake area. These results did not change after we excluded those who were officially certified as Minamata disease patients by that time.

Participants who had impairment of intelligence or mood and behavioral dysfunction had all of the neurological signs more frequently than those without psychiatric symptoms (Table 4). For example, about 50% of the participants who manifested impairment of intelligence had bilateral sensory disturbance compared with only 20% of those without impairment of intelligence. Furthermore, the results did not change substantially when we excluded those who were officially certified as Minamata disease patients.

Finally, scatter plots and (non-linear) relationships of age with impairment of intelligence and mood and behavioral dysfunction are shown in Figures 2a and 2b. Although prevalence of both outcomes increased as participants became older, there was an additional peak around age 20 in each outcome. This tendency did not change after we excluded those who were already officially certified as Minamata disease patients (Figures 2c and 2d).

4. Discussion

We recovered decades-old data from Minamata and neighboring communities to evaluate the association between methylmercury exposure and psychiatric symptoms. As expected, the data demonstrated higher prevalence proportions of impairment of intelligence and mood and behavioral dysfunction in the Minamata area, in both the older and younger age groups. Furthermore, participants with psychiatric symptoms in the Minamata area more often had neurological signs. Finally, there were peaks in the prevalence of psychiatric symptoms around age 20 and in older adults in the Minamata area. These findings did not change substantially when we excluded those officially

certified as Minamata disease patients by that time (August 1971).

It has already been established that fetal Minamata disease patients manifested psychiatric disorders as well as neurological signs and motor disturbance (Harada 1964). These various disorders observed among fetal Minamata disease patients were induced by diffuse damage to the brain (Minamata Disease Research Group 1966). In contrast, neurological signs of acquired Minamata disease patients are considered to have been induced from damage to granule cells in the cerebellum and cerebral cortex (somatosensory, primary visual, and primary auditory areas) due to methylmercury intoxication (Ekino et al. 2007). However, pathology studies demonstrated that the affected brain lesions resulting from methylmercury in acquired Minamata disease patients included not only the above-mentioned areas but also the frontal cortex and other areas in the temporal or parietal cortex (Minamata Disease Research Group 1966). Therefore, given the evidence that disturbance in the frontal, temporal, or parietal cortex induces psychiatric disorders (Bradley 2008), it is likely that fetal Minamata disease patients as well as acquired Minamata disease patients manifested psychiatric disorders, which supports the present findings.

Moreover, up to now, psychiatric symptoms only among “severe” intrauterine exposure cases (i.e., fetal Minamata disease patients) were emphasized in the outbreak in Minamata (Harada 1978). However, the present findings suggest that residents who had more moderate intrauterine exposure also manifested psychiatric symptoms.

Furthermore, the finding that participants with psychiatric symptoms had neurological signs more frequently in the Minamata area supports evidence that psychiatric symptoms were induced by methylmercury exposure. However, it should be noted that not all of the participants with psychiatric symptoms had neurological signs. This finding may suggest the possibility of earlier plasticity in neurological disorders

compared to psychiatric dysfunctions because these findings were collected in 1971 (years after severe exposure in the 1950s and early 1960s). It may also suggest the possibility that exposed participants manifested psychiatric symptoms only.

The existence of two peaks in prevalence of psychiatric symptoms, at around age 20 and in older age adults in the Minamata area, provides an insight regarding populations vulnerable to psychiatric disorders. This tendency was not observed in other areas (Goshonoura and Ariake). The increased prevalence of psychiatric symptoms in older adults could be explained by the following. First, methylmercury exerted an even more severe effect on degenerating brain cells related to aging. Second, the symptoms which were originally induced by methylmercury exposure became more pronounced as the number of brain cells decreased due to aging. The other generation showing a peak of prevalence (around 20 years of age) was the same generation in which fetal Minamata disease was diagnosed. Thus, this peak could be explained by neurodevelopmental disturbance (Grandjean et al. 1997) due to severe prenatal methylmercury exposure in that generation.

In the present study, compared with participants in the reference area, participants in the Minamata area showed a higher prevalence of psychiatric symptoms. Prevalence was lower in the Goshonoura area. In other words, we could not find a dose-response relationship between residential area and psychiatric symptoms. This finding contradicts the previous finding of a clear dose-response relationship between residential area and neurological signs (Yorifuji et al. 2008). In that neurological study, the highest prevalence of neurological signs was observed in the Minamata area, although the prevalence in the Goshonoura area was also higher than in the Ariake area. This contradiction, i.e. lack of a dose-response relationship with psychiatric symptoms, may have resulted from the following two possible scenarios: First, although there was

a dose-response relationship in reality, we could not detect it and only found a spurious association due to the flawed study design. For example, the examining doctors could not spend plenty of time (e.g., 30-60 minutes) and did not examine participants using stricter criteria or psychological batteries; they thus could not have detected milder psychiatric abnormalities. Moreover, there might be other risk factors (potential confounders) related to psychiatric symptoms between areas. Second, this observed finding, i.e., lack of dose-response relationship, might show the true relationship. For example, threshold of psychiatric symptoms might be higher than that of each neurological sign characteristics of methylmercury poisoning. Moreover, the severe and longer effects in the Minamata area may have made it possible to detect effects of methylmercury poisoning on psychiatric symptoms. Indeed, although the factory had discharged methylmercury since 1932, the pollution throughout the entire Shiranui Sea, including the Goshonoura area, started to be identified after the factory diverted wastewater directly into the Minamata River in 1958 (Harada 1995). Although we could not verify which scenario was true, these situations can not explain the observed effects in the Minamata area.

In this study, the validity of residential area as an exposure indicator in the main analyses should be examined. Because fishing in the Shiranui Sea had never stopped, the residents of that coastal area (Minamata and Goshoura) were presumably exposed to methylmercury at least until 1968. Furthermore, even in 1996, mercury was still deposited at the bottom of the Shiranui Sea, making a gradient from the east (highly deposited) to the west (Tomiyasu et al. 2000). Even the deposited mercury in the west exceeded the background levels (Tomiyasu et al. 2000). Therefore, residential area as an indicator of long-term exposure to methylmercury appears to be justified.

Differential disease misclassification is possible because many doctors knew of

the famous outbreak in Minamata. However, given that every examining doctor belonged to the neuropsychiatry department at a school of medicine, had at least 3 years of clinical experience, and was trained in the methodological examination by a supervisor before the investigation, the validity of diagnosis should have been maximized. Furthermore, the association between methylmercury exposure and psychiatric symptoms was not paid much attention at that time, especially in adults, compared to the association of exposure with neurological signs. Finally, even if there was differential exposure misclassification, the bias could have induced neither such large effects observed in the present study nor differential distribution of prevalence among age groups. Although we could not adjust for the examiner effect, as described, every doctor belonged to the same department, was trained before the investigation, and examined participants across different areas, therefore the method of diagnosis should have been standardized and the differences in diagnosis among the study areas should have been minimized.

Because the participation proportion was very high in all areas, selection bias should have been negligible. However, severely affected cases died in the 1950s, and there was a population outflow due to economic problems including shortage of jobs and low income in Minamata. Therefore, selection bias resulting from these missing cases may have caused an underestimate of the true magnitude of the effects.

In conclusion, the present study suggests a relationship between prenatal or postnatal exposure to methylmercury and psychiatric symptoms even after excluding residents who had been officially certified as Minamata disease patients by that time.

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Ethics

Informed consent was obtained orally by doctors in the 1971 investigation.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Figure captions

Figure 1. Map of the study area.

Figure 2a. A scatter plot and non-linear relationship between age and proportion of impairment of intelligence. A curve of natural spline represented by a thick black line (4 degrees of freedom) and its 95% confidence interval (dotted black line) are shown.

Figure 2b. A scatter plot and non-linear relationship between age and proportion of mood and behavioral dysfunction. A curve of natural spline represented by a thick black line (4 degrees of freedom) and its 95% confidence interval (dotted black line) are shown.

Figure 2c. A scatter plot and non-linear relationship between age and proportion of impairment of intelligence after excluding officially certified Minamata disease patients. A curve of natural spline represented by a thick black line (4 degrees of freedom) and its 95% confidence interval (dotted black line) are shown.

Figure 2d. A scatter plot and non-linear relationship between age and proportion of mood and behavioral dysfunction after excluding officially certified Minamata disease patients. A curve of natural spline represented by a thick black line (4 degrees of freedom) and its 95% confidence interval (dotted black line) are shown.

Table 1. Demographic characteristics of participants in the 1971 survey by study area

	Low Exposure Ariake area n=904	**Medium Exposure Goshonoura area n=1,700**	**High Exposure Minamata area n=913**
Mean Age, y; (SD)	37 (24)	36 (24)	38 (22)
Sex; n (%)			
Women	504 (56)	908 (53)	515 (56)
Familial Occupational Status; n (%)			
Fishermen	319 (35)	732 (43)	201 (22)
Part-time fishermen	247 (27)	196 (12)	190 (21)
Nonfishermen	336 (37)	761 (45)	484 (53)
Unknown	2 (0.2)	11 (0.6)	38 (4.2)
Officially certified patients; n	0	0	54
Diagnosed with congenital Minamata disease patients among certified patients; n	0	0	11

Total number of subjects and percentages may not sum due to missing data and rounding.
SD, standard deviation.

Table 2. Number and prevalence proportion of psychiatric symptoms by study area

	Low Exposure Ariake area n=904	Medium Exposure Goshonoura area n=1,700	High Exposure Minamata area n=913	P-value for trend
Impairment of intelligence; n (%)	50 (5.5)	55 (3.2)	186 (20.4)	0.00
Mood and behavioral dysfunction; n (%)	30 (3.3)	35 (2.1)	114 (12.5)	0.00
Dementia; n (%)	20 (2.2)	13 (0.8)	10 (1.1)	0.03
Neurotic tendency; n (%)	4 (0.4)	2 (0.1)	31 (3.4)	0.00
Depressive disorder; n (%)	5 (0.6)	3 (0.2)	4 (0.4)	0.68
Bipolar disorder; n (%)	4 (0.4)	5 (0.3)	0 (0)	0.06
Other emotional disorder; n (%)	5 (0.6)	13 (0.8)	9 (1.0)	0.29

Table 3. Adjusted associations (POR and 95% CI) of residential areas with selected psychiatric symptoms

	Low Exposure[a] Ariake area n=904	Medium Exposure Goshonoura area n=1,700	High Exposure Minamata area n=913
All participants[b]			
Impairment of intelligence	1.0	0.6 (0.4 - 0.9)	5.2 (3.7 - 7.3)
Mood and behavioral dysfunction	1.0	0.6 (0.4 - 1.0)	4.4 (2.9 - 6.7)
Dementia	1.0	0.3 (0.2 - 0.7)	0.5 (0.2 - 1.2)
Stratified by age category[b]			
Age: 0-38 (ys)			
Impairment of intelligence	1.0	0.7 (0.4 - 1.2)	2.8 (1.7 - 4.6)
Mood and behavioral dysfunction	1.0	0.8 (0.4 - 1.5)	1.8 (1.0 - 3.5)
Dementia	1.0	0.3 (0.1 - 0.8)	0.5 (0.2 - 1.4)
Age: ≥39 (ys)			
Impairment of intelligence	1.0	0.4 (0.2 - 0.8)	9.9 (6.1 - 16)
Mood and behavioral dysfunction	1.0	0.4 (0.2 - 1.0)	8.3 (4.6 - 15.1)
Dementia	1.0	0.3 (0.2 - 0.7)	0.5 (0.2 - 1.2)

[a]Reference category

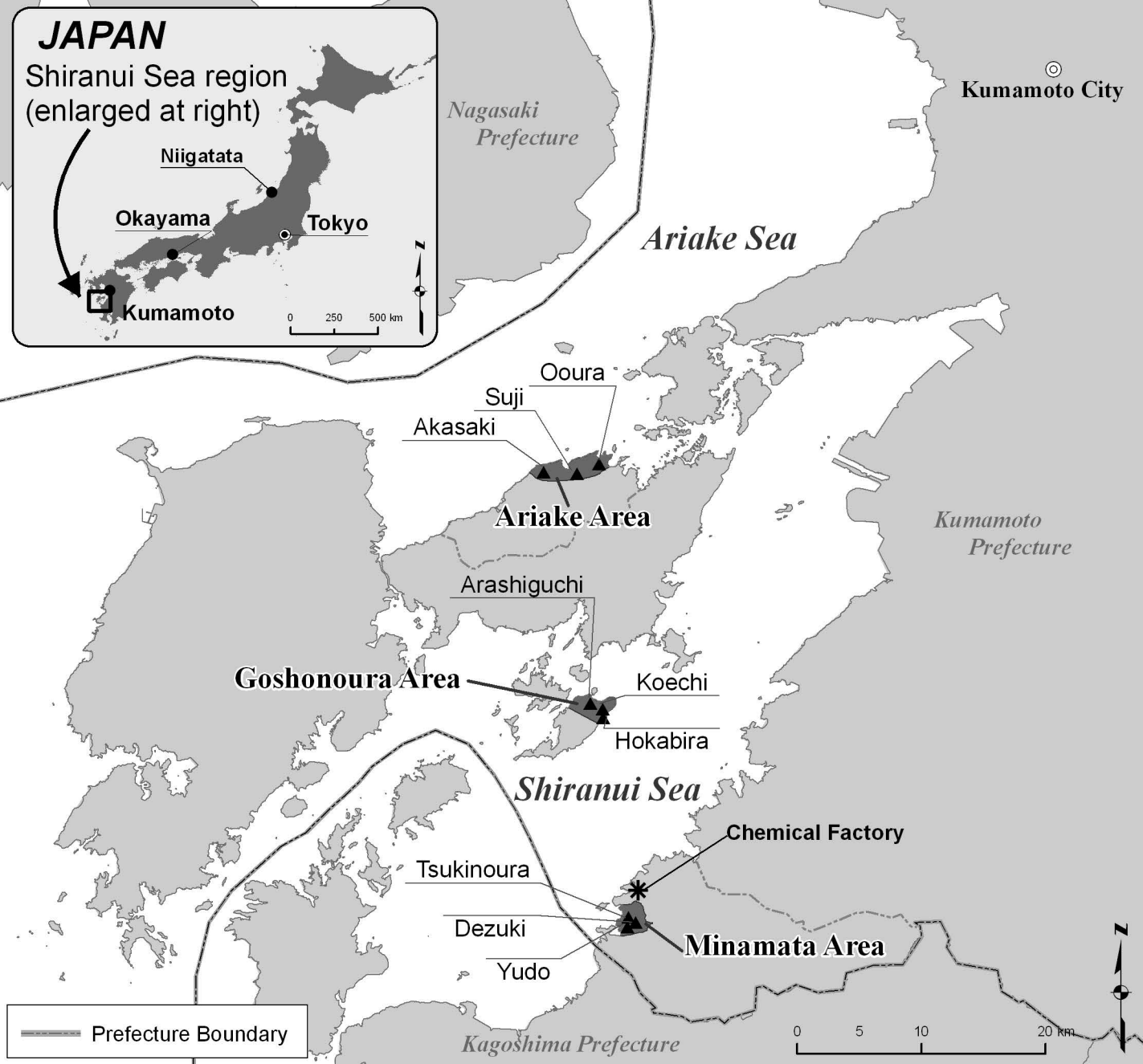
[b]Prevalence odds ratios were estimated compared with Ariake area and were adjusted for age, sex, and occupation.

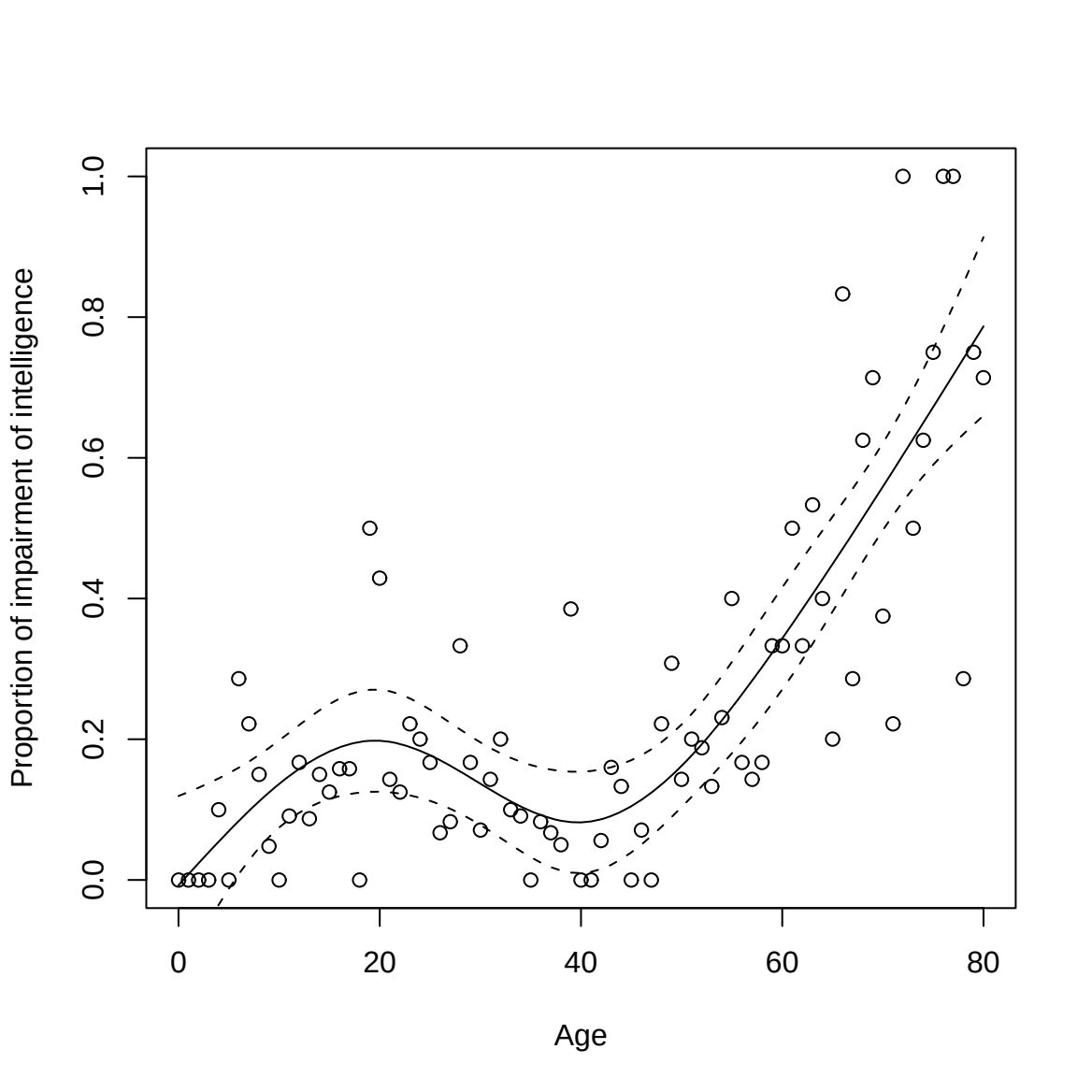
POR, prevalence odds ratio; CI, confidence interval

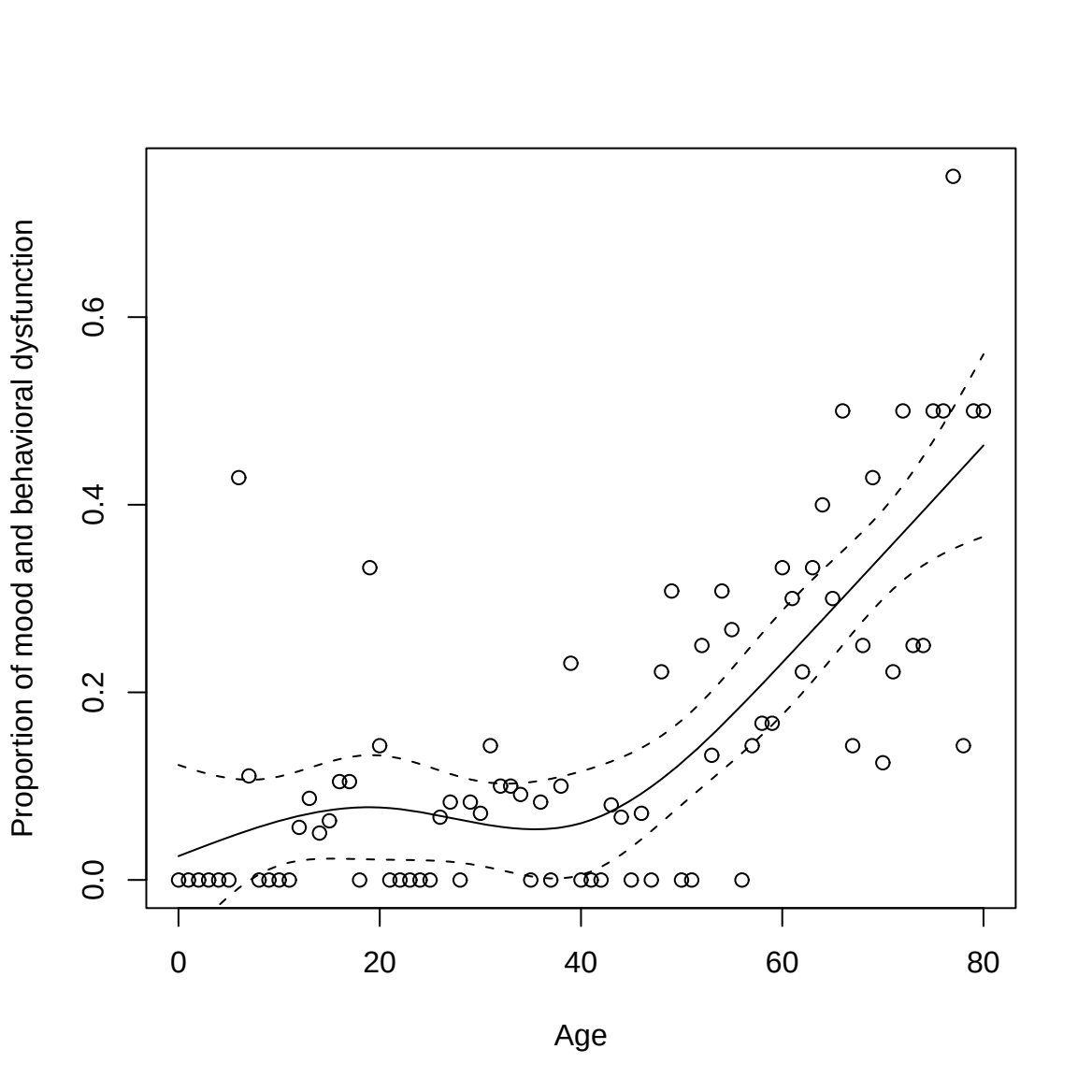
Table 4. Number and prevalence proportion of neurological signs by psychiatric symptom status of participants living in the Minamata area (*n* = 913)

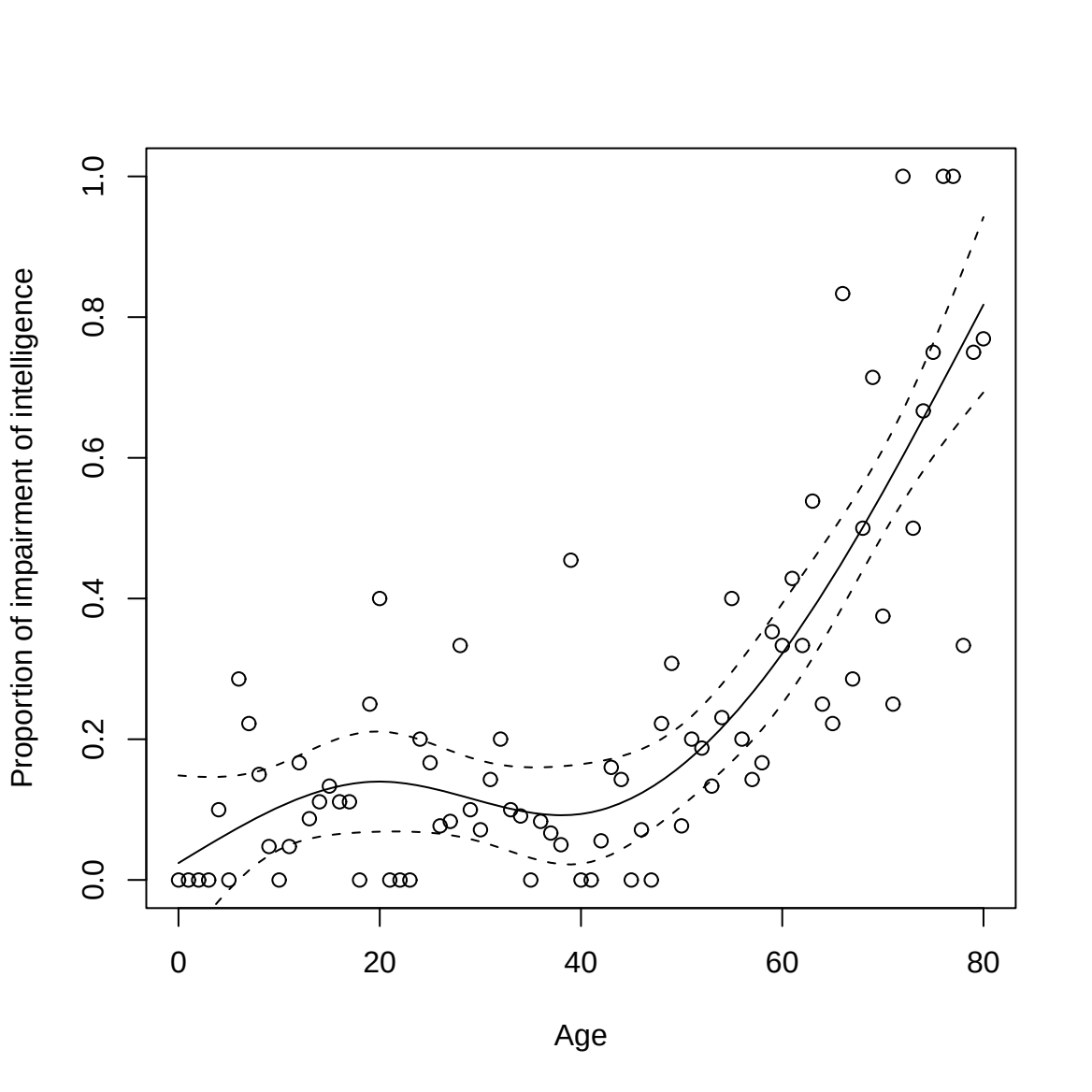
	Impairment of intelligence		Mood and behavioral dysfunction	
	Negative (n=727)	Positive (n=186)	Negative (n=799)	Positive (n=114)
Bilateral sensory disturbance[a]; n (%)	158 (21.9)	96 (52.2)	195 (24.7)	59 (51.8)
Perioral sensory loss; n (%)	53 (7.3)	44 (23.8)	69 (8.7)	28 (24.6)
Ataxia; n (%)	151 (20.8)	121 (65.1)	200 (25)	72 (63.2)
Dysarthria; n (%)	85 (11.7)	95 (51.1)	126 (15.8)	54 (47.4)
Tremors; n (%)	79 (10.9)	47 (25.3)	97 (12.1)	29 (25.4)
Pathologic reflexes; n (%)	32 (4.4)	18 (9.7)	42 (5.3)	8 (7)

[a]Bilateral sensory disturbance includes glove- and stocking-type sensory loss and bilateral diffuse sensory loss.


JAPAN
Shiranui Sea region
(enlarged at right)
Niigatata
Okayama
Tokyo
Kumamoto
0 250 500 km
N
Nagasaki Prefecture
Kumamoto City
Ariake Sea
Ooura
Suji
Akasaki
Ariake Area
Kumamoto Prefecture
Arashiguchi
Goshonoura Area
Koechi
Hokabira
Shiranui Sea
Chemical Factory
Tsukinoura
Dezuki
Yudo
Minamata Area
Prefecture Boundary
Kagoshima Prefecture
0 5 10 20 km
N


Proportion of impairment of intelligence
0.0
0.2
0.4
0.6
0.8
1.0
0
20
40
60
80
Age


Proportion of mood and behavioral dysfunction
0.0
0.2
0.4
0.6
0
20
40
60
80
Age


Proportion of impairment of intelligence
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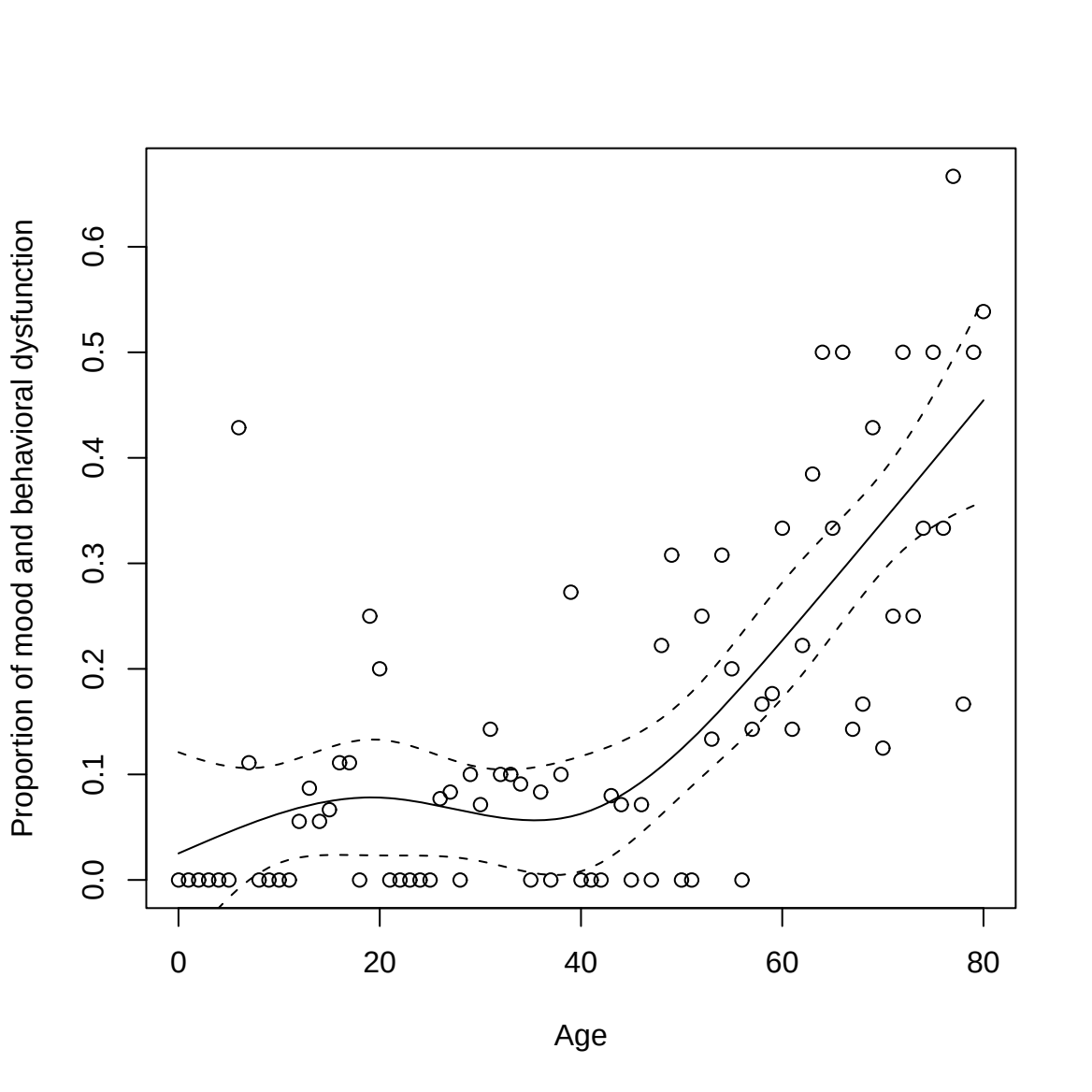
0.2
0.4
0.6
0.8
1.0
0
20
40
60
80
Age


Proportion of mood and behavioral dysfunction
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0
20
40
60
80
Age