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The relation between paracetamol use and asthma: a GA^{2}LEN European case-control study

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Abstract

Studies from the UK and the USA suggest that frequent use of paracetamol (acetaminophen) may increase the risk of asthma, but data across Europe are lacking.

As part of a multi-centre case-control study organised by the GA^{2}LEN network we have examined whether frequent paracetamol use is associated with adult asthma across Europe. The network compared 521 cases with a diagnosis of asthma and reporting asthma symptoms in the last 12 months with 507 controls with no diagnosis of asthma and no asthmatic symptoms in the last 12 months across 12 European centres. All cases and controls were selected from the same population defined by age (20-45 years) and place of residence.

In a random effects meta-analysis, after controlling for confounders, the adjusted odds ratio for asthma associated with weekly use of paracetamol, compared with less frequent use, was 2.87 (95% CI: 1.49 to 5.37), P=0.002. There was no evidence for heterogeneity across centres. No association was seen between use of other analgesics and asthma.

These data add to the increasing and consistent epidemiological evidence implicating frequent paracetamol use in asthma in diverse populations.

Background

In recent years evidence has been accumulating that frequent paracetamol (acetaminophen) use is associated with asthma in adults. Following the initial finding in a population-based case-control study of adult asthma in London, UK[1], other studies have replicated these observations. The Nurses Health Study in the USA reported a positive prospective association between paracetamol use and incident asthma in women[2]. Positive cross-sectional associations have also been found in Ethiopia in relation to allergic symptoms[3], and in the US NHANES study in relation to asthma and COPD[4]. We have also observed positive geographical correlations between paracetamol sales and asthma, wheeze, rhinitis and bronchial hyper-responsiveness in adults across Europe[5], but given the limitations of ecological studies, we wanted to see whether an association between frequent paracetamol use and adult asthma could be confirmed in individuals living in different environments. As part of a multi-centre case-control study organised by the GA^{2}LEN network, which was set up primarily to assess the relation of plasma selenium to adult asthma, we have examined the relation between analgesic use and asthma in European adults.

Methods

The study was a case-control study. Cases were aged 20 to 45 years, living in a defined area and had both a self-reported diagnosis of asthma and either wheezing, or shortness of breath, or waking at night with breathlessness in the previous 12 months[6]. Controls lived in the same area, were aged 20 to 45 years old and had neither a diagnosis of asthma nor any of the three symptoms. In the first instance cases and controls were identified from a population-based survey, mostly through a simple screening questionnaire sent by post. However, these surveys were not always large enough to find adequate numbers of cases and further cases could be recruited from clinics providing that they met the criteria and were not being treated in the clinic for another atopic condition. Each centre was asked to recruit 50 cases and 50 controls.

Once identified the participants were invited to complete a longer administered questionnaire and had their height and weight measured. Skin tests were undertaken using ALK-Abello reagents against timothy grass, cat dander, Dermatophagoides farinae, olive, birch parietaria, alternaria and histamine (10mg/ml) and diluent controls. Atopy was defined by the very sensitive criterion of any atopic wheal greater than the diluent control in the presence of a positive histamine control. Asthma cases who had night time symptoms twice or less per month, trouble breathing less than once a day, FEV_1 at least 80% predicted, and were using at most a medium dose of inhaled steroid, were classified as having intermittent and mild persistent disease; those with more severe symptoms, worse lung function and higher doses of steroids were classified as having moderate or severe persistent disease.

Central training was given to staff in each centre prior to involvement with the main data collection. Questionnaires were forward and back translated and the original

questionnaires and the back translations compared and reconciled. Participants were asked how often they took paracetamol and how often they took other painkillers not containing paracetamol (such as aspirin or ibuprofen). The options were: less than once a week, 1-2 days/week, 3-4 days/week, 5-6 days/week and daily. However, as very frequent use turned out to be uncommon, we collapsed down the top four categories into one 'weekly' category for the main analyses. Socio-economic status was assessed from current or last occupation and classified as professional, managerial, skilled, semi-skilled, unskilled or student. Smoking status was classified as: never smoked and exposed to less than one hour environmental tobacco smoke per day; never smoked and exposed to at least one hour of environmental tobacco smoke per day; ex-smokers; current smokers. Participants were asked if they took regular vitamin or mineral supplements. After examining the distributions of the variables, logistic regression was used to estimate the risk of being a case in each centre. These analyses controlled for the potential confounders gender, age, smoking, socio-economic status, supplement use, and body mass index (kg/m^2). After the initial within-centre analyses the results were combined across centres using random effects meta-analysis. All analyses were undertaken in Stata.

Local ethical committee approval was given in each centre and approval was given by the Norwegian Data Inspectorate. Each participant was provided with an information sheet explaining the study, and signed a consent form prior to taking part.

Results

The 12 centres recruited 521 cases and 507 controls in total . Clinic visits ran between May 2005 and May 2007.

Table 1 shows the distribution of potential confounders in cases and controls. Cases were more likely than controls to be overweight and obese, female, and less likely to be working in professional jobs. Smoking history, supplement use and mean age were similar in the two groups. The prevalence of atopy in cases and controls was 82% and 36%, respectively. Amongst cases, 54% were classified as having intermittent or mild persistent disease, and the remainder as having moderate or severe persistent disease.

Table 2 shows the frequency of use of paracetamol and other analgesics by centre and case-control status. In Italy (Palermo and Rome) no participants reported weekly paracetamol use and the highest frequency of weekly use was in Amsterdam. Overall, 8.9% of individuals reported taking paracetamol at least once a week. This was more common in cases (13.2%) than in controls (4.5%). In the main paracetamol analyses three centres were dropped (Vienna, Rome and Palermo) as there were too few individuals taking paracetamol weekly and this led to a failure of the regression model to converge. Similarly, we had to omit Amsterdam and Barcelona from the analyses of other analgesic use for the same reason.

Table 3 shows the unadjusted and adjusted odds ratios for asthma according to paracetamol use in each centre, and in all centres combined. This shows that weekly paracetamol use (compared with less frequent use) was positively associated with

asthma, and the overall effect estimate became stronger after controlling for confounders (adjusted odds ratio 2.87 (95% CI: 1.49 to 5.37), P=0.002). There was no significant heterogeneity between centres (P=0.61). The meta-analysis of the adjusted effects is summarised in Figure 1.

Table 4 shows the unadjusted and adjusted odds ratios for asthma according to other analgesic use in each centre, and in all centres combined. The overall adjusted effect estimate showed a non-significant positive association with asthma, and again there was no significant heterogeneity between centres. The meta-analysis of the adjusted effects is summarised in Figure 2. When we included paracetamol use and other analgesic use together in the regression model, the overall adjusted effect estimate for paracetamol was only slightly attenuated (OR 2.66 (1.33 to 5.33), P=0.006). 75% of cases reported rhinitis. If we included rhinitis in the model the adjusted odds ratio was reduced a little to 2.39 (1.06-5.37), P=0.036.

Discussion

In this multi-centre study across Europe we have confirmed a positive association between frequent use of paracetamol and adult asthma, in keeping with previous studies of individuals from the UK[1] and USA[2][4], and ecological observations across Europe[5]. Weekly users of paracetamol were more likely than those taking the drug less often to have asthma, and there was no significant heterogeneity in this result between centres. No significant relation was seen between use of other analgesics and asthma.

A strength of this study is that the methods and definitions were standardised across centres. However, there are some limitations. First, most individuals took paracetamol less than once a week and our questions on analgesic use did not enable us to categorise infrequent use in more detail and to distinguish those who never took paracetamol. Furthermore, there were insufficient numbers of weekly users to enable us to break this category down further. Hence we could not determine whether a dose-response relation was present. Second, the cross-sectional nature of the association makes a causal interpretation difficult, although taking paracetamol for asthma symptoms (reverse causation) seems unlikely, and findings from a cohort study in the USA indicated that frequent paracetamol use preceded the development of adult-onset asthma[2]. Third, we did not ask separate questions about frequency of use of aspirin and non-steroidal anti-inflammatory drugs, although these are likely to have been the most commonly taken non-paracetamol containing analgesics. If the findings for paracetamol had been explained by avoidance of aspirin and non-steroidal anti-inflammatory drugs by asthmatic individuals, we would have expected to see a negative association between other analgesic use and asthma, which was not the case. Finally, in an observational study of this kind we cannot rule out the

possibility that the association between paracetamol use and asthma has arisen through bias or unmeasured or residual confounding. However, cases and controls were selected from similar populations in each centre, making selection bias less likely. We did not collect information on indications for use, however, whilst it is possible that a minority of cases were taking paracetamol for conditions which are more common in people with asthma, such as rhinitis or migraine, it seems unlikely that such confounding would be of sufficient magnitude to account for the effect estimate for frequent paracetamol use. Our previous case-control study indicated that the majority of adults with asthma take weekly paracetamol for non-migrainous headache and musculoskeletal complaints, and only a minority take it for migraine or rhinitis, at least in the UK[1]. Furthermore, when we controlled for rhinitis in this study the overall effect estimate was only attenuated a little, indicating minor confounding, but suggesting that use of paracetamol for rhinitis is unlikely to be the major explanation for the association between paracetamol use and asthma.

We have previously suggested that glutathione depletion in the airways and increased oxidative stress may be the mechanism underlying the link between frequent paracetamol use and asthma[1]. Whilst evidence is lacking on effects of therapeutic doses of paracetamol on airway glutathione levels, *in vitro* studies have shown that clinically relevant doses of paracetamol can deplete intracellular GSH levels in animal alveolar macrophages and type 2 pneumocytes[7] and in human pulmonary macrophages *in vitro*[8], and that depletion of glutathione in antigen-presenting cells leads to preferential Th2 responses[9]. Furthermore, an *in vivo* study in humans demonstrated reductions in antioxidant capacity of the blood following maximum therapeutic doses of paracetamol for two weeks[10], although GSH levels were not measured. We therefore believe that frequent therapeutic doses of paracetamol may,

in susceptible individuals, have adverse effects on the lung, either through oxidative damage to the airways, or promotion of atopic responses, with consequences for asthma.

Given the increasing and consistent epidemiological evidence implicating paracetamol in adult asthma across diverse populations, and the high prevalence of asthma and paracetamol use in some countries, there is now a need to carry out suitable intervention studies to determine whether the link is causal.

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Table 1: Distribution of potential confounders in cases and controls

	Controls	Cases	Total
Overall Total	**507 (49.3%)**	**521 (50.7%)**	**1028**
Body Mass Index			
<20	51 (10.1%)	52 (10.0%)	103 (10.0%)
20-25	270 (53.3%)	238 (45.7%)	508 (49.4%)
25-30	135 (26.6%)	156 (29.9%)	291 (28.3%)
30+	51 (10.1%)	73 (14.0%)	124 (12.1%)
Gender			
Male	239 (47.1%)	206 (39.5%)	445 (43.3%)
Age			
Mean age in years (s.d.)	34.7 (7.48)	32.8 (7.37)	33.7 (7.48)
Socio-economic status			
Professional	242 (47.7%)	186 (35.7%)	428 (41.6%)
Managerial	29 (5.7%)	28 (5.4%)	57 (5.5%)
Skilled	139 (27.4%)	186 (35.7%)	325 (31.6%)
Semi skilled	29 (5.7%)	29 (5.6%)	58 (5.6%)
Unskilled	27 (5.3%)	39 (7.5%)	66 (6.4%)
Students	38 (7.5%)	43 (8.3%)	81 (7.9%)
Smoking			
Never smoker	139 (27.4%)	142 (27.3%)	281 (27.3%)
Exposed to environmental tobacco smoke	142 (28.0%)	150 (28.8%)	292 (28.4%)
Ex-smoker	93 (18.3%)	93 (17.9%)	186 (18.1%)
Current smoker	133 (26.2%)	136 (26.1%)	269 (26.2%)
Supplement use	106 (20.9%)	123 (23.6%)	229 (22.3%)

Table 2: Frequency of use of paracetamol and other analgesics by centre and case-control status

Paracetamol use

Centre	<once per week	1-2 days per week	3+ days per week	Total
Ghent	125 (91%)	10 (7%)	3 (2%)	**138**
Vienna	58 (98%)	1 (2%)	0 (0%)	**59**
Odense	78 (86%)	7 (8%)	6 (7%)	**91**
Berlin	60 (95%)	2 (3%)	1 (2%)	**63**
Palermo	94 (100%)	0 (0%)	0 (0%)	**94**
Rome	49 (100%)	0 (0%)	0 (0%)	**49**
Amsterdam	63 (78%)	16 (20%)	2 (2%)	**81**
Lodz	92 (96%)	2 (2%)	2 (2%)	**96**
Coimbra	87 (86%)	8 (8%)	6 (6%)	**101**
Barcelona	87 (89%)	8 (8%)	3 (3%)	**98**
Stockholm	50 (91%)	4 (7%)	1 (2%)	**55**
London	93 (90%)	7 (7%)	3 (3%)	**103**
Cases	**452 (86.8%)**	**49 (9.4%)**	**20 (3.8%)**	**521**
Controls	**484 (95.5%)**	**16 (3.1%)**	**7 (1.4%)**	**507**
Total	**936 (91.1%)**	**65 (6.3%)**	**27 (2.6%)**	**1028**

Use of other analgesics

Centre	<once per week	1-2 days per week	3+ days per week	Total
Ghent	128 (93%)	8 (6%)	2 (1%)	**138**
Vienna	54 (92%)	8 (8%)	0 (0%)	**59**
Odense	83 (91%)	4 (4%)	4 (4%)	**91**
Berlin	59 (94%)	0 (0%)	4 (6%)	**63**
Palermo	83 (88%)	11 (12%)	0 (0%)	**94**
Rome	43 (88%)	2 (4%)	4 (8%)	**49**
Amsterdam	80 (99%)	1 (1%)	0 (0%)	**81**
Lodz	91 (95%)	3 (3%)	2 (2%)	**96**
Coimbra	93 (92%)	4 (4%)	4 (4%)	**101**
Barcelona	95 (97%)	1 (1%)	2 (2%)	**98**
Stockholm	49 (89%)	4 (7%)	2 (2%)	**55**
London	95 (92%)	3 (3%)	5 (5%)	**103**
Cases	**473 (90.8%)**	**28 (5.4%)**	**20 (3.8%)**	**521**
Controls	**480 (94.7%)**	**18 (3.6%)**	**9 (1.8%)**	**507**
Total	**953 (92.7%)**	**46 (4.5%)**	**29 (2.8%)**	**1028**

Table 3: Odds ratio for asthma according to frequency of paracetamol use

Centre	<once per week	One or more days per week Unadjusted	One or more days per week Adjusted*
Ghent	1.00	4.61 (0.98-21.66) p=0.05	5.20 (0.97-27.77) p=0.05
Odense	1.00	1.93 (0.55-6.79) p=0.31	2.88 (0.53-15.58) p=0.22
Berlin	1.00	3.00 (0.26-34.95) p=0.38	1.86 (0.07-47.03) p=0.71
Amsterdam	1.00	1.38 (0.48-3.94) p=0.55	1.17 (0.32-4.26) p=0.82
Lodz	1.00	2.63 (0.26-26.26) p=0.41	4.30 (0.16-117.32) p=0.39
Coimbra	1.00	14.59 (1.83-116.39) p=0.01	16.11 (1.25-207.41) p=0.03
Barcelona	1.00	12.89 (1.58-105.18) p=0.02	14.34 (1.25-164.53) p=0.03
Stockholm	1.00	1.88 (0.19-18.23) p=0.59	2.77 (0.11-68.54) p=0.53
London	1.00	1.67 (0.44-6.31) p=0.45	1.73 (0.36-8.34) p=0.49
Overall	**1.00**	**2.57 (1.51-4.37) p=0.001 Test for heterogeneity =7.55 (8df) p=0.48**	**2.87 (1.49-5.37) p=0.002 Test for heterogeneity=6.29 (8df) p=0.61**

*Adjusted for age, sex, BMI, socio-economic status, smoking and supplement use

Figure 1: Forest plot of meta analysis of adjusted odds ratios for asthma according to weekly paracetamol use (vs < weekly use)

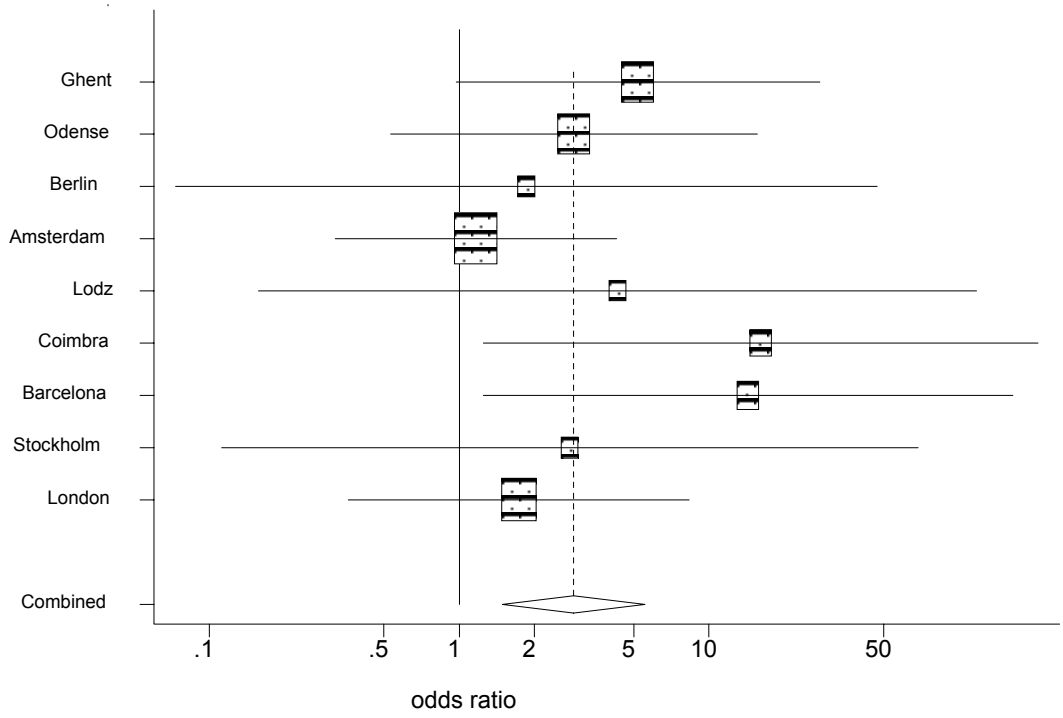

Table 4: Odds ratio for asthma according to use of other painkillers

Centre	<once per week	One or more days per week Unadjusted	One or more days per week Adjusted*
Ghent	1.00	1.13 (0.30-4.20) p=0.86	1.94 (0.37-10.34) p=0.44
Vienna	1.00	0.88 (0.09-8.58) p=0.91	0.14 (0.001-14.86) p=0.41
Odense	1.00	2.53 (0.48-13.29) p=0.27	3.80 (0.35-41.49) p=0.27
Berlin	1.00	4.70 (0.46-47.92) p=0.19	8.02 (0.39-165.49) p=0.18
Palermo	1.00	1.04 (0.29-3.66) p=0.96	0.26 (0.02-2.96) p=0.28
Rome	1.00	4.35 (0.47-40.39) p=0.20	9.97 (0.69-143.64) p=0.09
Lodz	1.00	3.58 (0.39-33.31) p=0.26	8.63 (0.41-183.41) p=0.17
Coimbra	1.00	1.50 (0.34-6.63) p=0.60	1.04 (0.18-6.05) p=0.97
Stockholm	1.00	2.42 (0.26-22.51) p=0.44	22.11 (0.57-855.75) p=0.10
London	1.00	1.07 (0.25-4.51) p=0.93	0.62 (0.11-3.47) p=0.58
Overall	**1.00**	**1.60 (0.94-2.73) p=0.09 Test for heterogeneity=3.84 (9df) p=0.92**	**1.85 (0.79-4.31) p=0.15 Test for heterogeneity=11.13 (9df) p=0.27**

*Adjusted for age, sex, BMI, socio-economic status, smoking and supplement use

Figure 2: Forest plot of meta analysis of adjusted odds ratios for asthma according to weekly use of other painkillers (vs < weekly use)