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**Symptoms are highly prevalent among HIV outpatients and associated with poor adherence and unprotected sexual intercourse**

**Running head:** Pain and symptom correlates in HIV

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## **KEY MESSAGES**

- The burden of psychological and physical symptoms among HIV outpatients with treatment access is seldom researched yet essential to improved management and patient outcomes.
- Among 778 UK outpatients, the 7-day period symptom prevalence was high. Being on treatment was not associated with lower symptom distress. Psychological symptoms were associated with poorer adherence and sexual risk behaviour.
- Clinical care should routinely assess multidimensional symptoms as these are controllable and may improve outcomes such as treatment response, transmission and quality of life.

## **ABSTRACT**

### **Objectives**

There is a paucity of data reporting the prevalence and burden of pain and symptoms among HIV patients in the era of antiretroviral therapy (ART). This study aimed to measure symptom prevalence and determine associations with key variables: demographics, treatment status, adherence and risk behaviours.

### **Design**

Cross-sectional self-completion questionnaire in five HIV outpatient clinics in London and South East of the UK.

### **Methods**

Consecutive patients were invited to participate, responding to clinical and behavioural variables including the Memorial Symptom Assessment Schedule (Short-form). Four multivariable models examined the relationship between dependent variables of 1) psychological, 2) physical, 3) global symptom burden scores, 4) number of symptoms and key independent variables. 778 patients participated, response rate 77% of all patients approached.

### **Results**

Both physical and psychological symptoms were highly prevalent: in the previous seven days, 70.8% experienced lack of energy, 69.9% worry, 53.6% diarrhoea, 53.5% sexual dysfunction, and 53.2% pain. In multivariable

analysis, both unprotected sexual intercourse with a partner of unknown status, and poorer ART treatment adherence were significantly and independently associated with psychological symptom burden. Lower educational achievement was significantly associated with increasing physical, psychological and global symptom burden, and with higher number of symptoms. Being on ART was not associated with any symptom distress measure.

### **Conclusions**

In the era of treatment, patients continue to experience high prevalence and burden of psychological and physical symptoms, which are not associated with treatment status. Attention to these distressing problems is essential and may enhance quality of life, enhance adherence and minimise risk behaviour.

## **Symptoms are highly prevalent among HIV outpatients and associated with poor adherence and unprotected sexual intercourse**

### **BACKGROUND**

HIV disease is associated with highly prevalent and distressing symptoms from the point of diagnosis(1) . A significant proportion of patients receiving antiretroviral therapy (ART) experience drug toxicities such as peripheral neuropathy and gastrointestinal problems(2), requiring drug discontinuation or treatment change within, and between, classes of ART(3). However, the vast majority of data on pain and symptom prevalence has been reported from the pre-ART era on patients with AIDS-defining illnesses, and it has been difficult to quantify the relative contribution of treatment to the presence and severity of symptoms(4).

The World Health Organisation (WHO) advocates pain and symptom control as an essential component of HIV clinical care(5). However, the evidence suggests inadequate clinical attention to pain and symptom assessment and management, as clinicians detect three-fold fewer HIV-related symptoms than their patients report(6), and patients perceive that their symptoms remain untreated(7;8).

In order to maximise clinical benefit from ART, adherence must be optimised and movement between classes of drugs minimised so that future treatment options can be retained. In order to achieve this, ART-related symptomatology must be taken into account. Further, clinicians need to be able to identify prevalent symptoms, and which patients may experience symptom distress,

as well as non-clinical potential ramifications of symptom distress such as risk behaviour and adherence variation. Currently, not only is there a lack of focus on pain and symptom prevalence in the era of ART, but these variables have not been assessed in relation to the key clinical and behavioural components of care such as treatment adherence and behavioural risk reduction.

Investigation into prevalence and correlates of symptoms is required to inform clinical practice and thereby improve clinical outcomes and quality of life(1;9;10).

## **METHODS**

### **Design and recruitment**

This study aimed to measure the prevalence and distress related to physical and psychological symptoms, and to determine the relationship between these and demographic variables, ART use and adherence, risk behaviour and HIV status disclosure.

This cross-sectional questionnaire study was conducted in five outpatient clinics in London and the South East of England during 2005/6. Consecutive attending patients were approached and invited to participate (n=1007). The inclusion criteria (HIV positive adults with sufficient English language and cognitive/physical ability to self-complete) were fulfilled by 904 patients (90%) who received a questionnaire, of which 778 were completed and returned (77% of all patients, 86% of those eligible to receive a questionnaire). Multi-

centre UK ethical approval was granted by the Royal Free Hospital Clinical Ethics Committee ref 05/Q1907/26.

### **Data collection**

The questionnaire comprised of four core components of items that were selected to meet the aims of the study in line with the existing literature.

Firstly, a demographic component ( addressing age, gender, ethnicity, employment, country of birth, sexuality, and education).

Second a behavioural component (unprotected sexual intercourse with a partner of unknown status in the previous three months; treatment optimism and infectiousness optimism on a standardised scale(11); and disclosure of HIV status to others based on Kalichman 2003(12)).

Third, treatment items (current treatment status was recorded as naïve, on first regimen, switched regimen or stopped; treatment adherence based on a seven day self report recall on three levels: fully adherent, partially adherent or non-adherent, a composite measure according to whether i) all doses were taken, ii) at the correct time and iii) in line with dietary requirements(13)).

Fourth, symptoms were measured using the Memorial Symptom Assessment Scale Short Form, a standardised scale reporting on symptom prevalence in the previous seven days, with three subscale indices of Physical Symptom Distress (MSAS-Phys), Psychological Symptom Distress (MSAS-Psych) and Global Distress Index (MSAS-GDI)(14). Each of these 3 subscales has a possible score range of 0-4. This well-validated multidimensional instrument captures the presence and distress of 26 physical and 6 psychological

symptoms. Total number of symptoms (out of a possible 32) was also ascertained. Although it was originally validated among cancer patients, it is commonly applied in a range of progressive conditions, and has the advantage of enabling comparison between patient populations.

## **Analysis**

Descriptive statistics were used to report the entire sample characteristics.

Then, the following analysis was conducted on the full sample.

Univariate linear regression analyses were conducted to test the association of various factors with the following four dependent variables: 1) physical symptom distress subscale, 2) psychological symptom distress subscale, 3), global symptom distress subscale and 4) number of symptoms. Each of these 4 dependent variables formed a separate model in the subsequent multivariable analyses described below.

Independent variables entered in univariate analysis for the whole sample were: age, gender/sexuality, ethnicity, UK-born or not, education, unprotected intercourse, disclosure, and current treatment status. For each model gender/sexuality, ethnicity, education, and treatment were collapsed to two levels: gay male/heterosexual, university educated/not, Caucasian/not Caucasian, and on ART treatment/not on treatment.

Subsequently, for the subsample of patients currently on ART treatment, the analysis was repeated for those patients only with additional treatment-related independent variables entered: treatment switching as two levels

(switched/not switched), and adherence entered as a three level variable: fully adherent/partially adherent/non-adherent. Current treatment status was not entered into these models.

Following each univariate regression, multivariable regressions models were constructed. Independent variables from the univariate analyses above were entered stepwise into the multivariable model if significant at the 25% level(15). Cases with missing data were excluded from the multivariable models .

The multivariable analysis was conducted first on the entire sample, then for the subsample currently on ART.

## **RESULTS**

### **Sample characteristics**

The sample mean age was 40.4 years (SD=8.6). The majority identified as gay or bisexual males (n=496, 65.7%), with n=183 (24.2%) female and n=76 (10.1%) heterosexual male (missing=23). The majority were Caucasian (n=513, 67.3%), with n=188 Black (24.7%), n=23 Asian (3.0%), and n=38 (5.0%) mixed/other (missing n=16). The majority were UK born (396, 50.9%). Educational attainment was reported as follows: no qualifications (n=67, 9.0%), exams attained at age 16 n=190 (25.4%), exams attained at age 18 n=154 (20.6%), university degree or above n=336 (45.0%), missing n=31.

### **Treatment variables**

Most patients were currently on ART (524, 67.4%), with 155 (19.9%) treatment naïve (the remaining 99 having stopped treatment). Adherence in the preceding seven days was as follows: fully adherent 41.5%, partially adherent 36.1%, non-adherent 22.4%. HIV status had not been disclosed to anyone by 47 respondents (6%). Unprotected sexual intercourse in the previous three months with a person who respondents were not sure was also HIV-infected was reported by 85 of the sample (10.9%).

With respect to treatment switching, of those on ART, 161 (32.7%) had not switched from their first treatment regimen, 135 (27.4%) had switched once, 196 (39.8%) reported multiple switches, (32 missing)

INSERT TABLE 1 HERE

### **Symptomatology**

The mean number of reported symptoms was 17.9 (SD=12.1), the mean (standard deviation) symptom distress subscale indices were physical distress 0.81 (0.7), psychological distress 1.34 (1.0) and global distress 1.16 (0.8).

The prevalence and distress of the ten most commonly reported symptoms are described in Table 1. Manifestations of fatigue were most common, namely lack of energy (70.8%) and feeling drowsy/tired (67.5%). Problems related to psychological distress included difficulty sleeping (61.8%), difficulty concentrating (60.7%), feeling worried (69.9%), feeling sad (66.3%) and

feeling irritable (56.6%). Other common physical symptoms were diarrhoea (53.6%), problems with sexual activity (53.5%) and pain (53.2%).

INSERT TABLES 2 and 3 HERE

### **Multivariable analysis**

For the full sample (n=778), Table 2 shows univariable associations and Table 3 shows multivariable regressions. In the multivariable models, lack of university-level education was significantly associated with poorer outcomes in all symptom distress indices; regression coefficients (b) for university-level versus other education were as follows: b=-0.111, p=0.004 for physical distress, b=-0.096, p=0.017 for psychological distress, b=-0.101, p=0.007 for global distress, b=-0.090, p=0.021 for total number of symptoms. Identifying as Caucasian was associated with lower global distress (b=-0.076, p=0.040). Having disclosed HIV status was significantly associated with lower number of symptoms (b=-0.090, p=0.021). Reporting unprotected intercourse in the previous three months with a person not known to be also HIV positive was associated with greater psychological symptom distress (b=0.080, p=0.047). Interestingly, currently being on ART was not significantly associated with any of the symptom measures.

Tables 4 and 5 show the analysis restricted to patients currently on ART (n=524) (see Tables 4 and 5). In multivariable models (Table 5), poorer ART adherence was significantly associated with both psychological (b for trend across adherence categories=0.126, p=0.001) and global symptom distress

( $b=0.125$ ,  $p=0.006$ ). Having ever switched treatment was significantly associated with higher physical symptom distress ( $b=0.135$ ,  $p=0.003$ ), higher psychological symptom distress ( $b=0.126$ ,  $p=0.006$ ), higher global symptom distress ( $b=0.152$ ,  $p=0.001$ ), and a greater number of symptoms ( $b=0.132$ ,  $p=0.013$ ). Being UK-born and university education were also independently associated with lower physical symptom burden.

INSERT TABLES 4 and 5 HERE

## **DISCUSSION**

The data, among out-patient HIV clinic attendees, reveal high seven-day prevalence, and associated distress, of burdensome symptoms. Psychological problems and pain were of particular concern. A symptom prevalence grid comparing evidence for end-stage patients reported on three of the most prevalent symptoms also reported in this study(16). Prevalence in our sample was at the top end of the reported range for both diarrhoea and fatigue, and in the mid-range for pain, compared to patients with advanced malignant, renal and pulmonary disease. Therefore, the symptom control needs of HIV outpatients, including those on treatment, are comparable to those with advanced malignant and non-malignant progressive diseases. This high prevalence of distressing symptoms should be taken into account to inform assessment and management within HIV clinical services.

The associations between symptom prevalence/burden and demographic, clinical and behavioural variables have identified significant relationships that should be taken account of to inform symptom assessment, adherence maximisation, and risk reduction. The associations with being non-UK born/not Caucasian may be a reflection of the tendency for this population to be diagnosed with more advanced disease. It may also be that persons born outside the UK, where HIV stigma is more prevalent, are less likely to disclose their infection and therefore experience a high symptom burden. The association between having switched regimen and greater number of symptoms may be due to those with more symptoms being more likely to wish to change treatment, having to take regimens with a higher side-effect burden, or simply having more advanced disease.

It is of particular note and importance that the data have shown that currently being on ART was not associated with having fewer symptoms or lower symptom distress, strongly indicating the continuing need for clinical attention to symptoms after initiating ART. Longitudinal studies are needed to identify causal relationships between initiating/maintaining specific treatment regimens and both physical and psychological symptomatology.

There are several potential limitations to our findings. Firstly, although the response rate was high (77% of all clinic attendees, 86% of eligible attendees), a small number of patients did not meet the inclusion criteria (i.e. ability to self-complete, in line with ethical review requirements). The period of recruitment (three months) would have enabled most patients to be approached in outpatient settings. The cross sectional nature of the study can

identify associations, but cannot identify causal relationships. Although the response rate is high, we do not have data to compare prevalence of symptoms between responders and non-responders. Additional data in future studies on the relationship between biological markers of disease (CD4 count, viral load) and symptomatology would add further understanding of the aetiology of these problems. We would also advocate further studies to investigate these relationships in resource-poor settings. Lastly, due to the early provision of needle exchange in the UK, we have a very small population of people infected via intravenous drug use. Further study is warranted in countries where this population constitutes a greater proportion of HIV patients.

The body of evidence on the symptom control needs of people living with HIV disease in the ART era has been limited, and has not previously been investigated in relation to other clinical and behavioural variables. There are many barriers to effective symptom control for people with HIV disease, including the lack of awareness of symptoms associated with HIV disease, patient belief that pain should be expected following an HIV diagnosis, and a focus on purely virological outcomes(17). Greater clinical attention must be paid to the high prevalence of distressing psychological symptoms experienced by the majority of people living with HIV, as a systematic review of the evidence demonstrates that symptoms can be effectively managed(18). It is essential that quality management of HIV disease routinely assesses these distressing problems, so that key outcomes of risk behaviours and adherence may be optimally influenced. An essential step toward holistic

management of the patient is to ensure that care protocols routinely ask about the full range of problems that the patient may experience. Physician-led identification of problems is likely to lead to improved identification and management of problems than by expectations that patients will present their physical and psychological symptoms. Effective treatment strategies should be implemented through integrated patient management between HIV clinicians, mental health providers, and symptom management specialists. Generalist palliation of problems should be a core skill among all clinicians, with clear referral guidelines to, and knowledge of, local symptom control and palliation teams. In terms of management strategies for control of the highly prevalent range of psychological problems (and manifestations such as fatigue), systematic reviews of the evidence are urgently required to identify the most effective approaches. As HIV prognosis has greatly improved and a chronic disease model prevails, interventions that are appropriate to longer-term coping are required. It is clear that despite advances in universal treatment, the patient burden of disease remains high, and outcomes are unlikely to be improved without careful attention to the patient experience of disease and a clinical focus beyond virology.

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## **CONFLICT OF INTERESTS**

The authors have no conflict of interests.

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## **CONTRIBUTIONS OF AUTHORS:**

LS&RH designed the study and were involved at all stages; HLD MF MJ SE and JA commented on design and participated in data collection and write up;

FL is the study statistician; SN and CL were the study research assistants and co-ordinated data collection and data handling.

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Table 1 - The ten physical and psychological symptoms with highest 7-day prevalence and their associated distress (MSAS-SF) (n=778)

Physical Symptom	% of patients reporting symptom	% who reported symptom but did not rate distress	Level of distress (as % of all patients)				
			Not at all	A little bit	Somewhat	Quite a bit	Very much
Lack of energy	70.8%	4.5%	10.8%	19.8%	12.3%	12.1%	10.8%
Feeling drowsy/tired	67.5%	4.9%	10.7%	19.8%	9.8%	12.3%	10.0%
Difficulty sleeping	61.8%	4.8%	13.5%	10.9%	9.5%	12.1%	10.9%
Difficulty concentrating	60.7%	4.0%	16.6%	15.2%	10.3%	9.1%	5.5%
Diarrhoea	53.6%	2.7%	17.6%	12.6%	7.6%	7.5%	5.4%
Problems with sexual activity	53.5%	3.6%	15.7%	8.1%	6.6%	7.1%	12.2%
Pain	53.2%	3.1%	18.0%	12.0%	5.9%	8.6%	5.4%
Psychological Symptom	% of patients reporting symptom	% who reported symptom but did not rate distress	How often				
			Rarely	Occasionally	Frequently	Almost constantly	
Worried	69.9%	5.4%	8.4%	25.4%	21.5%	9.1%	
Sad	66.3%	4.8%	11.8%	26.9%	16.7%	6.2%	
Irritable	56.6%	3.1%	10.4%	22.4%	16.3%	4.2%	

Table 2 – Associations of factors with symptom measures: univariable analysis whole sample n=778

Dependent Variable	Independent Variables							
	Age	Gender/ Sexuality: <i>gay male vs not male vs not</i>	Ethnicity: <i>Caucasian vs non-white</i>	UK-born: <i>UK born vs not</i>	Education <i>University vs not</i>	Disclosure: <i>Disclosed to anyone vs no-one</i>	Unprotected sex: <i>in previous 3 months vs not</i>	Current treatment status: <i>on ART vs not</i>
<b>Model 1: MSAS physical distress index</b>	B=-0.053 <i>p=0.147*</i>	B=0.007 <i>p=0.840</i>	B=-0.044 <i>p=0.228*</i>	B=-0.12 <i>p=0.737</i>	B=-0.105 <i>p=0.004*</i>	B=-0.077 <i>p=0.034*</i>	B=0.004 <i>p=0.911</i>	B=0.044 <i>p=0.220*</i>
<b>Model 2: MSAS psychological distress index</b>	B=-0.046 <i>p=0.209*</i>	B=0.068 <i>p=0.060*</i>	B=-0.087 <i>p=0.016*</i>	B=0.053 <i>p=0.141*</i>	B=-0.080 <i>p=0.028*</i>	B=0.017 <i>p=0.659</i>	B=0.065 <i>p=0.094*</i>	B=0.001 <i>p=0.972</i>
<b>Model 3: MSAS global distress index</b>	B=-0.013 <i>p=0.725</i>	B=-0.047 <i>p=0.200*</i>	B=-0.077 <i>p=0.034*</i>	B=0.031 <i>p=0.382</i>	B=-0.083 <i>p=0.022*</i>	B=-0.036 <i>p=0.324</i>	B=0.038 <i>p=0.331</i>	B=0.016 <i>p=0.649</i>
<b>Model 4: Total number of symptoms</b>	B=0.011 <i>p=0.768</i>	B=-0.037 <i>p=0.315</i>	B=0.012 <i>p=0.744</i>	B=-0.082 <i>p=0.025*</i>	B=-0.104 <i>p=0.005*</i>	B=-0.092 <i>p=0.012*</i>	B=-0.004 <i>p=0.927</i>	B=0.034 <i>p=0.328</i>

\*entered into multivariable model

Table 3 - Associations of factors with symptom measures: multivariable analysis models for whole sample n=778

Dependent variable	Independent variables							
	Age	Gender/sexuality: gay male vs not	Ethnicity: Caucasian vs non-white	UK-born: UK born vs not	Education: University vs not	Disclosure: Disclosed to anyone vs no-one	Unprotected sex: in previous 3 months vs not	Current treatment status: on ART vs not
<b>Model 1: MSAS Physical distress index</b>	B=0.059 <i>p</i> =0.126		B=-0.062 <i>p</i> =0.110		B=-0.111 <i>p</i> =0.004 <sup>†</sup>	B=-0.042 <i>p</i> =0.282		B=0.052 <i>p</i> =0.184
<b>Model 2: MSAS psychological distress index</b>	B=0.004 <i>p</i> =0.920	B=0.057 <i>p</i> =0.161	B=-0.063 <i>p</i> =0.117	B=-0.034 <i>p</i> =0.401	B=-0.096 <i>p</i> =0.017*		B=0.080 <i>p</i> =0.047*	
<b>Model 3: MSAS Global distress index</b>		B=-0.004 <i>p</i> =0.926	B=-0.076 <i>p</i> =0.040*		B=-0.101 <i>p</i> =0.007 <sup>†</sup>			
<b>Model 4: Total number of symptoms</b>				B=-0.057 <i>p</i> =0.148	B=-0.090 <i>p</i> =0.021*	B=-0.090 <i>p</i> =0.021*		

\*= sig at the 5% level, <sup>†</sup>= sig at the 1% level

Table 4 - Associations of factors with symptom measures: univariable analysis only for those on treatment n=524

Dependent Variable	Independent Variables								
	Age	Ethnicity: <i>Caucasian vs non-white</i>	Gender/ Sexuality: <i>gay male vs not</i>	UK-born: <i>UK born vs not</i>	Education: <i>University vs not</i>	Disclosure: <i>Disclosed to anyone vs no-one</i>	Unprotected sex: <i>in previous 3 months vs not</i>	Adherence\$: <i>Fully vs partially vs non-adherent</i>	Switching: <i>Switched vs not</i>
<b>Model 1: MSAS physical distress index</b>	B=0.016 <i>p=0.722</i>	B=-0.013 <i>p=0.768</i>	B=-0.015 <i>p=0.739</i>	B=-0.068 <i>p=0.121*</i>	B=-0.098 <i>p=0.028*</i>	B=-0.015 <i>p=0.745</i>	B=-0.020 <i>p=0.669</i>	B=0.053 <i>p=0.240*</i>	B=0.126 <i>p=0.005*</i>
<b>Model 2: MSAS psychological distress index</b>	B=-0.045 <i>p=0.304</i>	B=-0.047 <i>p=0.289</i>	B=-0.048 <i>p=0.279</i>	B=0.013 <i>p=0.768</i>	B=-0.091 <i>p=0.042*</i>	B=0.042 <i>p=0.373</i>	B=0.028 <i>p=0.554</i>	B=0.157 <i>p=0.001*</i>	B=0.106 <i>p=0.019*</i>
<b>Model 3: MSAS global distress index</b>	B=-0.012 <i>p=0.792</i>	B=-0.047 <i>p=0.291</i>	B=-0.038 <i>p=0.397</i>	B=-0.012 <i>p=0.790</i>	B=-0.086 <i>p=0.054*</i>	B=-0.037 <i>p=0.430</i>	B=0.015 <i>p=0.748</i>	B=0.111 <i>p=0.013*</i>	B=0.132 <i>p=0.005*</i>
<b>Model 4: Total number of symptoms</b>	B=-0.010 <i>p=0.816</i>	B=0.049 <i>p=0.272</i>	B=-0.103 <i>p=0.022*</i>	B=-0.130 <i>p=0.003*</i>	B=-0.086 <i>p=0.057*</i>	B=-0.086 <i>p=0.069*</i>	B=-0.056 <i>p=0.246*</i>	B=0.071 <i>p=0.119*</i>	B=0.109 <i>P=0.017*</i>

\*entered into multivariable model

\$ tests for trend

Table 5 - Associations of factors with symptom measures: multivariable models only for those on treatment n=524

Dependent variable	Independent variables									
	Age	Ethnicity: <i>Caucasian vs non-white</i>	Gender/ sexuality: <i>gay male vs not</i>	UK-born: <i>UK born vs not</i>	Education: <i>University vs not</i>	Disclosure: <i>Disclosed to anyone vs no-one</i>	Unprotected sex: <i>in previous 3 months vs not</i>	Adherence \$: <i>Fully vs partially vs non-adherent</i>	Switching: <i>Switched vs not</i>	
<b>Model 1: MSAS Physical distress index</b>				B=-0.095 <i>p=0.038*</i>	B=-0.093 <i>p=0.042*</i>			B=0.051 <i>p=0.986</i>	B=0.135 <i>p=0.003<sup>†</sup></i>	
<b>Model 2: MSAS psychological distress index</b>					B=-0.081 <i>p=0.072</i>			B=0.166 <i>p=0.001<sup>†</sup></i>	B=0.126 <i>p=0.006<sup>†</sup></i>	
<b>Model 3: MSAS Global distress index</b>					B=-0.073 <i>p=0.106</i>			B=0.125 <i>p=0.006<sup>†</sup></i>	B=0.152 <i>p=0.001<sup>†</sup></i>	
<b>Model 4: Total number of symptoms</b>			B=-0.036 <i>p=0.526</i>	B=-0.129 <i>p=0.015*</i>	B=-0.046 <i>p=0.383</i>	B=-0.080 <i>p=0.131</i>	B=-0.037 <i>p=0.480</i>	B=0.054 <i>p=0.309</i>	B=0.132 <i>p=0.013<sup>†</sup></i>	

\*= sig at the 5% level, †= sig at the 1% level, \$=test for trend