Association of adverse childhood environment and 5-HTTLPR Genotype with late-life depression.

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Association of adverse childhood environment with late-life depression

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ABSTRACT

Objective: Neurobiological and clinical studies suggest that childhood maltreatment may result in functional and structural nervous system changes which predispose the individual to depression. This vulnerability appears to be modulated by a polymorphism in the serotonin linked promoter region (*5-HTTLPR*). Little is known however, about the persistence of this vulnerability across the life-span although clinical studies of adult populations suggest that gene-environment interaction may diminish with ageing.

Method: Depressive symptomatology and adverse and protective childhood events were examined in a population of 942 persons aged 65 years and over, taking into account socio-demographic characteristics and proximal competing causes of depression (widowhood, recent life-events, vascular and neurological disorder, and disability). Subjects were diagnosed as depressed if they met one of three criteria: a diagnosis of major depression on the Mini International Neuropsychiatric Interview (MINI), over 16 on the CES-D or anti-depressant treatment.

Results: Exposure to traumatic events in childhood doubled the risk of late-life depression and increased the risk of repeated episodes. Not all events were found to be pathogenic; significant risk being associated with excessive sharing of parental problems, poverty, mental disorder in parents, excessive punishment, verbal abuse, humiliation and mistreatment by an adult outside the family. Interactions were observed between the *5-HTTLPR* 'L' allele, poverty and excessive sharing of parental problems.

Conclusions: Certain types of childhood trauma continue to constitute risk factors for depression in old age, outweighing more proximal causes. Gene-environment vulnerability interaction is linked in older age to the L-carrying genotype, modulating the effects of general environmental conditions rather than aggressive acts on the individual, perhaps due to increased cardiac reactivity.

KEY WORDS: depression, elderly, child abuse, *5-HTTLPR*, gene-environment interaction

INTRODUCTION

Neurobiological studies have demonstrated that childhood maltreatment may alter brain development by programming the glucocorticoid, noradrenergic and vasopressin stress response systems to over-react to new stressors (1-3), thus rendering the individual increasingly vulnerable to psychiatric disorder. These effects appear to be long-lasting (4) inducing structural and functional changes, notably reduced development of the hippocampus and amygdala, and abnormal fronto-temporal electrical activity (2). These brain structures having also been implicated in the aetiology of depression, it is not surprising that child abuse has been associated with increased risk for depression during childhood, and also in early adulthood (5, 6).

Not all children exposed to traumatic experiences subsequently develop psychopathology and accumulating evidence suggests that vulnerability for depression is influenced by variation in the serotonin transporter gene (*5-HTT*) (7, 8). A functional insertion/deletion polymorphism in the serotonin gene linked promoter region (*5-HTTLPR*) has been shown to modify the association between stressful life events (SLEs) and depression onset (7). The *5-HTTLPR* short (S) allele appears to reduce *in vitro* transcriptional activity of *5-HTTLPR*, resulting in decreased expression of the serotonin transporter (5-HTT). Most replication studies have confirmed this original finding, although a few have not, particularly when older subjects have been included (9). It has also been observed that a supportive early environment appears to reduce symptomatology in S/S homozygous subjects exposed to childhood trauma (8, 10).

Clinical studies of child abuse have focused on the implication of these events in childhood and adolescence on the assumption of a proximal effect of life events on psychological health. Little is known about the persistence of this vulnerability across the life-span, and whether adverse childhood events continue to constitute a significant risk factor for depression in old age. The role of the *5-HTTLPR* genotype in mediating the late-life impact of child abuse is also uncertain. In a small community sample of 194 elderly, depressive symptoms were observed to be associated with abuse

and neglect in childhood (11), however, the sample size was too small for adjustment for other possible causes of depression. A study by Surtees et al. (12) combining childhood and adult life events in a sample with an age range of 41-80 years, found a strong relationship between childhood events and recent episodes of major depression. No interaction effect was found with *5-HTTLPR* genotype; however, a trend was observed in the opposite direction, with the L allele constituting the interactive risk factor in men. Taylor et al. (13) noted that in elderly persons with depression smaller hippocampal volume was associated with earlier depression onset and the S/S genotype, as opposed to late-onset (over 50) depression in which reduced hippocampal volume was associated with the L/L genotype. Traumatic events were not examined.

Studies to date thus suggest that gene-environment interaction in the genesis of depression may not be the same in elderly populations as in childhood and young adults. Furthermore, while candidate environmental pathogens are generally considered to have greater impact when they are proximal to depression onset (14), biological evidence suggests that childhood trauma, occurring at critical stages of brain development, may lead to more permanent structural and functional changes. The present study aims to examine the relationship between childhood trauma and late-life depression in an elderly general population cohort, taking into account other more proximal risk factors for late-life depression, and *5-HTTLPR* genotype interaction. Adverse childhood events are examined individually along with potential environmental protective factors.

METHOD

Sample

Community dwelling persons, 65 years and over, were recruited by random selection from the fifteen electoral roles of the Montpellier district between March 1999 and February 2001 as part of the ESPRIT study of late-life psychiatric disorder (15). Refusers (of whom 3.3% were excluded due to severe disability) were replaced by another subject drawn at random from the same electoral division

such that each division is equally represented. Subjects refusing were slightly older and more likely to live alone than non-refusers. Subjects were subjected to a base-line examination and re-examined on two further occasions at two-yearly intervals.

Measures

Participants were asked to attend a half-day examination by a neurologist and a centre interviewer (nurse or psychologist) at the Gui de Chauliac Neurology Hospital (Montpellier, France). Disabled subjects unable to come to the study centre were interviewed in their homes. The following procedures were carried out:

A standardized health interview covering present state of health, individual and family medical history, medication use - subjects were asked to bring their medication to the centre and the type of medication was noted according to the World Health Organization's Anatomical Therapeutic Chemical (ATC) Classification (16). Disability was assessed by the Lawton Scale for Instrumental Activities of Daily Living (IADL) (17). Exposure to adverse life events in the past year was assessed using the Gospel Oak questionnaire (18), a 12-item list of major adverse events covering bereavement, rupture in significant relationships, financial and legal problems, dismissal, severe illness, loss of a highly valued object.

A standardized neurological examination based on ICD-10 criteria (19) to detect neurological and cardiovascular co-morbidity, including measures of sitting and standing blood pressure, was carried out at base-line and at each follow-up examination.

A standardized psychiatric interview to record life-time and current DSM-IV Axis I psychiatric disorder (20); the Mini International Neuropsychiatric Interview (MINI) (French version 5.00) previously validated within the general population setting (21). Positive cases were reviewed by a panel of psychiatrists. The Center for Epidemiologic Studies-Depression Scale (CES-D) (22) was used to detect high levels of depressive symptomatology. Case-level late-life depression was defined as a MINI diagnosis of current major depression, a score above the 16 cut-off point of the CES-D or current treatment with an anti-depressant at base-line or at each follow-up examination.

Childhood environment A retrospective self report questionnaire examining traumatic experiences during childhood and adolescence based on a review of existing instruments and covering 25 adverse and 8 protective factors, was given to subjects for completion in the third wave of the study (four years after recruitment) by which time the study interviewers had established close relationships with the cohorts, facilitating the request for sensitive information. Subjects were asked to respond yes or no to each item. Subjects were also given an opportunity to discuss the questionnaire contents with interviewers in case of doubt as to whether specific experiences corresponded with the items. Adverse factors included physical, verbal and sexual abuse, conflict at home, strict education, mental cruelty, neglect, mental disorder in parents, excessive sharing of parental problems, separation, illness, poverty, mistreatment at school, separation, war and natural catastrophe. Protective factors included maternal and paternal affection, availability of an adult friend, impression of having had a happy childhood, parents perceived as doing their best, feeling happy at school, having been raised by both parents.

Subjects were re-examined on a further two occasions at two-yearly intervals. At follow-up the neurological and psychiatric examinations were repeated and medication use and incident illness were recorded. The Gospel Oak questionnaire was used to record life-events occurring since the last examination. The present study was carried out on the 942 subjects for whom complete information was available on all variables used in the analyses (clinical examinations at all time points, childhood environment, genotype, depression measures and all potential confounding variables). Ethics approval for the study was given by the national ethics committee. All subjects gave their signed consent for participation in the study.

Blood samples for DNA collection for *5-HTTLPR* genotyping were taken after the base-line clinical interview. *5-HTTLPR* insertion/deletion polymorphisms were assayed in two stages. Genomic DNA was extracted from white blood cells harvested from 15 ml EDTA blood samples using DNA extraction kits from Amersham-Pharmacia Biotech. Subsequently, amplification of *5-HTTLPR* was

carried out using the primers HTTLPRF (GGCGTTGCCGCTCTGAATTGC) and HTTLPRR (GAGGGACTGAGCTGGACAACCCAC) in reaction mixtures with a total volume of 25 µl, with 200 ng of genomic DNA, 10 pM of the primers, 120 nM dNTP, containing 7-deaza-dGTP instead of dGTP (Roche), 5% DMSO (Sigma), 1.5 mM $MgCl_2$, and 1.25 U Taq polymerase (Eurobio, Brunschwig). Temperatures were 60°C for 30 s for annealing and 72°C for 1 mn for extension. PCR products (8 µl) were subjected to 45 mn electrophoresis at 120 V in a PCR CheckIT gel (Elchrom Scientific AG, Switzerland) before being viewed under UV to assess the *5-HTTLPR* genotypes. An adenosine/guanine (A/G) single nucleotide polymorphism (SNP; rs25531), located in the close vicinity of *5-HTTLPR*, has recently been reported to modify transcriptional activity (23). On the basis of these *in vitro* functional data it has been proposed to recode the *5-HTTLPR*/rs25531 allele as S' or "low expressing allele (S_A, S_G and L_G) and L' or "high expressing allele" (L_A) (24). As this new allelic dichotomy still awaits replication in *in vivo* studies, we initially examined both allelic systems (S/L and S'/L') within the present study. Recoding did not significantly alter results so we report here only analyses relating to S and L.

Statistical Analysis

Univariate logistic regression was used to determine differences in unadjusted social and clinical characteristics between participants with and without depressive symptomatology. Variables found to be associated with current depression were used as adjusted variables in analyses relating to the association between childhood events and current depression. Polytomous logistic regressions models were used to model the relationship between the number of depressive episodes (0, 1, 2 or more) and individual childhood events (binary) and to calculate the odds ratio and their 95% confidence interval (CI) for life time onset of a major depressive episode in relation to childhood events. The distribution of *5-HTTLPR* was tested by χ^2 for Hardy-Weineberg equilibrium.

We tested the hypothesis that *5-HTTLPR* genotype might modify the relationship between depressive symptomatology and childhood events using a logistic regression model. We therefore stratified our

analysis by *5-HTTLPR* genotype and then added the interaction term to the full model and tested for its significance using Wald's χ^2 test given by the logistic regression model. Significance level was set at $p<0.05$. The statistical analysis was carried out using SAS software (version 9.1).

RESULTS

The median age (min-max) of the sample was 72 years (65-92). 38.4% of subjects in this study scored over the cut-off point on the CES-D either at recruitment or at one of the two follow-up examinations, 23.5 % had been diagnosed with major depression during their life-time and 12.6% were taking anti-depressant medication at some point during the study. All subjects with diagnosed major depression scored over 16 on the CES-D and 27 subjects (2.9%) taking anti-depressant treatment did not meet either MINI or CES-D criteria for depression. These subjects were included as depressed on the assumption that a depressive episode had occurred but been effectively treated and thus was not detected by the MINI or CES-D. The period prevalence (over the four year observation period) of significant depressive symptomatology in this cohort is estimated at 41.3%. The socio-demographic and clinical characteristics of subjects with significant levels of depressive symptomatology are given in Table 1.

Table 1 here

Depressed subjects were observed to be more commonly female (odd ratio=2.92, 95% CI=2.21-3.86), older (odd ratio=1.60, 95% CI=1.11-2.31), to have medium-low education (odd ratio=2.07, 95% CI=1.44-2.96), to be divorced/separated (odd ratio=1.87, 95% CI=1.17-2.99) or widowed (odd ratio=2.15, 95% CI=1.56-2.96) and to have lower rates of hypertension (odd ratio=0.59, 95% CI=0.45-0.76). Experiencing recent adverse life events (in the year before and during follow-up) and before the onset of the depressive symptoms, showed a significant p trend. Subsequent analyses were thus adjusted for these competing causes of depression. No significant relationship was found between

depression and dementia or other neurological disorders, disability, recent cardio- or cerebro-vascular disorder or *5-HTTLPR* allele.

Previous research on child maltreatment and depression has principally highlighted personally threatening events (physical, sexual and verbal abuse; items 1 to 6, Table 2) as being the most pathogenic (25). In this older population we found exposure to at least one of these events significantly increased risk of late-life depression (odd ratio =2.28; 95%CI=1.53-3.41). Exposure to a major protective factor (maternal or paternal affection, availability of an adult friend; items 26 to 28, Table 2) conversely decreased overall risk (odd ratio=0.54; 95%CI=0.28-1.01).

We also examined the effects of childhood events on the number of depressive episodes occurring during the study period. Exposure to at least one adverse childhood event significantly increased the risk of having one episode of depression with an odd ratio=1.72 (95% CI=1.04-2.86), and for two or more episodes with an odd ratio=2.89 (95% CI=1.83-4.57) (p-value for heterogeneity between these 2 odds-ratio was 0.05). The presence of at least one protective factors gave a risk of odd ratio=1.03 (95%CI=0.42-2.53) for one depressive episode, and a protective effect of odd ratio=0.34 (95% CI=0.17-0.69) for two or more episodes (p-value for heterogeneity was 0.02) (data not shown).

The relationship between late-life depression and individual childhood life-events were also examined using a logistic regression model. No significant sex interaction effects with individual childhood life-events and depressive symptomatology were observed so analyses were not gender stratified. Table 2 shows that a significant risk was associated with excessive sharing of problems (odd ratio=1.53, 95% CI=1.04-2.27), poverty or financial difficulties (odd ratio=1.65, 95% CI=1.17-2.31), mental disorder experienced by the father (odd ratio=2.13, 95% CI=1.32-3.44) and mother (odd ratio=2.52, 95% CI=1.65-3.85), excessive punishment (odd ratio=2.77, 95% CI=1.41-5.46), verbal abuse by parents (odd ratio=2.90, 95% CI=1.57-5.38) humiliation and mental cruelty (odd ratio=4.31, 95% CI=1.87-9.93) and abuse by an adult outside the family (odd ratio=6.71; 95%CI=1.80-25.0). A protective effect

was observed for maternal affection (odd ratio=0.45, 95% CI=0.29-0.70), and having the overall impression that parents had done their best (odd ratio=0.53; 95%CI=0.30-0.92).

Table 2 here

The distribution of *5-HTTLPR* did not deviate from Hardy-Weineberg equilibrium (χ^2=0.06 , Df=2 , p=0.97). Interaction effects between *5-HTTLPR* genotype and childhood events having a significant relationship with depressive symptomatology were examined adjusting by age, gender, education, marital status, hypertension and recent life events with stratification by genotype.

The risk of depression in relation to too frequent sharing of parental problems with children was increased in LL subjects (odd ratio=1.93, 95%, CI =0.95-3.90) and in SL subjects (odd ratio=2.00, 95%, CI =1.15-3.48) with a non-significant tendency for protection in SS subjects (odd ratio=0.30, 95%, CI= 0.08-1.19). A comparable pattern was observed for poverty or financial difficulties. We observed a tendency for an increased risk in LL subjects (odd ratio=1.51, 95%, CI =0.82-2.77) which was significant in SL subjects (odd ratio=2.54, 95%, CI =1.55-4.15). In the SS subjects, we found a non-significant tendency for reduced risk (odd ratio=0.64, 95%, CI =0.26-1.53).

Significant gene-event interactions were found for parents excessively sharing problems (Wald χ^2=7.23, df =2, p=0.027) and for poverty or financial difficulties (Wald χ^2=7.38, df =2, p=0.025) (Figure 1).

Figure 1 here

As these results suggest a dominant effect of the L-carrying genotypes, we examined the effect of combining LL and LS subjects compared to SS subjects. The risk of depression with childhood poverty was significantly increased in LL/LS subjects (odd ratio=2.06, 95% CI=1.42-3.00) with a non-significant tendency to be reduced in SS subjects (odd ratio=0.64, 95% CI =0.26-1.53). The risk of depression in relation to too frequent sharing of parental problems with children was also increased

in LL/LS subjects (odd ratio=1.94, 95%, CI =1.26-2.98) with a non-significant tendency to be reduced in SS subjects (odd ratio=0.30, 95%, CI= 0.08-1.19).

Finally, the life-time risk of subjects for major depressive episodes (MDE) was also ascertained from the MINI adjusting for age, education and gender only (life events and hypertension at the time of the episode being unknown). Significant risk factors were found to be in ascending order sharing of parental problems with children (odd ratio=1.68, 95% CI=1.11-2.54), maternal mental illness (odd ratio=1.69, 95% CI=1.11-2.59), verbal abuse from parents (odd ratio=1.94, 95% CI=1.07-3.55), poverty or financial difficulties (odd ratio=1.97, 95% CI=1.37-2.83), maternal affection (odd ratio=0.51, 95% CI=0.33-0.79), home conflict (odd ratio=2.09, 95% CI=1.43-3.05), physical and/or sexual abuse (odd ratio=2.72, 95% CI=1.04-7.08). Alcohol abuse by father, neglect and abuse by schoolmates are only significant risk factors for cases of early-onset depression (occurring before age 50; data not shown).

DISCUSSION

Our study of an elderly cohort suggests that adverse childhood events may continue to constitute a significant risk factor for depression throughout the life span. Exposure to traumatic events in childhood was observed to double the risk of late-life depression and increase the risk of repeated episodes. On the other hand protective factors were seen to diminish the risk of late-life depression and repeated episodes. A relationship between trauma and risk of chronicity has also been observed by Bernet and Stein (5) who found increasing number of life-time episodes to be also associated with severity of trauma, but numbers in our study were too small to break down number of depressive episodes by individual items.

Recent studies of the impact of life events on psychological functioning have underlined the necessity of examining the impact of individual stressors rather than summating events in aggregate measures

due to the differential effect of specific events (26). Our findings support this observation. Of the 25 negative factors studied, late-life depression was found to be significantly associated with only 8: verbal abuse from parents, mental cruelty, excessive punishment by parents, abuse by an adult outside the family, parental mental disorder, poverty, home conflict and excessive sharing of parental problems with children. Physical and sexual abuse did not quite reach significance, however, only a small number of cases (n=13) were reported. Maternal affection, impression of having had a happy childhood and feeling that parents did their best constituted protective factors. These early life events were found to be pathogenic or protective even when potential proximal causes of depression (blood pressure, widowhood and separation, recent life events) were taken into account. No interactive effect was found with sex, although previous studies have reported gender differences in vulnerability to adverse life events occurring later in life (27). Examining individual childhood events and life-time risk for MDE, we found certain events to be related only to MDE occurring before age 50 (neglect, paternal alcohol problems and mistreatment at school by classmates), and others to be related to MDE onset both before and after age 50 (verbal and physical abuse, maternal mental disorder and poverty), suggesting some events to have less far-reaching effects than others.

No association was found between 5-*HTTLPR* and late-life depression. This observation is in accordance with previous meta-analyses suggesting that these polymorphisms do not directly modulate vulnerability to depression (9). Significant interaction was observed, however, between these polymorphisms and some childhood environmental factors. Interestingly, these gene-environment interactions appear to concern more general and long lasting environmental conditions, such as poverty, rather than specific aggressive acts of limited duration. This latter type of event may interact on the other hand with genes coding for proteins involved in the development and plasticity of the central nervous system, such as brain derived neurotrophic factor (28). Most previous human GxE studies report a susceptibility (co-dominant, dominant or recessive) effect with the S-carrying genotypes (9). On the contrary, in the present population we found a susceptibility dominant effect with the LL/SL genotypes. Surtees et al. (12) reported a similar interaction for past-year prevalent

depression and adverse experience in childhood in men (LL homozygotes: odd ratio= 1.69, 95% CI 1.17–2.44 and LS heterozygotes: odd ratio=1.26, 95% CI 0.91–1.75). This interaction did not quite reach significance and the authors suggest this may be due to the fact that it may have occurred predominantly in older subjects; the wide age range of the sample (41 to 80 years) masking the true effect. Our results lend further support to the hypothesis of a different form of interaction in late-life as opposed to early-onset depression. The L allele has very recently been linked with increased cardiovascular reactivity to mental stress (29) which may in turn lead to subcortical ischaemic disease and volumetric changes, notably in the hippocampus. The authors noted furthermore that increased cardiovascular reactivity in adulthood was also observed to be associated with childhood poverty.

We conclude from this study that certain types of early childhood trauma continue to constitute risk factors for depression in old age; their effect outweighing more recent life events and other proximal causes of depression. *5-HTTLPR* genotype alone does not modulate the effect of highly pathogenic events involving individual victimization, but may increase vulnerability to global environmental factors such as poverty and excessive sharing of parental problems. Strengths of this study were the large representative general population cohort which allowed us to take into account competing causes of depression, analysis of a wide range of individual childhood events, and clinical assessment of late-life depressive episodes. There were two principal short-comings in this study (i) we assumed that subjects taking anti-depressant treatment were depressed which may not have been the case as anti-depressants may be prescribed for other neurological conditions. This may have weakened the associations examined, however we could not eliminate these subjects as they would at least in part constitute a successfully treated depressed group; (ii) the use of a self-report measure of childhood events may also have weakened the associations examined in this study; prospective data from birth cohorts would have been preferable in terms of reducing recall bias. Further studies of this cohort examining possible biological correlates of the impact of adverse childhood events, such as persistence of abnormal basal cortisol levels and elevated ACTH response, as observed in cohorts of abused children (30), may provide further validation of self reported adversity and support for the

hypothesis that childhood abuse leads to permanent structural and functional changes of the nervous system.

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TABLE 1. Relationship between sociodemographic variables, clinical characteristics and depression

	Late-life depression						
	No N=553		*Yes N=389*				
	n	*%*	*n*	*%*	*Odds Ratio*	*95% CI*	*P-value*[*]
Gender							
Men	289	52.26	106	27.25	1		
Women	264	47.74	283	72.75	2.92	2.21-3.86	<.0001
Age Group (years)							
≤68.5	150	27.12	89	22.88	1		
]68.5-71.6]	144	26.04	88	22.62	1.03	0.71-1.50	0.0440
]71.6-75.4]	137	24.77	96	24.68	1.18	0.82-1.71	
>75.4	122	22.06	116	29.82	1.60	1.11-2.31	
Education							
High	170	30.74	76	19.54	1		
Medium-High	113	20.43	101	25.96	2.00	1.37-2.93	0.0002
Medium-Low	145	26.22	134	34.45	2.07	1.44-2.96	
Low	125	22.60	78	20.05	1.40	0.94-2.06	
Marital Status							
Married or living together	399	72.15	219	56.30	1		
Single	21	3.80	19	4.88	1.65	0.87-3.13	<0.0001
Divorced/Separated	39	7.05	40	10.28	1.87	1.17-2.99	
Widowed	94	17.00	111	28.53	2.15	1.56-2.96	
History of stroke, myocardial infarction, angina pectoris, arteritis							
No	501	90.60	363	93.32	1		
Yes	52	9.40	26	6.68	0.69	0.42-1.13	0.1377
Systolic blood pressure ≥160 or diastolic blood pressure ≥95 mm Hg or intake of antihypertensive drugs							
No	201	36.35	192	49.36	1		
Yes	352	63.65	197	50.64	0.59	0.45-0.76	<.0001
Dementia							
No	546	98.73	383	98.46	1		
Yes	7	1.27	6	1.54	1.22	0.41-3.66	0.7206
Disability							
No	505	91.32	366	94.09	1		-
Yes	48	8.68	23	5.91	0.66	0.40-1.11	0.1153
Recent life events							
0	126	22.78	90	23.14	1		
1	238	43.04	130	33.42	0.76	0.54-1.08	0.0052
2 or more	189	34.18	169	43.44	1.25	0.89-1.76	
5-HTTLPR							
LL	156	28.21	110	28.28	1		
SL	274	49.55	200	51.41	1.04	0.76-1.40	0.7572
SS	123	22.24	79	20.31	0.91	0.63-1.32	

[*] p-value (for variables with more than two categories, the p-value of the test for trend is given)

TABLE 2. Relation between individual childhood events and late-life depression adjusting by age, gender, education, marital status, hypertension and recent life events

		Late-life depression					
		No N=553		*Yes N=389*			
		n	*%*	*n*	*%*	*Odds Ratio*	*95% CI*
Traumatic factors		55	9.95	77	19.79	2.28**	1.53-3.41
1.	*Neglect*	25	4.52	27	6.94	1.50	0.83-2.74
2.	*Verbal abuse from my parents*	19	3.44	34	8.74	2.90**	1.57-5.38
3.	*Humiliation, harassment or mental cruelty*	9	1.63	23	5.91	4.31**	1.87-9.93
4.	*Physical and/or sexual abuse*	5	0.90	13	3.34	2.67	0.90-7.90
5.	*Excessive physical punishment for misbehaviour*	16	2.89	27	6.94	2.77**	1.41-5.46
6.	*Other mistreatment by an adult outside the family*	3	0.54	13	3.34	6.71**	1.80-25.0
7.	*Father suffered from mental problems*	38	6.87	47	12.08	2.13**	1.32-3.44
8.	*Mother suffered from mental problems*	45	8.14	74	19.02	2.52**	1.65-3.85
9.	*Father had problems with alcohol, drugs*	37	6.69	33	8.48	1.30	0.77-2.20
10.	*Conflict, nervous stress at home*	86	15.55	79	20.31	1.42	0.98-2.04
11.	*Parents divorced or separated*	35	6.33	26	6.68	1.19	0.67-2.09
12.	*Parents hospitalized, prisoner for extended period*	77	13.92	73	18.77	1.38	0.94-2.00
13.	*Parents had serious illness*	87	15.73	58	14.91	0.96	0.65-1.41
14.	*Strict, authoritarian education*	267	48.28	198	50.90	1.11	0.84-1.47
15.	*Serious childhood illness*	56	10.13	54	13.88	1.44	0.94-2.20
16.	*Poverty, financial difficulties*	113	20.43	103	26.48	1.65**	1.17-2.31
17.	*Parents too often shared their problems with children*	67	12.12	67	17.22	1.53*	1.04-2.27
18.	*Mistreatment at school by teacher*	13	2.35	17	4.37	2.01	0.92-4.40
19.	*Mistreatment at school by schoolmates*	8	1.45	10	2.57	2.22	0.81-6.08
20.	*No mistreatment but disliked school*	74	13.38	47	12.08	0.97	0.63-1.47
21.	*Experienced adverse war events or natural catastrophe*	298	53.89	217	55.78	1.22	0.92-1.62
22.	*Suicide attempt by family member*	22	3.98	14	3.60	0.71	0.34-1.46
23.	*Death of a parent*	97	17.54	64	16.45	0.99	0.68-1.43
24.	*Sent to a foster family*	9	1.63	10	2.57	2.00	0.76-5.26
25.	*Witnessed abuse of other family members*	5	0.90	8	2.06	2.22	0.67-7.33
Protective factors		532	96.20	363	93.32	0.54	0.28-1.01
26.	*Paternal affection*	461	83.36	319	82.01	0.87	0.60-1.26
27.	*Maternal affection*	510	92.22	326	83.80	0.45**	0.29-0.70
28.	*Had an adult friend outside the family*	146	26.40	119	30.5	1.08	0.80-1.47
29.	*Raised by both parents*	495	89.51	353	90.75	1.07	0.67-1.72
30.	*Happy childhood*	519	93.85	343	88.17	0.45**	0.27-0.74
31.	*Happy at school*	494	89.33	348	89.46	1.00	0.64-1.57
32.	*Impression that parents did their best*	525	94.94	356	91.52	0.53*	0.30-0.92
33.	*Normal education*	527	95.30	364	93.57	0.77	0.42-1.41

*p<0.05 **p<0.01

FIGURE 1. Interaction between occurrence of specific childhood events and probability of late-life depression