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Paracetamol sales and atopic disease in children and adults: an ecological analysis

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Paracetamol sales and atopic disease in children and adults: an ecological analysis. R.B. Newson, S.O. Shaheen, S. Chinn, P.G.J. Burney. ©ERS Journals Ltd 2000.

ABSTRACT: The authors recently observed that frequent paracetamol use was positively associated with asthma and rhinitis in young adults. Therefore, an ecological analysis was performed to measure international associations between paracetamol sales and atopic disease prevalences in children and adults.

Published data from the International Study of Asthma and Allergies in Childhood (ISAAC) on the prevalence of four atopic symptoms in 13–14-yr-olds (112 centres) and 6–7-yr-olds (66 centres) in 1994/1995, and European Community Respiratory Health Survey (ECRHS) data on the prevalence of asthma symptoms, diagnosed asthma and rhinitis (44 centres), prevalence of atopy, mean bronchial responsiveness and mean total immunoglobulin E levels (34 centres) in young adults in 1991/1992, were used. Their associations with national 1994/1995 per capita paracetamol sales were measured using linear regression.

Paracetamol sales were high in English-speaking countries, and were positively associated with asthma symptoms, eczema and allergic rhinoconjunctivitis in 13–14-yr-olds, and with wheeze, diagnosed asthma, rhinitis and bronchial responsiveness in adults. The prevalence of wheeze increased by 0.52% in 13–14-yr-olds and by 0.26% in adults ($p<0.0005$) for each gram increase in per capita paracetamol sales.

These ecological findings require cautious interpretation, but raise the possibility that variation in paracetamol usage may explain some of the variation in atopic disease prevalence between countries.

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There is wide international variation in the prevalence of asthma in adults [1] and children [2], which is largely unexplained. In particular, it is not known why the prevalence tends to be higher in English-speaking countries. One hypothesis is that the dietary intake of antioxidants has fallen in these populations and that this has reduced levels of pulmonary antioxidants in individuals, thus rendering them more susceptible to oxidative stress [3]. However, pulmonary antioxidant defences could also have been compromised if the oxidant burden in the lung had increased. Although exposure to inhaled oxidants is thought to have decreased in the latter part of the 1900s [3], the possibility that pulmonary exposure to oxidative stress might have increased *via* systemic sources deserves consideration. In particular, a number of drugs and toxins are metabolized to produce free radicals or deplete antioxidant defences [4]. In animals, paracetamol (acetaminophen) depletes the lung of the antioxidant glutathione in a dose-dependent fashion [5, 6]. In humans, reduced glutathione is present in high concentrations in airway lining fluid [7] and there is some evidence to suggest that it acts to counter oxidative stress in asthmatic airways [8–10]. Glutathione is also present in nasal lavage fluid [11]. These observations led to the examination of the relation between paracetamol use and asthma and rhinitis in a population-based study of adults. It was found that frequent (daily or weekly) use of paracetamol was positively associated with asthma, asthma severity and rhinitis [l2].

In view of these findings, an ecological study was carried out in order to investigate whether the prevalences of asthma and other atopic diseases in children and adults are higher in countries with higher sales of paracetamol.

Methods

Outcome measures in children: the International Study of Asthma and Allergies in Childhood

The International Study of Asthma and Allergies in Childhood (ISAAC) was conducted in 1994–1995 [13]. Symptom prevalences for asthma [2], atopic eczema [14] and allergic rhinoconjunctivitis [15] were measured in up to 155 centres throughout the world, using standardized questionnaires, in children aged 13–14 yrs (self-assessed) and 6–7 yrs (parentally assessed). From these published data, 12-month prevalences (percentages) of wheeze, wheeze disturbing sleep, atopic eczema and allergic rhinoconjunctivitis (rhinitis and itchy eyes) were extracted.

Outcome measures in adults: the European Community Respiratory Health Survey

The European Community Respiratory Health Survey (ECRHS) was conducted in Europe, the USA, Australia

and New Zealand in 1991–1992 [16]. Phase 1 of the survey used a standardized questionnaire to study random samples of adults aged 20–44 yrs across 48 centres in 22 countries. Published data from phase 1 [1] on the age/sex-standardized prevalences of wheeze, waking at night with shortness of breath, rhinitis (hay fever or nasal allergies) and diagnosed asthma (asthma attacks or taking medication) in each centre were used. In phase 2, random samples of phase 1 respondents from some of the centres were assessed in greater detail. A smoking history was obtained, spirometry and bronchial challenge with methacholine (35 centres) were carried out [17], and total and specific immunoglobulin E (IgE) levels (37 centres) were measured [18]. Bronchial responsiveness was measured as a methacholine dose/response "slope", expressed in ECRHS units [17]. (On this scale, zero represents the highest possible responsiveness, 10 represents no responsiveness and scores of >10 are assigned to patients whose airways appear to relax (instead of constricting) in response to methacholine.) Atopy was defined as a specific IgE titre of >0.35 $kU \cdot L^{-1}$ to any of the four common allergens tested in each centre, namely *Dermatophagoides pteronyssinus*, timothy grass, cat and *Cladosporium herbarium* [18]. For each centre, arithmetic mean "slope", geometric mean IgE level and prevalence of atopy, standardized by sex, age (<30 or ≥30 yrs) and smoking (current smokers or nonsmokers) to a hypothetical standard population, were calculated. This standard population was assumed to be 50% male and 50% female, with 60% of each sex aged ≥30 yrs, and 60% of each combination of sex and age group were assumed to be current nonsmokers.

Paracetamol sales and gross domestic product

Data on national paracetamol sales for 1994/1995 (the earliest year of availability) were obtained from IMS-Health, London, UK, which collects sales data on drugs from pharmacies and hospitals in >100 countries. In the case of pharmacies, lMS-Health receives sales records from a majority sample of wholesalers, and also from a stratified sample of retailers (typically several hundred per country), to measure the smaller direct sales from manufacturers to retailers. In the case of hospitals, IMS-Health collects drug purchase data from a sample of hospitals in each country, the sampling fraction being ≥25% in all countries and >50% in some countries. In both cases, appropriate projection factors and stratified sampling methods are used. These data, and 1994 gross domestic products (GDPs) [19], were divided by 1994 populations (all ages) [20], yielding per capita paracetamol sales ($g \cdot person^{-1} \cdot yr^{-1}$) and GDP ($US\$ \cdot person^{-1} \cdot yr^{-1}$) for each national market.

Statistical methods

The associations of outcomes with per capita paracetamol sales and GDP were measured using the Stata statistical package (Stata Statistical Software, Release 6.0; Stata Corporation, College Station, TX, USA) to compute linear regression coefficients. Confidence limits were calculated using Huber variances, because of concern that residual variability might be unequal around different parts of the regression line. The increase (between countries) of per capita paracetamol sales with per capita GDP, as well as the increase (between centres) in atopic outcomes (prevalences or means) per gram increase in per capita paracetamol sales, with and without adjustment for a linear effect of per capita GDP was measured.

Results

Paracetamol sales and gross domestic product

Paracetamol sales data were available for 14 national markets represented in both the ISAAC and the ECRHS, 22 represented in the ISAAC alone and four in the ECRHS alone. Per capita sales varied from 1.07 $g \cdot person^{-1} \cdot yr^{-1}$ in Uruguay to 43.61 $g \cdot person^{-1} \cdot yr^{-1}$ in Denmark. Per capita GDP varied from US$447 in Pakistan to US$37,553 in Japan. Figure 1 shows the scatter plot of national per capita paracetamol sales and GDP for countries represented in either of the two studies. The poorest countries in the ISAAC purchased very little paracetamol. On average, paracetamol sales increased by 0.54 $g \cdot person^{-1} \cdot yr^{-1}$ (95% confidence interval (CI) 0.15–0.94) for each US$1,000 increase in per capita GDP. However, affluent countries showed great variation in sales. The highest rates (>20 $g \cdot person^{-1} \cdot yr^{-1}$) were found in France, the Scandinavian countries (Sweden, Norway and Denmark) and the "white anglophone" countries (the UK, Eire, the USA, Canada, Australia and New Zealand). In contrast, Japan, Germany, Austria and Switzerland (all with per capita GDP of >US$25,000) had paracetamol sales of <8 $g \cdot person^{-1} \cdot yr^{-1}$.

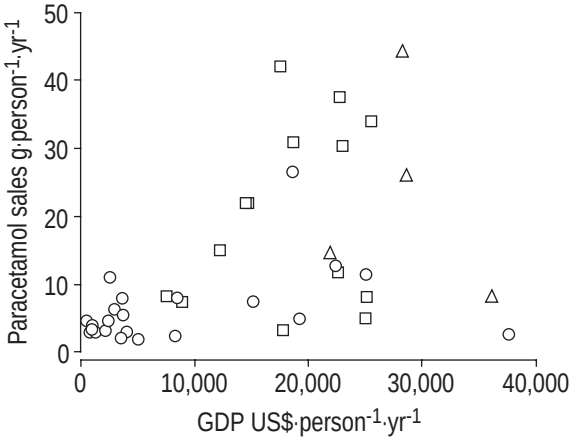

Fig. 1. – Scatter plot of 1994–1995 per capita paracetamol sales against 1994 per capita GDP. □: countries represented in both the International Study of Asthma and Allergies in Childhood (ISAAC) and the European Community Respiratory Health Survey (ECRHS) (Australia, Austria, Belgium, Eire, France, Germany, Greece, Italy, New Zealand, Portugal, Spain, Sweden, the UK and the USA); ○: countries represented in the ISAAC alone (Argentina, Brazil, Canada, Chile, Finland, Hong Kong, Indonesia, Japan, Kuwait, Latvia, Malaysia, Mexico, Morocco, Pakistan, Peru, Philippines, Poland, Singapore, South Africa, South Korea, Thailand and Uruguay); △: countries represented in the ECRHS alone (Denmark, the Netherlands, Norway and Switzerland).

Atopic outcomes in children: International Study of Asthma and Allergies in Childhood centres

Paracetamol sales were positively associated with all four atopic symptoms in 13–14-yr-olds. Table 1 gives the regression coefficients before and after controlling for GDP. For example, the prevalences of wheeze and eczema increased by 0.52 and 0.21% respectively, for each gram increase in per capita paracetamol sales adjusted for GDP. Figure 2 shows the scatter plots of paracetamol sales and each symptom in 13–14-yr-olds. In 6–7-yr-olds, significant associations were seen for all outcomes after controlling for GDP, although the regression coefficients for wheeze were smaller than in 13–14-yr-olds, and the confidence intervals were wider, reflecting smaller numbers of centres (table 1).

Atopic outcomes in adults: European Community Respiratory Health Survey centres

GDP was negatively associated with prevalence of waking at night with shortness of breath. After controlling for paracetamol sales, the prevalence of this symptom decreased by 0.19% (95% Cl 0.05–0.34) for each US$1,000 increase in per capita GDP (p=0.011). However, GDP was not significantly associated with any of the other ECRHS outcomes (data not shown).

Table 2 shows the regression coefficients of outcomes with respect to paracetamol sales, before and after controlling for GDP. Paracetamol sales were positively associated with the prevalences of wheeze, asthma and rhinitis, and negatively with mean "slope", indicating a positive association with bronchial responsiveness. For example the prevalence of wheeze and rhinitis increased by 0.26 and 0.35%, respectively, for every gram increase in per capita paracetamol sales. Paracetamol sales were not associated with the prevalence of waking at night with shortness of breath, or with mean total IgE levels, although there was some evidence for a positive association with atopy. Figure 3 shows the scatter plots of paracetamol sales and respiratory symptoms, asthma and rhinitis.

Post hoc *analyses*

From figures 2 and 3, it was noticed that the prevalences of most outcomes were, broadly speaking, highest in centres in countries with paracetamol sales of >20 g·person^{-1}·yr^{-1} and lowest in centres in countries with sales of <20 g·person^{-1}·yr^{-1}. The former group of centres were mainly anglophone (the remainder being French and Scandanavian). It was therefore decided, *post hoc*, to carry out further regression analyses, controlling additionally for the "anglophone effect". As a result, the paracetamol effects for most outcomes were greatly attenuated or abolished and most became nonsignificant. An exception was the effect on atopic eczema in 13–14-yr-olds in the ISAAC, which, although reduced, remained highly significant (0.13% (95% CI 0.06–0.20); p<0.0005).

Discussion

In the present study, it was found that national paracetamol sales were positively associated with the prevalences of wheeze, asthma, rhinitis and atopic eczema in children across centres participating in the ISAAC. The association with wheeze in 13–14-yr-olds was strong, the prevalence increasing by 0.5% for each gram increase in per capita paracetamol sales. Paracetamol sales were also positively associated with the prevalence of wheeze, asthma and rhinitis and with mean bronchial responsiveness in young adults across centres participating in the ECRHS, which is in keeping with the recent observation that frequent use of paracetamol was positively associated with asthma and rhinitis in adults [12].

Strengths and limitations of the study

The substantial variation in the prevalence of asthma and other atopic diseases, and in paracetamol sales, across countries in the ISAAC and ECRHS provided a good opportunity to test the authors' hypothesis using an ecological approach. A strength of the study is that the outcomes were measured in individuals in these large surveys,

Table 1. – International Study of Asthma and Allergies in Childhood regression coefficients (b) of symptom prevalences with respect to national per capita paracetamol sales*

	Unadjusted		Adjusted for per capita GDP	
	b (95% CI)	p-value	b (95% CI)	p-value
13-14-yr-olds[+]				
Wheeze	0.49 (0.41–0.58)	<0.0005	0.52 (0.44–0.59)	<0.0005
Wheeze disturbing sleep	0.05 (0.03–0.06)	<0.0005	0.06 (0.05–0.07)	<0.0005
Atopic eczema	0.21 (0.18–0.25)	<0.0005	0.21 (0.16–0.26)	<0.0005
Rhinoconjunctivitis	0.14 (0.09–0.19)	<0.0005	0.12 (0.07–0.17)	<0.0005
6-7-yr-olds[#]				
Wheeze	0.28 (0.11–0.45)	0.002	0.31 (0.14–0.48)	0.001
Wheeze disturbing sleep	0.03 (-0.02–0.07)	0.251	0.04 (0.00–0.08)	0.033
Atopic eczema	0.17 (0.10–0.25)	<0.0005	0.18 (0.08–0.29)	0.001
Rhinoconjunctivitis	0.11 (0.03–0.18)	0.007	0.12 (0.04–0.19)	0.002

*: % prevalence increase·g^{-1}·person^{-1}·yr^{-1}; [+]: 112 centres (110 for eczema) in 36 national markets; [#]: 66 centres (65 for eczema) in 28 markets (27 for eczema). GDP: gross domestic product; CI: confidence interval.

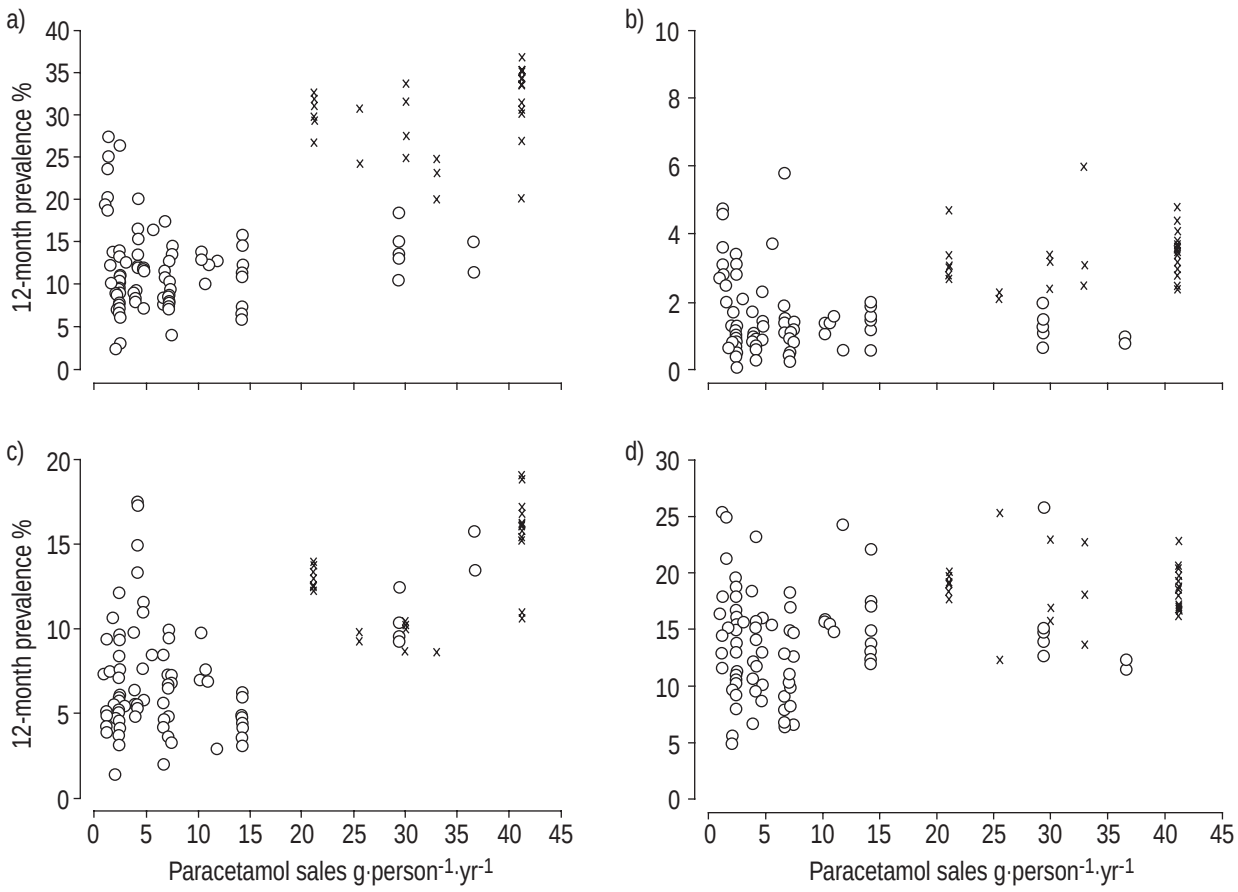

Fig. 2. – Twelve-month prevalences of: a) wheeze; b) wheeze disturbing sleep; c) atopic eczema; and d) allergic rhinoconjunctivitis in 13–14-yr-olds against national per capita paracetamol sales in the International Study of Asthma and Allergies in Childhood. ×: "white anglophone" countries (the UK, Eire, the USA, Canada, Australia and New Zealand); ○: others.

using standardized methodology. The authors believe that the paracetamol data used in the present analyses, which comprise estimates of total over-the-counter and hospital sales, are the most comprehensive international data of their kind available. Furthermore, the uniform method of data collection and the large proportion of outlets sampled in each country makes it less likely that the variation in paracetamol sales is artefactual.

A limitation of the study, as with any ecological analysis, is the use of an aggregate and proxy measure of exposure. National per capita paracetamol sales were used as an indicator of frequent paracetamol use, since it seems likely that the proportion of individuals who use paracetamol frequently in a country will increase as mean per capita sales increase. Furthermore, total national sales were used as indicators of paracetamol use in children and adults across centres in the ISAAC and ECRHS, as data were not available for paediatric and adult sales separately, nor for sales at the centre level. It was, therefore, assumed that the proportion of adult to paediatric sales did not vary substantially between countries, and that national paracetamol sales were representative of sales in different centres within countries. Although paracetamol sales data for 1991/1992 would have been more appropriate for the ECRHS analyses, these were not available. However, the authors believe that the 1994/1995 data were broadly representative of sales 3 yrs previously, since, when the 3 yrs after 1994/1995 were investigated, it was found that the ranking of countries according to paracetamol sales remained virtually the same (data not shown).

Confounding

GDP was positively related to paracetamol sales and was therefore a potential confounder. However, the present findings were not substantially altered when GDP was controlled for. Furthermore, in the ECRHS analyses, symptom prevalences were standardized for age and sex, and BHR and atopy were standardized additionally for smoking. This is in keeping with a previous study of individuals, in which frequent paracetamol use was associated with asthma and rhinitis after controlling for age, sex, smoking and detailed socioeconomic factors [12], as well as dietary factors (authors′ unpublished data). Nevertheless, in an ecological study of this kind, the possibility that the association between paracetamol sales and prevalence of atopic disease is explained by other confounding factors, in particular those which are associated with the anglophone culture but which are not associated with the level of economic development, cannot be ruled out.

A possible mechanism

An alternative explanation for these findings is that, in countries with higher paracetamol sales, high usage of

Table 2. – European Community Respiratory Health Survey (ECRHS) regression coefficients (b) of outcomes with respect to per capita paracetamol sales*

Outcome (centres/markets)	Unadjusted		Adjusted for per capita GDP	
	b (95% CI)	p-value	b (95% CI)	p-value
Standardized prevalence (%)[+]				
Wheeze (44/18)	0.23 (0.13–0.34)	<0.0005	0.26 (0.16–0.37)	<0.0005
Waking with SOB (43/17)	0.00 (-0.05–0.05)	0.935	0.02 (-0.03–0.06)	0.706
Diagnosed asthma (43/18)	0.09 (0.05–0.13)	<0.0005	0.10 (0.06–0.14)	<0.0005
Rhinitis (41/17)	0.36 (0.22–0.51)	<0.0005	0.35 (0.21–0.49)	<0.0005
Standardized level[#]				
BHR "slope" ECRHS units (34/15)[‡]	-0.02 (-0.03–0.00)	0.009	-0.02 (-0.03–0.00)	0.009
Total IgE kU·L^{-1} (34/14)[§]	-0.10 (-0.37–0.18)	0.488	-0.09 (-0.36–0.18)	0.496
Atopy % (34/14)	0.20 (-0.02–0.42)	0.072	0.20 (-0.02–0.41)	0.071

*: increase·g^{-1}·person^{-1}·yr^{-1}; [+]: by age group and sex; [#]: by age group, sex and smoking; [‡]: arithmetic mean; [§]: geometric mean. GDP: gross domestic product; CI: confidence interval; SOB: shortness of breath; IgE: immunoglobulin E.

paracetamol is contributing directly to a higher prevalence of atopic disease. The authors' earlier observation that asthma was associated with increased use of paracetamol in individuals supports such a causal interpretation. This contrasts with the indirect link proposed by VARNER *et al.* [21], who suggested that substitution of paracetamol for aspirin over time may have contributed to the rise in childhood asthma, not because paracetamol had a detrimental effect but because a protective effect of aspirin had been lost. It has been speculated that frequent use of paracetamol might influence asthma and rhinitis by depleting levels of reduced glutathione in the nose and airways, thus shifting the oxidant/antioxidant balance in favour of oxidative stress and increasing inflammation [12]. The authors believe that such a mechanism is plausible for two reasons. First, there are clues that glutathione plays a role in asthma. In adults, airway levels of total and oxidized glutathione are increased in stable asthma [8, 9] and levels of reduced glutathione are decreased in acute asthma [10], indicating a response to oxidative stress.

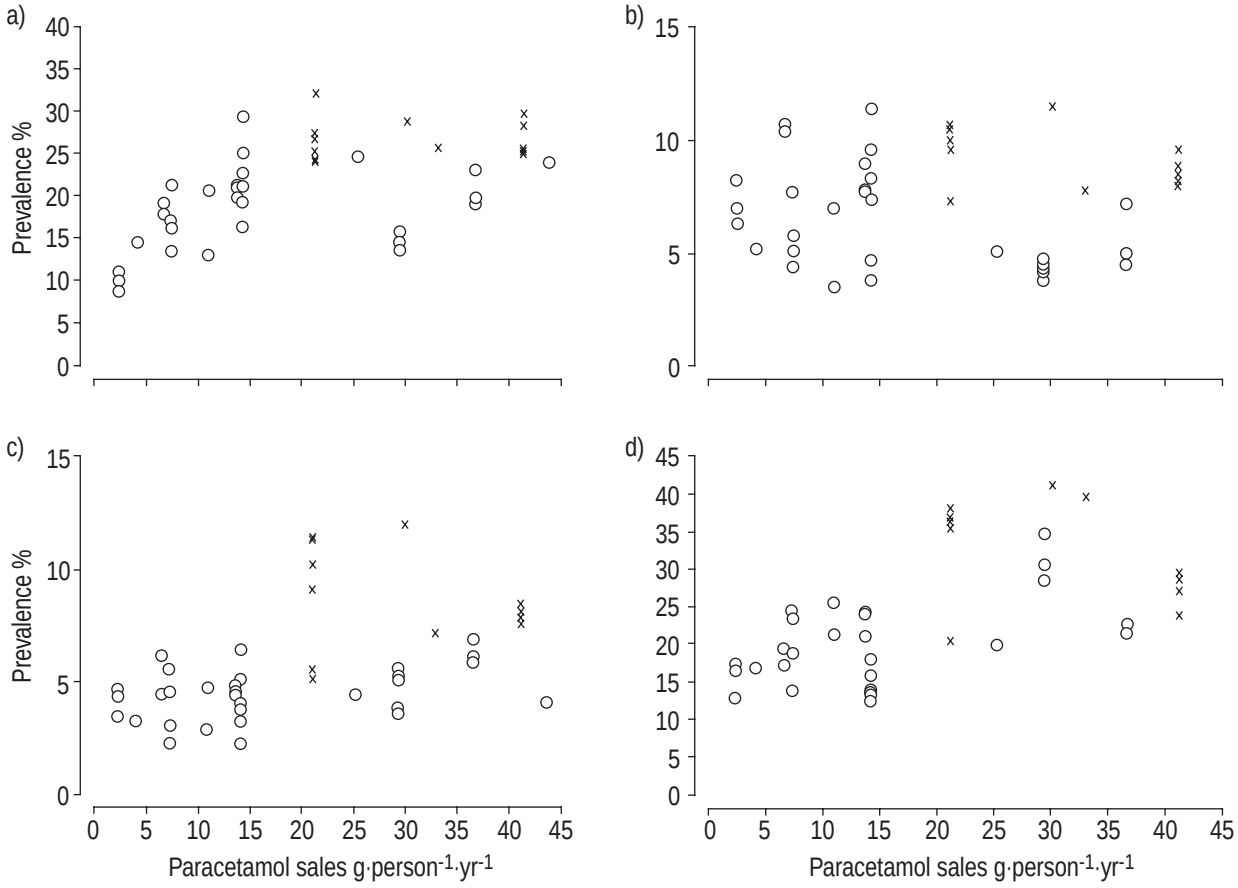

Fig. 3. – Prevalences of: a) wheeze; b) waking at night with shortness of breath; c) diagnosed asthma; and d) rhinitis in adults aged 20–44 yrs against national per capita paracetamol sales in the European Community Respiratory Health Survey. ×: "white anglophone" countries (the UK, Eire, the USA, Australia and New Zealand); ○: others.

Also, the ability of glutathione to downregulate nuclear factor-κB [22], and the inverse association between alveolar glutathione levels and bronchial responsiveness [9], suggests that glutathione may modify asthma inflammation. Secondly, studies in animals have found that paracetamol can deplete the lung of glutathione [5, 6]. Recent *in vitro* work has shown that clinically relevant concentrations of paracetamol deplete glutathione in alveolar macrophages and type 2 pneumocytes in rats [23] and in human pulmonary macrophages (S. Dimova and B. Nemery, Laboratory of Pneumology, Catholic University of Louvain, Louvain, Belgium, personal communication). These effects in macrophages raise the possibility that paracetamol might also influence atopic diseases more generally through another mechanism, namely the promotion of atopy, since depletion of glutathione in antigen-presenting cells promotes T-helper cell 2-type cytokine responses [24]. This might explain why, in children, paracetamol sales were associated with atopic eczema as well as with asthma and rhinitis. The lesser contribution of atopy to wheeze in younger children might explain the weaker association observed between paracetamol sales and wheeze in 6–7-yr-olds compared with 13–14-yr-olds. Although the ECRHS analyses provide some evidence for an association between paracetamol and atopy, the relation was weak, suggesting that, at least in adults, depletion of antioxidant defences may be the predominant mechanism by which paracetamol influences asthma and rhinitis.

The anglophone link

It has been noted previously that centres in English-speaking Western countries in the International Study of Asthma and Allergies in Childhood and the European Community Respiratory Health Survey tend to have some of the highest prevalences of atopic symptoms, bronchial responsiveness and atopy, a phenomenon which has hitherto been unexplained [1, 17, 18, 25]. Interestingly, these countries also appear to have some of the highest paracetamol sales (>20 $g \cdot person^{-1} \cdot yr^{-1}$) (figs. 2 and 3). When this was investigated, *post hoc*, and the "anglophone effect" controlled for, the associations between paracetamol and all outcomes, with the exception of atopic eczema in older children, were greatly attenuated or abolished and most became nonsignificant. There are two possible interpretations: either some unknown confounding factor, strongly associated with anglophone culture and paracetamol sales, is responsible for the findings or high paracetamol usage explains some of the higher prevalence of atopic disease in English-speaking countries, particularly in children. Although the first explanation may seem more likely, the authors believe that the association between paracetamol use and atopic disease warrants further investigation using more rigorous epidemiological approaches.

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