Adolescent development of psychosis as an outcome of hearing impairment: a 10-year longitudinal study

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Background. It has long been acknowledged that hearing impairment may increase the risk for psychotic experiences. Recent work suggests that young people in particular may be at risk, indicating a possible developmental mechanism.

Method. The hypothesis that individuals exposed to hearing impairment in early adolescence would display the highest risk for psychotic symptoms was examined in a prospective cohort study of a population sample of originally 3021 adolescents and young adults aged 14–24 years at baseline, in Munich, Germany (Early Developmental Stages of Psychopathology Study). The expression of psychosis was assessed at multiple time points over a period of up to 10 years, using a diagnostic interview (Munich Composite International Diagnostic Interview; CIDI) administered by clinical psychologists.

Results. Hearing impairment was associated with CIDI psychotic symptoms [odds ratio (OR) 2.04, 95% confidence interval (CI) 1.10–3.81], particularly more severe psychotic symptoms (OR 5.66, 95% CI 1.64–19.49). The association between hearing impairment and CIDI psychotic symptoms was much stronger in the youngest group aged 14–17 years at baseline (OR 3.28, 95% CI 1.54–7.01) than in the older group aged 18–24 years at baseline (OR 0.82, 95% CI 0.24–2.84).

Conclusions. The finding of an age-specific association between hearing impairment and psychotic experiences suggests that disruption of development at a critical adolescent phase, in interaction with other personal and social vulnerabilities, may increase the risk for psychotic symptoms.

Introduction

Recent meta-analyses of general population surveys suggest that psychometric liability for psychosis in the form of subclinical psychotic experiences, such as paranoid delusional thinking and fleeting auditory hallucinations, is present in 5–10% of healthy people (van Os *et al.* 2009; Linscott & van Os, 2010). There is consistent evidence that the highest rates are observed in adolescents and young adults (Verdoux *et al.* 1998; Peters *et al.* 1999; Rossler *et al.* 2007; Lataster *et al.*

2009). Follow-up studies indicate that the majority of low-grade psychotic phenomena are benign and transitory (Hanssen *et al.* 2005; Cougnard *et al.* 2007). However, there is evidence from two birth cohorts (Poulton *et al.* 2000; Welham *et al.* 2009), three representative general population cohorts (Hanssen *et al.* 2005; Dominguez *et al.* 2009; Weiser *et al.* 2009) and other longitudinal work (Chapman *et al.* 1994) that low-grade psychotic experiences such as delusional thinking and mild hallucinatory experiences may precede the diagnosis of psychotic disorder and hospital admission for schizophrenia by many years. It has been suggested that environmental risk factors operating in early adolescence may interact with background genetic risk (van Os *et al.* 2008) in producing low-grade delusional ideation and

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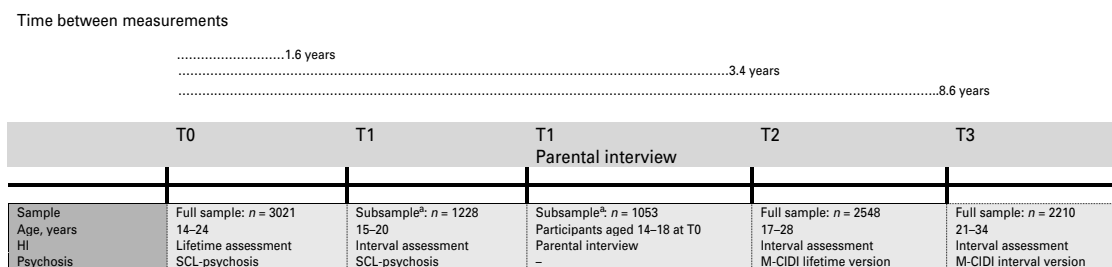
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Time between measurements

Fig. 1. Design of the Early Developmental Stages of Psychopathology Study. The time-line shows the assessments at each time point. [a] The subsample of participants aged 14–17 years at baseline. For 1053 of these, parental interviews were completed. Parental reports of childhood hearing impairment (HI) were available for 723 participants. T0, Time 0 (baseline investigation); T1, time 1 (follow-up investigation 1); T2, time 2 (follow-up investigation 2); T3, time 3 (follow-up investigation 3); SCL, self-report Symptom Checklist; M-CIDI, Munich Composite International Diagnostic Interview.

hallucinatory experiences that in some cases, if persistent, may progress to full-blown clinical psychotic states (Dominguez et al. 2009; Kaymaz & van Os, 2010).

There is evidence suggesting that hearing impairment (HI) increases the risk for psychosis (Stefanis et al. 2006; van der Werf et al. 2007), particularly in young people (David et al. 1995; Thewissen et al. 2005). Although the mechanism by which HI may increase risk for psychosis in young people remains elusive, a number of hypotheses have been put forward. First, HI and psychosis may be the consequence of a common underlying cause. For example, exposure to perinatal infections affecting the central nervous system, such as rubella and meningitis (Brown et al. 2000; Leask et al. 2002; Dalman et al. 2008), may explain the association between early HI and later psychosis. Second, psychotic experiences may be a direct or indirect consequence of processes triggered by hearing loss. For example, experimental studies have demonstrated psychotomimetic effects induced by sensory deprivation (Leff, 1968; Mason & Brady, 2009). In addition, it has been proposed that hearing loss may indirectly increase psychosis risk through social defeat stress (Selten & Cantor-Graae, 2007). Finally, HI originating early in life may have an impact on risk for psychosis by interfering with critical developmental phases for language, cognition and social skills (Bess et al. 1998).

The current investigation focused on the expression of psychosis in adolescents with HI. It was hypothesized that adolescent HI, particularly in the phase of early adolescence, would be associated with an increased risk for psychotic symptoms. We relied on assessments of psychotic experiences by trained and experienced clinical psychologists in order to reduce the risk of false positive ratings. In addition, the longitudinal design allowed for the examination of possible alterations in exposure assessment induced by high levels of psychosis proneness at baseline.

Method

Sample and study design

The Early Developmental Stages of Psychopathology (EDSP) Study is a prospective longitudinal cohort community study which collected data on the prevalence, incidence, risk factors and course of mental disorders. Following ethics committee approval, the sample was randomly drawn from the 1994 government population registers. The sample consisted of adolescent and young adults living in the Munich area (Germany), aged 14 to 24 years at baseline. Participants completed a baseline investigation (T0) and three follow-up investigations (T1, T2 and T3). At baseline, 3021 interviews were completed (response rate: 71%). Because the study primarily intended to examine the incidence and developmental risk factors for psychopathology, the younger group (14–15 years) was sampled at twice the rate of persons aged 16–21 years, and the oldest group (22–24 years) was sampled at half this rate. Furthermore, participants aged 14–17 years were assessed three times (T1, T2, T3) and participants aged 18–24 years were assessed only two times (T2, T3) after baseline. The follow-up periods had mean durations of approximately 1.6 years (T0–T1, s.d. = 0.2), 3.4 years (T0–T2, s.d. = 0.3) and 8.6 years (T0–T3, range 7.4–10.6 years, s.d. = 0.7). The risk set consisted of the 3021 individuals at baseline and their T1 (n = 1228, response rate = 88%), T2 (n = 2548, response rate = 84%) and T3 (n = 2210, response rate = 73%) follow-up measurements. Fig. 1 shows an overview of the study design and lists the measurements conducted at the different time points. Written informed consent was obtained from all participants. More detailed information about the EDSP Study can

be found elsewhere (Wittchen *et al.* 1998*b*; Lieb *et al.* 2000).

Instruments

Assessment of psychotic experiences

Psychotic experiences were assessed using the computer-assisted version of the Munich Composite International Diagnostic Interview (DIA-X/M-CIDI) (Wittchen & Pfister, 1997), an updated version of the World Health Organization's CIDI version 1.2 (WHO, 1990). The DIA-X/M-CIDI is a comprehensive, fully standardized computer-assisted diagnostic interview for the assessment of symptoms, syndromes and diagnoses of various mental disorders in accordance with the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria, along with information about psychosocial impairment as well as the onset, duration and severity of symptoms. The DIA-X/M-CIDI was developed specifically for use in adolescents and young adults. High validity (Reed *et al.* 1998) and high inter-rater and test–retest reliability of the CIDI have previously been shown (Wittchen, 1994; Wittchen *et al.* 1998*a*). Fully trained and experienced clinical psychologists, who were allowed to probe with clinical follow-up questions, conducted the interviews to ensure validity and reliability of assessments. The lifetime version of the DIA-X/M-CIDI was used at baseline and the interval version was applied at each of the follow-ups, covering the respective time periods between interviews.

The presence of psychotic experiences was assessed using the 20 core psychosis items of the DIA-X/M-CIDI-G section (G1, G2a, G3–G5, G7–G13, G13b, G14, G17, G18, G20, G20c, G21 and G22a) including symptoms of delusions, hallucinations and passivity phenomena. Participants first read a list of all the psychotic experiences and were then asked whether they ever experienced these symptoms (list and phrasing available upon request). All items could be rated as absent or present, without intermediate levels. Data on the DIA-X/M-CIDI-psychosis section were collected at T2 (lifetime version) and T3 (interval version) only. The mean interval between T2 and T3 measurements was 4.9 years. Two different outcome measures were created: (i) a dichotomous variable indicating the presence or absence of at least one positive rating on the 20 core psychotic items (hereafter: CIDI-psychosis) and (ii) in order to examine dose–response in the association between HI and psychotic experiences at increasing levels of psychosis severity, four progressively stricter psychosis subcategories were constructed (hereafter: CIDI-psychosis severity) with: no symptoms (0), one or two symptoms

(1), three or four symptoms (2) and at least five symptoms (3).

In addition, participants completed the self-report Symptom Checklist-90-Revised at T0 (SCL-90-R; Derogatis, 1983). The SCL-90-R is a multidimensional self-report symptom inventory that assesses psychopathology as a continuous dimension of human experiences and enables screening of nine dimensions of psychopathology (Derogatis, 1983; Arrindell & Ettema, 2003). Reliability and validity have been established previously (Bonicatto *et al.* 1997). Baseline psychosis proneness was assessed using the paranoid ideation (six items) and psychoticism (10 items) subscales. These subscales include self-reports on psychotic experiences that can be regarded, if not as clear-cut psychotic symptoms, as an expression of psychosis proneness. In accordance with previous analyses in this sample (Henquet *et al.* 2005), the total scores of both subscales were combined into a single dimension reflecting psychotic experiences. In line with previous work (Henquet *et al.* 2005), and as validated recently (Dominguez *et al.* 2009), baseline psychosis proneness was defined dichotomously as the group of participants with the highest 10% of scores (hereafter: SCL-psychosis).

T0–T3 assessment of HI

The presence of HI was based on self-report and assessed at T0 (lifetime assessment) and over the T0–T1, T1–T2 and T2–T3 intervals (interval assessments). The assessment was included in a questionnaire enquiring about a range of somatic complaints, including sensory deficits. At T0, participants were asked the following question: 'Did you ever experience a period in which you were unable to hear anything at all?', yielding a binary exposure variable. At the T1, T2 and T3 follow-ups, HI was assessed using the same question, restricted to the interval since the last interview. Since complete deafness was an exclusion criterion for EDSP study participation at baseline, the impairment assessed referred to a period of transient or permanent severe HI. The most common causes of severe hearing loss that may temporarily or permanently affect young people include syndromal or non-syndromal genetic disorders, prenatal and perinatal infections and noise exposure (for reviews, see Olusanya & Newton, 2007; Tharpe & Sladen, 2008).

Childhood HI

Although previous work suggests that self-reported HI has adequate sensitivity and specificity (Sindhusake *et al.* 2001), an additional parental indicator of childhood HI was used to validate the exposure of HI in the current study. A parental

investigation was conducted at T1 in the subsample of participants aged 14–17 years at baseline ($n = 1053$). Using a standardized checklist (Wittchen *et al.* 1999), information was gathered about family and early childhood variables, including sensory deficits. Parental reports of childhood HI, rated dichotomously, were available for 723 participants.

Statistical analysis

All analyses were conducted in Stata, version 10 (StataCorp., USA). Prevalence estimates of HI and cumulative lifetime incidence of CIDI-psychosis were calculated. As data were acquired at multiple points in time, associations between exposure and outcome were analysed with data in the long format, i.e. each individual in the study contributed multiple observations (the variable 'time' expressing the number of measurements for each person, with a maximum of four measurements at T0, T1, T2 and T3). Clustering of observations within subjects was controlled for by adjusting for the variable 'time' in the model. Based on previous work, all analyses were adjusted for sex, age at baseline and education (low, medium, high). As young people may acquire hearing loss at a young age by attending pop concerts, during which exposure to illicit drugs may also occur, analyses were additionally adjusted for use of any illicit drugs at baseline (including cannabis, amphetamine, cocaine and other stimulants) at least five times lifetime ('0' no, '1' yes).

Association between HI and psychotic experiences at T2 and T3

The association between HI and CIDI-psychosis at T2 and T3 was examined by logistic regression analysis, with associations expressed as odds ratios (ORs) and their corresponding 95% confidence intervals (CIs). In order to exclude the possibility that any association between HI and psychotic symptoms would be confounded by high levels of baseline psychosis proneness (given that this measure may possibly be associated with over-reporting of HI and, independent of that, with psychotic symptoms at follow-up), analyses of association between HI and T2–T3 CIDI-psychosis were repeated with additional adjustment for T0 SCL-psychosis. In addition, analyses were also repeated on a subsample from which participants with the 50% highest baseline SCL-psychosis scores were excluded. Finally, as previous research has shown that the effect of certain predictors of psychosis [e.g. cannabis (Henquet *et al.* 2005) and childhood trauma (Spauwen *et al.* 2006)] is stronger in individuals already showing some degree of psychosis proneness at baseline, we examined whether the association between HI and T2–T3 CIDI-psychosis was stronger in

those with higher levels of baseline psychosis proneness. To this end, a HI × baseline SCL-psychosis interaction term was included in the model.

Associations at different levels of psychosis severity

The magnitude of the association between HI and different levels of psychosis severity was examined using multinomial logistic regression with the Stata MLOGIT routine, with the lowest psychosis-severity subcategory serving as the reference group.

Age-dependent association

The hypothesized age-dependent association between HI and psychosis was tested by splitting the baseline sample around the median age, creating a young (14–17 years) and an old (18–24 years) age group. An age × HI interaction term was fitted followed by calculation of age-stratified effects from the model including the interaction by applying the appropriate linear combinations using the Stata LINCOM routine.

Childhood HI

In order to validate the self-report measure of HI used in the current study, the association between childhood HI (based on parental report; see Fig. 1), and T0 HI (which should include any childhood experience of HI) was assessed by logistic regression analysis. In addition, the association between childhood HI and baseline SCL-psychosis was examined using logistic regression analysis. Finally, the association between HI and CIDI-psychosis was examined after excluding all individuals with HI whose parents had not reported a similar impairment during childhood.

Results

Mean age at baseline was 18.3 years (S.D. = 3.3) and 49.3% were male. The cumulative lifetime incidence of CIDI-psychosis at T3 was 17.9% ($n = 848$). The prevalence of HI over time was: T0 = 92 (3.1%), T1 = 8 (0.7%), T2 = 18 (0.8%) and T3 = 33 (1.6%), yielding a total of 151 (1.8%) observations of HI. Of the subjects, seven reported HI at two time points and one at three time points. Neither CIDI-psychosis (OR 0.99, 95% CI 0.97–1.01) nor HI (OR 1.04, 95% CI 0.99–1.09) were associated with age.

Association between HI and psychotic experiences at T2–T3

There were 47 participants who reported HI at either T2 or T3, and two participants who reported HI at both T2 and T3, yielding a total of 51 observations of HI in

Table 1. *Associations between cumulative lifetime incidence of hearing impairment (time points T0 to T3) and psychotic symptoms (CIDI-psychosis) at different levels of severity*

CIDI-psychosis	Outcome level	Hearing impairment n^a (%)	No hearing impairment n^a (%)	Unadjusted model RR (95% CI)	Adjusted model[b] RR (95% CI)
Severity level	No symptoms[c]	36 (70.6)	3543 (81.7)	–	–
	1–2 symptoms	8 (15.7)	623 (14.4)	1.46 (0.67–3.18)	1.41 (0.65–3.08)
	3–4 symptoms	4 (7.8)	116 (2.7)	4.14 (1.43–11.98)	3.82 (1.31–11.17)
	5 or more symptoms	3 (5.9)	56 (1.3)	6.33 (1.87–21.41)	5.66 (1.64–19.49)

T0, Time 0 (baseline investigation); T3, time 3 (follow-up investigation 3); CIDI, Composite International Diagnostic Interview; RR, relative risk; CI, confidence interval.

[a] *n* Refers to multiple observations clustered in individuals.

[b] Adjusted for sex, education, drug abuse and time.

[c] Reference category.

the combined T2–T3 assessments. The association between HI and CIDI-psychosis was significant (OR 2.16, 95% CI 1.17–4.01). Adjustment for age, sex, education and drug abuse (OR 2.04, 95% CI 1.10–3.81) and baseline SCL-psychosis (OR 1.99, 95% CI 1.06–3.73) did not attenuate the association.

The magnitude of the association with HI increased with increasing levels of CIDI-psychosis severity (Table 1). A negative interaction between HI and age was apparent in the model of CIDI-psychosis ($\chi^2 = 5.86$, $p = 0.016$). Stratified analyses indicated that the association was strong in young (age 14–17 years: OR 3.28, 95% CI 1.54–7.01), but not in older participants (age 18–24 years: OR 0.82, 95% CI 0.24–2.84). There was no evidence for moderation by baseline SCL-psychosis ($\chi^2 = 0.00$, $p = 0.99$). Finally, the association remained large and significant after exclusion of participants with the 50% highest SCL-psychosis scores at baseline (OR 4.15, 95% CI 1.25–13.82).

Childhood HI

In the subsample with parental reports of childhood HI ($n = 723$), 36 participants were rated positive for childhood HI (5.0%). Childhood HI was strongly associated with the T0 self-report of HI (OR 13.08, 95% CI 4.79–35.67). In addition, childhood HI was strongly associated with the continuous baseline SCL-psychosis score (adjusted $b = 2.15$, 95% CI 0.26–4.03). Finally, the adjusted OR for the association between HI and CIDI-psychosis, excluding individuals with a self-report of HI that was not matched by parental report of childhood HI, was 5.61 (95% CI 0.34–91.4).

Discussion

The finding of an association between HI and psychotic symptoms replicates earlier work (Stefanis *et al.* 2006; van der Werf *et al.* 2007). There was evidence for a dose–response relationship, as the association grew stronger with increasing levels of symptom severity. In a subsample with parental reports of childhood sensory deficits, childhood HI similarly predicted later psychotic experiences. Finally, the association was restricted to young adolescents, which is congruent with recent accounts of an age-dependent association between HI and psychosis (Stefanis *et al.* 2006; van der Werf *et al.* 2007). The age-dependent effect of HI suggests that disruption of development during a critical phase, in interaction with other social and personal vulnerabilities, may render an individual more susceptible to psychotic interpretations of internal and external stimuli (Kapur *et al.* 2005).

HI and psychosis: a shared cause?

Numerous conditions in young people may affect hearing acuity, resulting in transient or permanent impairment (for reviews, see Olusanya & Newton, 2007; Tharpe & Sladen, 2008). Causes of HI in young people that may also have an impact on the risk for psychotic experiences include birth trauma (Herrgard *et al.* 1995) and prenatal and postnatal exposure to infections (Dalman *et al.* 2008; Zammit *et al.* 2009). Rubella and meningitis may harm the developing central nervous system, and exposure has been associated with an increased risk for both hearing deficits (Fortnum & Davis, 1993) and psychosis (Brown *et al.* 2000; Leask *et al.* 2002; Dalman *et al.* 2008). Thus, HI and psychosis may be the result of a single underlying causative mechanism. This hypothesis is strengthened by a study reporting that rubella increased the risk for non-affective psychotic disorder independent of HI (Brown *et al.* 2000).

HI and psychosis: causality?

Not hearing what other people say may, directly or indirectly, trigger paranoid ideation and hallucinatory experiences. There is experimental evidence that sensory deprivation, mimicking profound hearing loss, induces feelings of paranoia and hallucinations (Leff, 1968; Mason & Brady, 2009). Sensory restriction may not only produce patterns of nerve impulses that give rise to hallucinatory experiences (Schultz & Melzack, 1991), it may also result in reality-testing failures when the input from the outside world is significantly reduced. Failures of reality testing may cause a person to misattribute internal events to an external source. This mechanism may underlie the experience of hallucinations (Leff, 1968; Bentall, 1990). Second, social adversity has been shown to mould the risk for psychosis (Boydell *et al.* 2004; Veling *et al.* 2007). HI, whether originating early in life, or acquired later in life, is associated with social isolation, low self-esteem and increased feelings of loneliness and stress (Romans-Clarkson *et al.* 1990; Bess *et al.* 1998; Paykel *et al.* 2000; Kramer *et al.* 2002). The adverse emotional and social consequences of HI may give rise to social defeat stress (Selten & Cantor-Graae, 2007). Prolonged exposure to social defeat stress may represent an intermediate mechanism linking multiple environmental exposures to an underlying biological mechanism of psychosis (Selten & Cantor-Graae, 2007; van Winkel *et al.* 2008). Thus, social defeat stress may mediate the link between HI and psychosis.

HI and psychosis: developmental impact?

Finally, HI with onset early in life may compromise the development of language, cognition and social skills (Bess *et al.* 1998), giving rise to developmental alterations as observed in children destined to develop psychotic symptoms later in life (Cannon *et al.* 2002). Language and cognitive problems associated with HI may thus contribute to an increased risk in young people with a pre-existing vulnerability for psychosis. In addition, persecutory delusions and auditory hallucinations may develop as a result of delays in the acquisition of Theory of Mind (Frith, 1992; Janssen *et al.* 2003) in children with HI. Theory of Mind abilities normally emerge during preschool years (Peterson *et al.* 2005) and are highly dependent on day-to-day social interactions (Russell *et al.* 1998). Selective deprivation of access to these early conversations by HI during critical developmental phases may interfere with Theory of Mind acquisition. Evidence to support this notion comes from studies showing significant delays in the mastery of Theory of Mind in hard-of-hearing children (Marschark, 1993; Peterson &

Siegal, 1995, 1998). Thus, HI originating early in life may have an impact, during critical developmental phases, on language, cognition and social skills, increasing the risk for psychosis.

HI and psychosis: towards a multifactorial model

The association between HI and psychosis shows variation with age. Although the evidence to date suggests an increased risk in young people (David *et al.* 1995; Stefanis *et al.* 2006), the association has also been found in older people (Cooper & Curry, 1976; Stein & Thienhaus, 1993). This latter implies the operation of multiple mechanisms contributing to the increase in psychosis risk, with differential impact across the age span. HI with onset during critical developmental phases may have an impact on risk by delaying the development of social reasoning skills, language and cognition, whilst other mechanisms may be operating in people who acquire HI later in life. Considering the negative impact of HI on perceived quality of life, as expressed by increased feelings of loneliness and a tendency for social isolation, social defeat stress may represent a more general mechanism mediating the link between HI and psychosis, regardless of age. Therefore, to the degree that HI moulds risk for psychosis, it is likely to do so in combination with a range of other factors.

Limitations

Several limitations should be considered when interpreting these results. First, the study used a measure of HI that was based on self-report and consisted of a single question. Although this may not seem a very reliable measure, self-reports of HI have been found to yield reasonable sensitivity and specificity (Sindhusake *et al.* 2001). Also, EDSP interviewers were allowed to follow-through with follow-up questions to clarify if participants had understood the question. Finally, parental reports of childhood HI were strongly associated with T0 HI, suggesting validity in the sense that adolescent HI was continuous with earlier permanent or recurrent HI. In addition, the validity of the findings was supported by the fact that if exposure status was restricted to those participants with HI who also had evidence of childhood HI according to parental report, the OR was also very high, albeit statistically inconclusive due to the small number of participants. Furthermore, to the degree that misclassification may have arisen, it is difficult to see how this could have been differential with regard to the psychosis outcome.

Second, the assessment of psychotic experiences confers the risk of false-positive answers, increasing

random error. However, not only was the DIA-X/M-CIDI specifically developed for use in young and adolescent populations, there is also a substantial literature on the validity of self-reported psychotic experiences (van Os *et al*. 2009). In addition, the assessment of psychotic experiences in the current study was based on both self-report and diagnostic interview by trained and experienced clinical psychologists, lowering the risk for false-positive ratings.

Finally, although observational studies cannot provide evidence for causality in the association between HI and psychotic symptoms, no evidence to date exists to support reverse causality (psychosis provoking spurious reports of having impaired hearing). Furthermore, the association remained highly significant after exclusion of those people at baseline with high psychosis scores, rendering reverse causality as an explanation for the findings less likely.

Declaration of Interest

R.L. has received speaker honoraria from Wyeth. H.W. has received research support from Novartis, Pfizer and Schering-Plough, has been a consultant for Novartis, Pfizer, Wyeth, Organon and Lundbek, and has received speaker honoraria from Novartis, Schering-Plough, Pfizer, Wyeth and Servier. J.v.O. is/has been an unrestricted research grant holder with, or has received financial compensation as an independent symposium speaker from, Eli Lilly, BMS, Lundbeck, Organon, Janssen-Cilag, GSK, AstraZeneca, Pfizer and Servier – companies that have an interest in the treatment of psychosis.

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