Does normal developmental expression of psychosis combine with environmental risk to cause persistence of psychosis? A psychosis proneness–persistence model

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ABSTRACT

Background. Research suggests that low-grade psychotic experiences in the general population are a common but transitory developmental phenomenon. Using two independent general population samples, the hypothesis was examined that common, non-clinical developmental expression of psychosis may become abnormally persistent when synergistically combined with developmental exposures that may impact on behavioural and neurotransmitter sensitization such as cannabis, trauma and urbanicity.

Method. The amount of synergism was estimated from the additive statistical interaction between baseline cannabis use, childhood trauma and urbanicity on the one hand, and baseline psychotic experiences on the other, in predicting 3-year follow-up psychotic experiences, using data from two large, longitudinal, random population samples from the Netherlands [The Netherlands Mental Health Survey and Incidence Study (NEMESIS)] and Germany [The Early Developmental Stages of Psychopathology (EDSP) study].

Results. The 3-year persistence rates of psychotic experiences were low at 26% in NEMESIS and 31% in EDSP. However, persistence rates were progressively higher with greater baseline number of environmental exposures in predicting follow-up psychotic experiences ($\chi^2 = 6.9$, df = 1, $p = 0.009$ in NEMESIS and $\chi^2 = 4.2$, df = 1, $p = 0.04$ in EDSP). Between 21% and 83% (NEMESIS) and 29% and 51% (EDSP) of the subjects exposed to both environmental exposures and psychotic experiences at baseline had persistence of psychotic experiences at follow-up because of the synergistic action of the two factors.

Conclusion. The findings suggest that environmental risks for psychosis act additively, and that the level of environmental risk combines synergistically with non-clinical developmental expression of psychosis to cause abnormal persistence and, eventually, need for care.

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INTRODUCTION

Recent lines of evidence suggest an interactive developmental model of psychosis (Cunningham Owens & Johnstone, 2006). First, the expression of psychosis, whether it be psychotic disorders (prevalence 1%), isolated psychotic symptoms (prevalence around 5%) or broadly defined psychotic experiences (prevalence around 15%) is much more common in young people and declines with age (Verdoux *et al.* 1998; Peters *et al.* 1999; Van Os *et al.* 2000; Johns & Van Os, 2001; Myin-Germeys *et al.* 2003). Second, follow-up studies of young people with expression of psychosis at the subclinical level reveal that the great majority do not display psychosis at any level at follow-up (Hanssen *et al.* 2005). Third, the expression of psychosis at the subclinical or 'schizotypal' level clusters in families and is influenced in part by genetic factors (Linney *et al.* 2003; Hanssen *et al.* 2006). Finally, the generally good (because the symptoms are only transitory) outcome of subclinical psychotic experiences can be modified to poorer outcomes of persistence and clinical need for care if subjects are exposed to additional (proxy) environmental risk factors. Examples of these are trauma (Spauwen *et al.* 2006*b*), cannabis (Van Os *et al.* 2002; Henquet *et al.* 2005) and urbanicity (Van Os *et al.* 2003, 2004; Spauwen *et al.* 2004, 2006*a*).

The above findings suggest a model of psychosis that considers genetic background factors impacting on a broadly distributed and transitory population expression of psychosis during development, poor prognosis of which, in terms of persistence and clinical need, is predicted by environmental exposures interacting with genetic risk. In other words, transitory developmental expression of psychosis may become abnormally persistent and clinically relevant depending on the degree of environmental risk the person is additionally exposed to (Fig. 1). In the current paper, this model was tested in two separate samples, using measures of environmental risk combining several likely environmental exposures. In addition, recent statistical models of interaction (Darroch, 1997; Van Os & Sham, 2003) allow for estimation of the amount of synergy between environmental risks and developmental expression of psychosis, as an indication of the morbidity
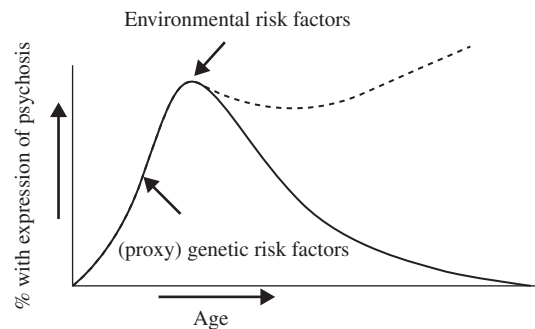

Fig. 1. Development of psychotic disorder: abnormal persistence (---) of developmental expression of psychosis.

specifically caused by the combination of the two factors.

METHOD
Sample

The Netherlands Mental Health Survey and Incidence Study (NEMESIS)

NEMESIS is a study of the prevalence, incidence, course and consequences of psychiatric disorders in the Dutch general population. The overall design of the study is prospective (3 years), consisting of a T0 baseline survey in 1996, and two follow-up surveys at T1 (assessing the period between T0 and T1) in 1997, and at T2 (assessing the period between T1 and T2) in 1999. A comprehensive description of the project objectives, sample procedure, response, diagnostic instruments, quality control procedures and analyses is provided in previous publications (Bijl *et al.* 1998*a, b*). NEMESIS is based on a multistage, stratified, random sampling procedure, in 90 municipalities. A sample of private households within each municipality and members with the most recent birthday within each household were selected (Bijl *et al.* 1998*a, b*). Subjects were aged 18–64 years and sufficiently fluent in Dutch to be interviewed. Individuals living in institutions were not eligible for interview. A total of 7076 individuals provided informed consent and were interviewed at T0, representing a response rate of 69·7%. Previous analyses have shown that psychopathology had only weak effects on attrition rate over the follow-up periods

and was mainly related to failure to locate and morbidity/mortality rather than refusal (de Graaf *et al.* 2000).

The Early Developmental Stages of the Psychopathology (EDSP) study

The EDSP study (Lieb *et al.* 2000) collected data on the prevalence, incidence, risk factors, co-morbidity and course of mental disorders in a random, representative population sample of adolescents and young adults (age range 14–24 years at baseline) in the Munich area (Germany). The overall design of the study is prospective (average 42 months), consisting of a baseline survey (T0, $n = 3021$), three follow-up surveys (of which only the first two were used in the current paper – T1 and T2) and a family supplement. Fourteen- to 15-year-olds were sampled at twice the rate of persons 16–21 years of age, and 22- to 24-year-olds were sampled at half this rate. Because the primary goal of the study was to examine the incidence of psychopathology, the young group with the presumed highest incidence density was included at twice the rate and the oldest group at half the rate. A complete and detailed description of design, sample, instruments, procedures and statistical methods of the EDSP is given elsewhere (Wittchen *et al.* 1998*b*).

The T0 sample was drawn in 1994 from the government registries in Munich, Germany, of registrants expected to be 14–24 years of age at the time of the T0 interview in 1995. Details about the sampling and representativeness of the whole EDSP sample, along with its socio-demographic characteristics, have been presented previously (Wittchen *et al.* 1998*b*; Lieb *et al.* 2000). A total of 3021 interviews were completed at T0 (response rate, 71%). The first follow-up study (T1) was conducted only for respondents aged 14–17 years at T0, whereas the second follow-up study (T2) was conducted for all respondents. Of the 3021 respondents of the T0 study, a total of 2548 interviews were completed at T2, which occurred at an average of 42 months after T0 (response rate 84%).

For the current report, the risk set consisted of all respondents with valid data at T0 and T2, on average 42 months later.

Instruments
NEMESIS

Subjects were interviewed at home by using the Composite International Diagnostic Inter-view (CIDI), version 1.1 (Smeets & Dingemans, 1993), at T0 ($n = 7076$), T1 ($n = 5618$) and T2 ($n = 4848$). The CIDI is a structured interview developed by the World Health Organization (WHO), and generates diagnoses pertaining to DSM-III-R (APA, 1994). It was designed for use by trained interviewers who are not clinicians. Interviewers read the questions and recorded the answers of respondents, making the CIDI essentially a self-report instrument (Eaton *et al.* 2000). At T0, the lifetime version of the CIDI was used. At each of the follow-up assessments, the CIDI interval version was applied, which refers to the period of assessment from the last interview until the present. Data on the CIDI-G-section about psychosis were collected at each assessment (T0, T1, T2). At T0 and T2, telephone clinical reinterviews were held with individuals endorsing psychotic experiences as reported previously, to correct false-positive reports (Van Os *et al.* 2001; Hanssen *et al.* 2005). At T1, no clinical reinter-views were held, but interviewers were allowed to probe with clinical follow-up questions if individuals endorsed psychotic experiences and discussed these items later with a psychiatrist.

EDSP

Subjects were assessed with the computer-assisted version of the Munich-CIDI (DIA-X/M-CIDI; Wittchen & Pfister, 1997), an updated version of the WHO CIDI version 1.2 (WHO, 1990). Diagnostic findings, according to the explicit diagnostic criteria of DSM-IV (APA, 1994), were obtained by using the M-CIDI diagnostic algorithms. Most interviews were carried out in the homes of the respondents. The M-CIDI is designed for use by trained interviewers who are not clinicians and has high inter-rater reliability and high test–retest reliability (Wittchen, 1994; Wittchen *et al.* 1998*a*). The assessment of psychotic disorders with CIDI by lay interviewers is not considered reliable (Anthony *et al.* 1985). Therefore, in the EDSP, trained psychologists who were allowed to probe with follow-up clinical questions conducted the interviews. At T0, the lifetime

version of the M-CIDI was used. At each of the follow-up assessments, the M-CIDI interval version was applied, which refers to the period of assessment from the last interview until the present.

Data on the M-CIDI-G-section about psychosis were only collected at T2, at which time lifetime ratings of psychotic experiences were made without diagnostic differentiation, yielding cumulative incidence data up to the respective age of the respondents at T2.

At T0, and again at T2, participants also completed the self-report Symptom Checklist-90-R (SCL-90-R) to screen for a broad range of psychological problems and symptoms of psychopathology. The SCL-90-R measures nine primary symptom dimensions and is designed to provide an overview of patients' symptoms and their severity (i.e. symptoms are scored dimensionally on a severity scale from 0 to 4) in the past 2 weeks. The reliability and validity of the SCL-90-R have been established previously (Bonicatto *et al.* 1997; Derogatis, 1977).

Assessment of T0 psychotic experiences

NEMESIS

The CIDI psychosis section (G-section) was used to measure psychotic experiences at T0. This section consists of 17 psychosis items concerning delusions (13 items) and hallucinations (four items): items G1–G13, G15, G16, G20 and G21. Each item is scored on a scale of 1–6: 1, no symptom; 2, psychotic symptom present but not clinically relevant (not bothered by it and not seeking help for it); 3, symptom is always the result of substance use; 4, symptom is always the result of somatic disorders or conditions; 5, true psychotic symptom; 6, interviewer is in doubt because there appears to be some plausible explanation for what appears to be a psychotic symptom. 'Baseline psychotic experiences' was defined as any CIDI rating of 2, 3, 4, 5 or 6 on any of the T0 17 CIDI psychosis items.

EDSP

The SCL-90-R subscales 'Psychoticism' and 'Paranoia' were used to measure liability for psychosis at T0. These scales include self-reports on thought interference, hallucinations and suspiciousness, and can be regarded, if not as

clear-cut psychotic symptoms, as a subclinical expression of psychotic experiences (items 7, 8, 16, 18, 35, 43, 62, 68, 76, 77, 83–85, 87, 88, 90). The T0 'Psychoticism' and 'Paranoia' scales were combined into one psychosis scale by adding their scores and dividing the sum by two as described previously (Henquet *et al.* 2005). For the purpose of the analyses, 'baseline psychotic experiences' was *a priori* defined dichotomously as the group of individuals with the highest 10% of scores as described previously (Henquet *et al.* 2005).

Assessment of psychosis outcome

NEMESIS

The ratings from the 17 CIDI core psychosis items on delusions (13 items) and hallucinations (four items) were used to assess the presence of psychotic experiences (items G1–G13, G15, G16, G20, G21). 'Follow-up psychotic experiences' in this study was defined as any CIDI rating of 2, 3, 4, 5 or 6 on any of the 17 CIDI psychosis items at T1 or T2.

EDSP

The ratings at T2 from the 15 M-CIDI core psychosis items on delusions (11 items) and hallucinations (four items) were used to assess the presence of psychotic experiences (items G3–G5, G7–G14, G17, G18, G20, G21) in the sample. All psychosis items could be rated in two ways: 0 (no) and 1 (yes). Onset of psychotic experiences was recorded as within the last year or before that time. 'Follow-up psychotic experiences' in EDSP was defined as at least one positive rating on any of the 15 M-CIDI core psychosis items.

Assessment of exposure variables
Cannabis exposure

NEMESIS

Consistent with previous work (Van Os *et al.* 2002), the L-section of CIDI assesses use of cannabis. Cannabis exposure at T0 was defined as any lifetime cannabis use.

EDSP

Consistent with previous work (Henquet *et al.* 2005), the L-section of the M-CIDI assesses use of cannabis. Cannabis exposure at T0 was defined as lifetime cannabis use of five times or more.

Trauma

NEMESIS

At T0, subjects were asked, using a semi-structured interview, whether they had experienced any kind of emotional, physical, psychological or sexual abuse before age 16 years, providing an example of each type of trauma. Subjects answered 'yes' or 'no' to each of the questions and were asked to give an indication about the frequency on a six-point scale: 1, never; 2, once; 3, sometimes; 4, regular; 5, often; 6, very often. Consistent with previous work (Janssen *et al.* 2004; Bak *et al.* 2005), in the analyses, experience of trauma was *a priori* dichotomized as follows: 'no early trauma' if the score on any item was ≤3 and 'early trauma' if the score on any item was >3.

EDSP

Self-reported lifetime exposure to trauma was measured in the entire sample using the Post-traumatic stress disorder (PTSD) and Trauma module from the CIDI at T0 (Spauwen *et al.* 2006*b*). This module started with trauma screening questions in which respondents could indicate a positive response on a visually presented list of nine groups of specified traumatic events such as 'experienced physical threat', 'experienced serious accident' or 'being sexually abused as a child'. A category of 'any traumatic event' indicated exposure to any of the nine traumata. The visual presentation of the list allowed respondents and interviewers to avoid speaking about sometimes embarrassing and stigmatizing traumata by simply indicating the number of the event. Consistent with previous work, affirmative responses to any of the events were labelled 'self-reported trauma' (Spauwen *et al.* 2006*b*).

Urbanicity exposure

NEMESIS

Consistent with previous work, the original five-level classification of the urbanization measure expressed as density of addresses per km² (Van Os *et al.* 2001, 2003) was dichotomized as follows: levels 1 (<500), 2 (500–900) and 3 (1000–1499) were coded as 0 and levels 4 (1500–2499) and 5 (≥2500) as 1.

EDSP

Consistent with previous analyses (Spauwen *et al.* 2004, 2006*a*), urbanicity was defined as the German city of Munich *versus* the surrounding areas of Munich. The population density of the surrounding areas was 553 persons per square mile and that of the city was 4061 persons per square mile.

Statistical analyses

All standard errors and tests statistics were estimated using the software package STATA, version 9.1 (StataCorp, 2005).

The dependent variable in the analyses was follow-up psychotic experiences, with environmental risk factors and baseline psychotic experiences as the independent variables. The risk of persistence of baseline psychotic experiences was defined as the strength of the association between baseline psychotic experiences and follow-up experiences. If the association between baseline psychotic experiences and follow-up psychotic experiences is significantly different for different levels of an environmental exposure (i.e. there is statistical interaction between baseline psychotic experiences and an environmental exposure), there is support for the hypothesis that this environmental exposure affects the persistence of baseline psychotic experiences.

For the analyses, the variable 'environmental load' was created. Environmental load was categorized into four levels: level 0, corresponding to no exposure (neither cannabis nor trauma nor urbanicity); level 1, corresponding to only one of the three exposures (cannabis or trauma or urbanicity); level 2, corresponding to two of the three exposures (cannabis and trauma or cannabis and urbanicity or trauma and urbanicity); and level 3, corresponding to all exposures (cannabis, trauma and urbanicity).

In line with recent advances in the conceptualization of interaction, we calculated the statistical additive interaction and estimated from that the population amount of synergism between baseline psychotic experiences and environmental load (Darroch, 1997; Van Os *et al.* 2002; Van Os & Sham, 2003). This was done using the calculations developed by Darroch (1997) (see Appendix). For these analyses, a dichotomized measure of environmental load was used (levels 0 and 1 were coded 0 and levels 2 and 3 were coded 1; hereafter: high environmental load). For all other analyses, including the statistical additive interaction, the four-level continuous Environmental

Load measure was used. To calculate the statistical interaction under an additive model, the BINREG procedure in STATA software (Stata-Corp, 2005) was used, which fits generalized linear models for the binomial family estimating risk differences (risk difference regression). Main effects were thus expressed on the additive scale (i.e. as a risk difference rather than a risk ratio). Estimates for risk differences were *a priori* adjusted for age, sex, educational level and any T0 CIDI lifetime DSM-III-R diagnosis. Interactions between environmental load and baseline psychotic experiences were fitted in the risk set of both NEMESIS and EDSP with environmental load entered both as a linear variable and as dummy variables with category 0 as the reference category, allowing estimation of baseline psychotic experiences effect sizes for each level of environmental load separately by calculating the appropriate linear combinations using the STATA LINCOM routine.

Risk set

NEMESIS

All the analyses were conducted in the group of individuals who had completed the CIDI psychosis G-section at T0 (7075 of 7076 subjects, 99·9%), whose cannabis, trauma and urban exposures were documented ($n = 7055$) and who had completed the CIDI psychosis G-section at T1 and T2 ($n = 4792$), yielding a risk set of 4786.

EDSP

All the analyses were conducted in the group of individuals who had completed the SCL-90-R subscales 'Psychoticism' and 'Paranoia' at T0 (3013 of 3021 subjects, 99·7%), whose cannabis, trauma and urban exposures at T0 were documented ($n = 2926$) and who had completed the M-CIDI psychosis G-section at T2, yielding a risk set of 2452.

Sensitivity analysis

In accordance with previous work conducted in the EDSP study sample (Spauwen *et al.* 2003, 2004), a sensitivity analysis was used in the EDSP risk set, to ensure that current findings relate only to prediction of incident psychotic experiences assessed with the M-CIDI. Thus, subjects who had reported psychotic experiences according to the M-CIDI at follow-up with onset longer than 1 year ago were excluded from the sensitivity analysis, thus ensuring that psychotic experiences reported at follow-up were not the same as those reported at baseline.

RESULTS

Subjects

In the risk set of 4786 subjects in the NEMESIS cohort, subjects were older than the 2452 subjects in the risk set of the EDSP cohort. Other differences related to demographic and instrument differences are depicted in Table 1. Of the 768 individuals with baseline psychotic experiences in NEMESIS, follow-up psychotic experiences were present in 200 (26%). Of the 229 individuals with baseline psychotic experiences in EDSP, follow-up psychotic experiences were present in 71 (31%).

Synergism between baseline psychotic experiences and environmental load

NEMESIS

The rate of follow-up psychotic experiences in the eight exposure levels defined by baseline psychotic experiences and environmental load are depicted in Table 2. For each level of exposure, the risk of having follow-up psychotic experiences was higher in subjects with baseline psychotic experiences than in the subjects without baseline psychotic experiences. The risk differences, i.e. the difference between the risk of having follow-up psychotic experiences in the groups with and without baseline psychotic experiences, separately for each level of environmental load, revealed that the association with follow-up psychotic experiences became progressively stronger as the level of environmental load went up. The risk difference effect size increased from 18·2% for unexposed subjects (environmental load '0'), to 33·9% for subjects exposed to all environmental factors (environmental load '3'). These differences in effect size were significant, as evidenced by a significant positive interaction between environmental load and baseline psychotic experiences (Wald $\chi^2 = 6·9$, df $= 1$, $p = 0·009$). This interaction changed only minimally after adjustment for age, sex, educational level and any T0 diagnosis (Wald $\chi^2 = 6·6$, df $= 1$, $p = 0·01$).

The risk of follow-up psychotic experiences, in the group with neither baseline psychotic

Table 1. *Characteristics of subjects at T0, T0 exposure, baseline psychotic experiences and follow-up psychotic experiences, the Netherlands Mental Health Survey and Incidence Study (NEMESIS) and the Early Developmental Stages of Psychopathology study (EDSP)*

	NEMESIS ($n=4786$)		EDSP ($n=2452$)	
	n	%	*n*	%
T0				
Age (years)	41·02	11·9 (18–64)	18·3	3·3 (13–25)
Gender				
Male	2227	46·5	1256	51·2
Female	2559	53·5	1196	48·8
Level of education[a]				
1	1434	30·3	298	12·2
2	1752	37·1	738	30·1
3	363	7·7	1416	57·8
4	1178	24·9	N.A.	N.A.
Any T0 DSM diagnosis[b]				
No	2880	60·2	1361	55·5
Yes	1906	39·8	1091	44·5
Exposure status				
Baseline psychotic experiences[c]				
No	4018	83·9	2223	90·7
Yes	768	16·1	229	9·3
Cannabis				
No use	4341	90·7	2131	86·8
Any use	445	9·3	321	13·2
Trauma				
Non-exposed	4157	86·9	1970	80·3
Exposed	629	13·1	482	19·7
Urbanization				
Rural	2998	62·4	728	29·7
Urban	1798	37·5	1724	70·3
Environmental load[d]				
Zero	2482	51·9	539	22·0
One	1785	37·5	1386	56·5
Two	450	9·4	440	17·9
Three	59	1·2	87	3·6
T2				
Follow-up psychotic experiences[e]				
No	4472	93·4	2026	82·6
Yes	314	6·6	426	17·4

N.A., Not applicable.

[a] NEMESIS: 1=primary, basic vocational, 2=lower secondary, 3=higher secondary, 4=higher professional university. EDSP: 1=low, 2=medium, 3=high.

[b] NEMESIS: T0 any DSM-III-R diagnosis. EDSP: T0 any DSM-IV diagnosis.

[c] NEMESIS: any Composite International Diagnostic Interview (CIDI) rating of 2, 3, 4, 5 or 6 on any of the T0 17 CIDI core psychosis items. EDSP: defined dichotomously as the group of individuals with the highest 10% of Symptom Checklist-90-R (SCL-90-R) scores.

[d] Zero=no exposure; one=subjects exposed to only one of the three exposures; two=subjects exposed to two of the three exposures; three=subjects exposed to all exposures.

[e] NEMESIS: any CIDI rating of 2, 3, 4, 5 or 6 on any of the 17 CIDI psychosis items at T1 or T2. EDSP: at least one positive rating on any of the 15 M-CIDI core psychosis items at T2.

experiences nor high environmental load (the dichotomized measure of environmental load as defined in Method section) was 2·6% (95 of 3688). For the group exposed to high environmental load alone, this was 5·8% (19 of 330), 23·6% (139/589) for those exposed to baseline psychotic experiences alone, rising to 34·1% (61/179) in those exposed to both baseline

psychotic experiences and high environmental load. Following the procedure developed by Darroch (1997) (see also formulas and tables in the Appendix), the proportion of individuals with follow-up psychotic experiences at T2 exposed to both baseline psychotic experiences and high environmental load that was attributable to the synergistic action of these factors

Table 2. *Interaction between baseline psychotic experiences and environmental load on the additive scale* (*risk difference*), *the Netherlands Mental Health survey and Incidence Study* (*NEMESIS*)

Environmental load[a]	Baseline psychotic experiences[b]	With follow-up psychotic experiences[c] (n)	Without follow-up psychotic experiences (n)	Risk of having follow-up psychotic experiences (%)	Risk difference (%)	95% CI	p
Zero	No	43	2161	1·9	18·2	13·4–22·9	0·000
	Yes	56	222	20·1			
One	No	52	1432	3·5	23·1	18·2–28·1	0·000
	Yes	83	228	26·7			
Two	No	14	285	4·7	26·4	18·6–34·2	0·000
	Yes	47	104	31·1			
Three	No	5	26	16·1	33·9	11·3–56·5	0·003
	Yes	14	14	50·0			
Additive interaction[d]					$\chi^2 = 6\cdot9$	df = 1	0·004

CI, Confidence interval; df, degrees of freedom.

[a] Zero = no exposure; one = subjects exposed to only one of the three exposures; two = subjects exposed to two of the three exposures; three = subjects exposed to all exposures.

[b] Any Composite International Diagnostic Interview (CIDI) rating of 2, 3, 4, 5 or 6 on any of the T0 17 CIDI core psychosis items.

[c] Any CIDI rating of 2, 3, 4, 5 or 6 on any of the 17 CIDI psychosis items at T1 or T2.

[d] Test for significant difference in increase in risk with one unit change in exposure rating between group with and without psychotic experiences.

was calculated. This calculation yielded figures for synergism between 0·073 and 0·283, representing respectively 21% and 83% of the psychosis risk in those exposed to both baseline psychotic experiences and high environmental load (0·073/0·341 = 21% and 0·283/0·341 = 83%). In other words, an estimated 21–83% of the individuals exposed at baseline to both baseline psychotic experiences and at least two of the environmental risk factors under examination had persistence of psychotic experiences at follow-up because of the synergistic action of the two factors.

EDSP

The rates of follow-up psychotic experiences in the eight exposures states are depicted in Table 3. The risk difference effect size increased from 8·3% for unexposed subjects, to 37·9% for subjects exposed to all three environmental risk factors. Again a significant positive interaction was evident between environmental load and baseline psychotic experiences (Wald $\chi^2 = 4\cdot2$, df = 1, $p = 0\cdot04$). This interaction was not reduced after adjustment for age, sex, educational level and any T0 diagnosis (Wald $\chi^2 = 5\cdot3$, df = 1, $p = 0\cdot02$). In the sensitivity analysis, the results similarly did not change after the exclusion of

subjects presenting with an onset of psychotic experiences, according to the M-CIDI, more than 1 year ago (Wald $\chi^2 = 4\cdot2$, df = 1, $p = 0\cdot04$). The risk of follow-up psychotic experiences was 14·8% in subjects exposed to neither baseline psychotic experiences nor high environmental load, 24·5% in those exposed to high environmental load alone, 20·7% in those exposed to baseline psychotic experiences alone, and 42·7% for those exposed to both baseline psychotic experiences and high environmental load. Filling in these risks in the formulas by Darroch (1997) revealed that between 29% and 51% of the individuals exposed to both baseline psychotic experiences and high environmental load had persistence of baseline psychotic experiences because of the synergistic action of these two factors.

DISCUSSION

To our knowledge, this is the first study that examined and replicated possible synergism between continuous developmental environmental load and psychotic experiences in predicting the minority of individuals who will display persistence of psychosis experiences. The two analyses presented replicated the finding

Table 3. *Interaction between psychotic experiences and environmental load on the additive scale (risk difference), the Early Developmental Stages of Psychopathology study (EDSP)*

Environmental load[a]	Baseline psychotic experiences[b]	With follow-up psychotic experiences[c] (*n*)	Without follow-up psychotic experiences (*n*)	Risk of having follow-up psychotic experiences (%)	Risk difference (%)	95% CI	*p*
Zero	No	66	427	13·4	8·3	−3·9 to 20·6	0·2
	Yes	10	36	21·7			
One	No	197	1088	15·3	10·4	1·7 to 19·2	0·02
	Yes	26	75	25·7			
Two	No	76	300	20·2	17·3	4·7 to 29·8	0·007
	Yes	24	40	37·5			
Three	No	16	53	23·2	37·9	13·3 to 62·5	0·003
	Yes	11	7	61·1			
Additive interaction[d]					$\chi^2 = 4·2$	df = 1	0·04

CI, Confidence interval; df, degrees of freedom.

[a] Zero = no exposure; one = subjects exposed to only one of the three exposures; two = subjects exposed to two of the three exposures; three = subjects exposed to at all exposures.

[b] Defined dichotomously as the group of individuals with the highest 10% of Symptom Checklist-90-R (SCL-90-R) scores.

[c] At least one positive rating on any of the 15 Munich-Composite International Diagnostic Interview (M-CIDI) core psychosis items at T2.

[d] Test for significant difference in increase in risk with one unit change in exposure rating between group with and without psychotic experiences.

that the probability of persistence of psychotic experiences was substantially greater in subjects exposed to all three environmental exposures compared to those with a lesser degree of exposure. Between 21% and 83% (NEMESIS), and 29% and 51% (EDSP), of the subjects exposed to both environmental exposures and psychotic experiences at T0 had persistence of expression of psychosis at follow-up because of the synergistic action of the two causes. These findings suggest that (i) the effect of different environmental risk factors for psychosis is additive, and (ii) if the environmental load were reduced, the prognosis of developmental expression of psychosis in the general population could be modified considerably, assuming causality.

In accordance with previous studies that examined associations with each environmental factor separately (cannabis use, trauma and urbanicity) (Van Os *et al.* 2002; Spauwen *et al.* 2004, 2006*a*, *b*; Van Os, 2004; Henquet *et al.* 2005), this triad of exposures may impact on risk for psychotic disorder by causing an abnormal persistence of a developmentally common expression of psychotic experiences, reflecting a plausible mechanism by which these risk factors may increase the risk for psychotic disorder. In addition, the environmental risk factors act additively in increasing the risk for persistence of psychotic experiences; the separate associations with each risk factor become a joint strong effect (Van Os *et al.* 2005*b*). Thus, under the influence of these three environmental factors, the first phase of the onset of psychotic disorder may be construed as the abnormal persistence and deterioration of a distributed developmental expression of psychosis.

Analytical models of persistence of psychosis

The central question of the analysis was persistence of psychotic experiences from baseline to follow-up. Analytically, this was tested using an interaction between baseline psychotic experiences and environmental load in the model of follow-up psychotic experiences. This model, however, assumes that environmental load does not increase the risk of baseline psychotic experiences (i.e. the variables making up the interaction are independent). If environmental load increases the risk for baseline psychotic experiences, the analysis cannot distinguish between a model of environmental load causing poor prognosis of prevalent psychotic experiences, and a model of environmental load causing incident poor prognosis psychotic experiences. In practice, however, the distinction between these two is academic, and in fact for

most environmental exposure in psychiatry both mechanisms are likely to be true (Van Os *et al.* 2005*a*). Thus, a *post-hoc* analysis revealed that high environmental load was associated with baseline psychotic experiences in both NEMESIS [odds ratio (OR) 1·95, 95% confidence interval (CI) 1·79–2·14, *p* < 0·01] and EDSP (OR 1·49, 95% CI 1·25–1·78, *p* < 0·01). Similarly, several risk factors for psychosis are associated not only with incidence, but also with persistence (Van Os *et al.* 1997, 1998). Thus, cannabis is associated not only with onset, but also with poor prognosis of psychotic illness (Grech *et al.* 2005).

Possible mechanism of risk

A hypothesis of a causal mechanism may reside in the more direct and indirect effects of cannabis, trauma and urbanicity during development, on what has been called dopamine sensitization (Laruelle, 2000; Howes *et al.* 2004). Thus, cannabis may have a direct developmental impact on dopamine sensitization. The primary active constituent of cannabis is delta-9-tetrahydrocannabinol (THC), affecting in particular the cannabinoid CB1 receptor in the brain (Freund *et al.* 2003; Howlett *et al.* 2004). The use of cannabis activates the CB1 receptor with a net effect of increased dopamine release in the limbic system (Cheer *et al.* 2004). Studies conducted in rats and human have suggested that puberty and adolescence are vulnerable periods with regard to THC exposure (Arseneault *et al.* 2002; Schneider & Koch, 2003; Henquet *et al.* 2005). Repeated exposure to cannabis may lead to prolonged changes in the functioning of the dopamine system, and eventually dopamine sensitization (Henquet *et al.* 2005). These changes may be more important for subjects with a pre-existing vulnerability to dysregulation of the cannabinoid and related neurotransmitter systems (Caspi *et al.* 2005; Dean & Murray, 2005; Henquet *et al.* 2005, 2006).

Recent studies have reported that neurotoxicity may be on the pathway between childhood trauma and schizophrenia supporting the traumatogenic neurodevelopmental (TN) model (Walker & Diforio, 1997). In this model, childhood trauma may lead to neurodevelopmental abnormalities and particularly produce permanent damage in the stress regulation mechanism

in the hypothalamic–pituitary–adrenal (HPA) axis (Bremner, 2005). The persistence of exposition to stressors and the chronicity of heightened glucocorticoid release, can induce permanent changes in the HPA axis and, through this, affect the dopamine system (Walker & Diforio, 1997). Thus, exposure to stressors increases both cortisol release and dopamine, the latter being known as a neurotransmitter associated with the expression of psychosis (Kapur, 2003). It has been suggested that dopamine plays an important role by mediating the 'salience' of environmental events and internal representations (Berridge & Robinson, 1998; Waelti *et al.* 2001). Schizophrenia may be associated with endogenous dopamine sensitization, a state characterized by hyper-responsiveness of dopamine neurons to environmental stimuli, in which even exposure to moderate levels of stress is associated with excessive dopamine (Lieberman *et al.* 1990; Duncan *et al.* 1999; Laruelle & Abi-Dargham, 1999; Laruelle *et al.* 1999). Thus, a dysregulated, hyperdopaminergic state may lead to stimulus-independent dopamine release, which may take over the normal process of contextually driven salience attribution and then lead to aberrant assignment of salience to external objects and internal representations during the acute phase of psychosis (Kapur, 2003). In line with this, studies have reported that dopamine mediates the expression of psychotic experiences in patients with schizophrenia (Marcelis *et al.* 2004; Myin-Germeys *et al.* 2005*a, b*).

The mechanism of behavioural or neurochemical sensitization may be involved in a comparable way for the developmental exposure referred to as 'urbanicity', reflecting in all likelihood an environmental exposure in urban environments. Growing up in an urban environment may increase the risk for people to be exposed to environmental stresses such as violence and victimization, social isolation and pollution rather than selection (Marcelis *et al.* 1998; Verheij *et al.* 1998; Pedersen & Mortensen, 2001). Stressful environments might also give rise to behavioural sensitization as a reflection of dopamine sensitization (Myin-Germeys *et al.* 2005*a, b*).

Thus, cumulative exposure to these additively acting developmental environmental risk factors in subjects with liability for psychosis, as

evidenced by psychotic experiences may result in cumulative changes in the functioning of the dopamine system, possibly affecting the persistence and deterioration of developmental psychotic features.

Methodological issues

Persistence of psychotic experiences and transition to psychotic disorder

In the NEMESIS and EDSP datasets, the psychotic experiences at follow-up were assessed respectively with the CIDI and the M-CIDI, which are very close conceptually and logistically. Psychotic experiences are much more prevalent than psychotic disorders and the question arises as to what degree they reflect the same underlying phenotype. Research suggests that psychotic experiences reflect the lower end of a continuum, with more severe states such as schizophrenia at the highest end (Kendler *et al.* 1993; Chapman *et al.* 1994; Poulton *et al.* 2000; Van Os *et al.* 2000, 2001; Johns & Van Os, 2001). Previous studies have shown that the environmental and genetic risk factors for schizophrenia, including the environmental risk factors examined in this study, have an impact on the occurrence of both clinical psychotic disorder and subclinical psychotic experiences (Verdoux *et al.* 1998; Johns & Van Os, 2001; Van Os & Jones, 2001; Van Os *et al.* 2001, 2002; Krabbendam *et al.* 2002; Spauwen *et al.* 2003; Janssen *et al.* 2004; Henquet *et al.* 2005). As transition from a subclinical state to a clinical disorder necessarily involves a degree of persistence and subsequent deterioration, our findings suggest that exposure to the three environmental risk factors influences not only the persistence of psychotic experiences but also, through this, the emergence of psychotic disorder. However, further research is needed to examine whether and how persistence of psychotic experience leads to the development of need for care and a diagnosable disorder.

Baseline psychotic experiences at T0

The SCL-90-R was used to measure psychotic experiences at T0 in EDSP. The fact that this instrument covers only the past 2 weeks may have led to an underestimation of the true positives at T0. Nevertheless, the repercussions of this misclassification would only be a decrease in risk differences between groups, and is thus unlikely to result in spurious findings. The validity of the measure of psychotic experiences by a self-report instrument may be questionable. However, a recent study demonstrated the validity of the assessment of psychotic experiences by self-report in a general population sample (Konings *et al.* 2006), and the longitudinal validity of self-reported psychotic experiences in population samples has also been established (Poulton *et al.* 2000; Hanssen *et al.* 2005).

Psychotic experiences at T2

The CIDI and M-CIDI were used in the NEMESIS and EDSP studies respectively to measure psychotic experiences at follow-up. The limitation of the CIDI is that this instrument is not considered reliable to assess psychotic disorders by lay interviewers (Anthony *et al.* 1985). However, subjects were assessed by face-to-face interview, which may have yielded better results than a self-report questionnaire. In addition, clinical reinterviews were conducted in both NEMESIS and EDSP, the psychologists who conducted the interviews were allowed to probe with follow-up questions, thus making the interview clinical rather than self-report (Spauwen *et al.* 2006 *b*).

APPENDIX

Estimation of the amount of biological synergism between baseline psychotic experiences and environmental load (see Darroch, 1997; Van Os *et al.* 2002; Van Os & Sham, 2003)

To quantify the extent to which (proxy) genetic risk and environmental factors act synergistically in disease causation, we have to consider the population that has developed psychosis after exposure to both (proxy) genetic and environmental risk factors, taking into account the possibility that among those subjects some of them would have developed psychosis after the exposure to either (proxy) genetic risk or environmental risk alone, which refers to parallelism (Darroch, 1997; Van Os *et al.* 2002; Van Os & Sham, 2003). If there is parallelism (proxy) genetic and environmental risks are competitive in causing psychosis. Thus, if the proportion of subjects that develops psychosis because the

co-participation of (proxy) genetic risk and environmental risk decreases, there is more competition between both risk factors. It is not possible to calculate the amount of synergy and the amount of parallelism in subjects exposed to both (proxy) genetic liability and environmental exposure. However, the estimation of the amount of biological synergism can be approximated, in part, from the calculation of which synergism exceeds parallelism (Darroch, 1997; Van Os *et al.* 2002; Van Os & Sham, 2003).

To calculate this excess of synergism, we use the risk effects associated with the four exposure states. For illustration, the table of risk effects for subjects from the NEMESIS study is constructed:

	(proxy) Genetic risk Psychotic experiences	
	+	−
Environmental risk +	$R(GE) - R = 0.341$	$R(E) - R = 0.236$
Environmental load −	$R(G) - R = 0.058$	$R = 0.026$

The risk of having follow-up psychotic experiences in the group exposed to neither psychotic experiences nor more than one environmental exposure was 2·6% (95/3688). The risks in those only exposed to psychotic experiences and no or one environmental risk factor was 5·8% (19/330), in those exposed to environmental exposures alone 23·6% (139/589), and the risk in those exposed to both factors 34·1% (61/179).

The excess of the combined effects of (proxy) genetic and environmental risk over the sum of their solitary effects is the effect associated with the combined exposure to (proxy) genetic and environmental risk minus the effect associated with the exposure to (proxy) genetic risk alone and minus the effect associated with environmental risk alone. The amount by which synergism exceeds parallelism equals the excess of the combined effect of (proxy) genetic risk and environmental risk over the sum of the solitary effects of (proxy) genetic risk and environmental risk, which is the statistical additive interaction (Darroch, 1997; Van Os *et al.* 2002; Van Os & Sham, 2003).

$$[R(GE) - R(G) - R(E) + R] = |synergism|$$
$$- |parallelism| = \text{statistical additive interaction.}$$

If synergism is positive, then the statistical additive interaction is positive, if synergism is equal to zero, the statistical additive interaction is inferior or equal to zero.

For example, filling in the risks of the NEMESIS study in the previous formula:

$$[R(GE) - R(G) - R(E) + R]$$
$$= 0.341 - 0.058 - 0.236 + 0.026 = 0.073$$

The statistical additive interaction is positive (0·073), indicating that baseline psychotic experiences and environmental load interact on the additive scale.

The next step is to fill these risks in, in the following table (Darroch, 1997):

|Synergism|	×2	R(GE) − R(G) = 0·341 − 0·058 = 0·283
×1	|Parallelism|	R(G) − R = 0·058 − 0·026 = 0·032
R(GE) − R(E) = 0·341 − 0·236 = 0·105	R(E) − R = 0·236 − 0·026 = 0·21	

Synergism was between 0·073 and 0·283, which represents respectively 21% and 83% of the psychosis risk in those exposed to both psychotic experiences and environmental load (0·073/0·341 = 21% and 0·283/0·341 = 83%). Thus, an estimated 21% to 83% of subjects exposed to both exposures and baseline psychotic experiences had follow-up psychotic experiences because of the synergistic action of the two causes.

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DECLARATION OF INTEREST

None.

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