Risk of acute exacerbation between acetaminophen and ibuprofen in children with asthma

Lin-Shien Fu [1, 2] , Che-Chen Lin [3] , Chia-Yi Wei [3] , Ching-Heng Lin [Corresp., 3] , Yung-Chieh Huang [Corresp. 1, 4]

[1] Department of Pediatrics, Taichung Veterans General Hospital, Taichung, Taiwan

[2] Department of Pediatrics, National Yang-Ming University, Taipei, Taiwan

[3] Department of Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan

[4] Division of Pediatrics, Puli Branch, Taichung Veterans General Hospital, Nantou, Taiwan

Corresponding Authors: Ching-Heng Lin, Yung-Chieh Huang
Email address: epid@vghtc.gov.tw, huang1985john@yahoo.com.tw

Background. Antipyretics are widely prescribed in pediatric practice. Some reports have mentioned that acetaminophen and non-steroid anti-inflammatory drugs may negatively affect asthma control by causing asthma exacerbation (AE). However, many confounding factors can also influence the risks. We assessed the impact of using acetaminophen or ibuprofen on AE in asthmatic children, especially those with strong risk factors. **Methods.** We used the 2010 Taiwan National Health Insurance Research Database and identified 983 children with persistent asthma aged 1–5 years old; among them, 591 used acetaminophen alone and 392 used ibuprofen alone in 2010. Then, we analyzed the risk of AE over 52 weeks in the patients with and without severe AE in the previous year. **Results.** The ibuprofen group had a higher risk of an ER visit or hospitalization for AE (odds ratio [OR]= 2.10, 95% confidence interval [CI]= 1.17–3.76, *P*= 0.01). Among asthmatic children who had severe AE in the previous year, the risk of AE was higher in the ibuprofen group than in the acetaminophen group (OR= 3.28, 95% CI= 1.30–8.29, *P*= 0.01), where as among those who did not, the risks of AE were similar between the acetaminophen and ibuprofen groups (OR= 1.52, 95% CI= 0.71–3.25, *P*= 0.28). **Conclusions.** Among young asthmatic children, use of ibuprofen was associated with a higher risk of AE than acetaminophen, if they had severe AE with ER visit or hospitalization in the previous year. Pediatricians should use antipyretics among children with asthma after a full evaluation of the risk.

1   **Risk of acute exacerbation between acetaminophen and ibuprofen in children with asthma**

2   Lin-Shien Fu[1,2], Che-Chen Lin[3], Chia-Yi Wei[3], Ching-Heng Lin[3], Yung-Chieh Huang[1,4]

3   **Affiliations:**[1]Department of Pediatrics, Taichung Veterans General Hospital, Taichung, Taiwan;
4   [2]Department of Pediatrics, National Yang-Ming University, Taipei, Taiwan; [3]Department of
5   Medical Research, Taichung Veterans General Hospital, Taichung, Taiwan; [4]Division of
6   Pediatrics, Puli Branch, Taichung Veterans General Hospital, Nantou, Taiwan.

7   **Corresponding authors:**

9   **Yung-Chieh Huang**, e-mail: huang1985john@yahoo.com.tw
10   **Ching-Heng Lin,** e-mail: epid@vghtc.gov.tw

12   **Short Title:** Risk of exacerbation in child with asthma

Abstract

Background. Antipyretics are widely prescribed in pediatric practice. Some reports have

mentioned that acetaminophen and non-steroid anti-inflammatory drugs may negatively affect

asthma control by causing asthma exacerbation (AE). However, many confounding factors can

also influence the risks. We assessed the impact of using acetaminophen or ibuprofen on AE in

asthmatic children, especially those with strong risk factors.

Methods. We used the 2010 Taiwan National Health Insurance Research Database and

identified 983 children with persistent asthma aged 1–5 years old; among them, 591 used

acetaminophen alone and 392 used ibuprofen alone in 2010. Then, we analyzed the risk of AE

over 52 weeks in the patients with and without severe AE in the previous year.

Results. The ibuprofen group had a higher risk of an ER visit or hospitalization for AE (odds

ratio [OR]= 2.10, 95% confidence interval [CI]= 1.17–3.76, P= 0.01). Among asthmatic children

who had severe AE in the previous year, the risk of AE was higher in the ibuprofen group than in

the acetaminophen group (OR= 3.28, 95% CI= 1.30–8.29, P= 0.01), where as among those who

did not, the risks of AE were similar between the acetaminophen and ibuprofen groups (OR=

1.52, 95% CI= 0.71–3.25, P= 0.28).

Conclusions. Among young asthmatic children, use of ibuprofen was associated with a higher

risk of AE than acetaminophen, if they had severe AE with ER visit or hospitalization in the

33 previous year. Pediatricians should use antipyretics among children with asthma after a full

34 evaluation of the risk.

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36

37 **Abbreviations:**
38 AE: asthma exacerbation
39 ER: emergency room
40 NHIRD: National Health Insurance Research Database
41 OR: odds ratio
42 OPD: outpatient department
43 CI: confidence interval
44 RTI: respiratory tract infection
45 ICS: inhaled corticosteroid
46 LTRA: leukotriene receptor antagonist
47

48 **Introduction**

49 Acetaminophen and ibuprofen are the most widely used medications in children, the major

50 indication of their use being fever. Studies have suggested that the risk of asthma and wheezing

51 increases after acetaminophen use in several situations, including prenatal administration,

52 administration in infants, and exposure in the previous year.(L. B. Bacharier et al. 2008; F. J.

53 Gonzalez-Barcala et al. 2013; A. J. Henderson & S. O. Shaheen 2013; E. Kreiner-Moller et al.

54 2012; M. Muc et al. 2013; A. R. Scialli et al. 2010; S. O. Shaheen et al. 2000; K. Thiele et al.

55 2013; G. W. Wong et al. 2007) However, none of these studies have reported on ibuprofen use,

56 even though it is another frequently used antipyretic. Furthermore, these studies did not rule out

57 the confounding effect of concurrent respiratory tract infection (RTI), which may play a more

58 important role in asthma than acetaminophen use.(E. Schnabel & J. Heinrich 2010; J. E. Sordillo

59 et al. 2015) Studies assessing the influence of acetaminophen on lung function have shown

60 conflicting results in adults and children.(S. J. Ioannides et al. 2014; T. M. McKeever et al. 2005;

61 R. Soferman et al. 2013)

62 Studies comparing acetaminophen and ibuprofen for asthma control have also revealed

63 inconsistent results. Short-term use of acetaminophen for febrile illness in children aged 6

64 months to 12 years with asthma did not lead to more hospitalizations but did result in more

65 unscheduled outpatient department (OPD) visits for asthma exacerbation than ibuprofen use.(S.

66   M. Lesko et al. 2002) However, after comparing the as-needed use of acetaminophen and

67   ibuprofen for 48 weeks, a recent double-blind randomized controlled study revealed no

68   difference in asthma control or asthma treatment with systemic corticosteroids in children aged

69   1–5 years with mild persistent asthma.(W. J. Sheehan et al. 2016) Matok and colleagues

70   examined the association between antipyretics and wheezing in children with febrile illness, and

71   found that ibuprofen was associated with a lower risk of wheezing.(I. Matok et al. 2017)

72   According to reports from the Global Initiative for Asthma, severe asthma exacerbation (AE) in

73   the past year is the strongest independent predictor of AE.(Global Initiative for Asthma 2017)

74   AE is defined as an acute or sub-acute episode of a progressive increase in asthma symptoms,

75   associated with airflow obstruction; the most commonly examined exacerbation outcomes are

76   the need for systemic corticosteroids and urgent unscheduled asthma-related care, specifically

77   ER visits, hospitalization, or unscheduled OPD visits.(N. G. Papadopoulos et al. 2012) In this

78   study, we used the Taiwan National Health Insurance Research Database (NHIRD) to compare

79   the risk of AE between1-year use of acetaminophen and 1-year use of ibuprofen in children aged

80   1–5 years with persistent asthma, focusing on the risk factors, including severe AE in the past

81   year.

82   **Patients and Methods**

83   **Data source**

84   Taiwan established the National Health Insurance program in 1995, and more than 98% of

85   Taiwan residents were insured under this system. The NHIRD was provided by the National

86   Health Research Institutes of Taiwan. The diagnostic codes in the database were based on the

87   International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). In

88   this study, we used the 2010 NHIRD, which contained the original claims data of 1 000 000

89   beneficiaries randomly sampled from the whole population.

90   **Study design**

91   Figure 1 presents a flowchart of patient inclusion in the study. There were 4444 pediatric asthma

92   cases in the database on January 1, 2010. The diagnosis of asthma was based on ICD-9-CM

93   493.X in at least 1emergency room (ER) visit, 1hospital admission, or 3 OPD visits, and the

94   asthma drugs used included inhaled corticosteroids (ICSs), leukotriene receptor antagonists

95   (LTRAs), systemic corticosteroids, and short-acting β-agonists (SABAs).

96   The primary endpoint of this study was development of AE, which was identified on the basis of

97   an ER visit or hospital admission with a primary ICD-9-CM code of 493.X within 1 year. We

98   considered AE and systemic corticosteroid treatment for asthma in the previous year as risk

99   factors in this study.

100   This study was approved by the institutional review board of Taichung Veterans General

101   Hospital (No. CE16220B). For the protection of privacy, the identities of the patients, physicians,

102 and institutions were scrambled in accordance with the Personal Electronic Data Protection Law.

103

104 **Statistical analysis**

105 We evaluated the baseline characteristics of the patients with asthma, including age, sex, age at

106 asthma onset, asthma status, and medication status in the year preceding the baseline. Continuous

107 variables were expressed as the mean± standard deviation, and the difference between 2 groups

108 was assessed using the *t*test. Categorical variables were calculated, and differences in the

109 distribution were assessed using the chi-square test. To compare the risks of AE between

110 acetaminophen and ibuprofen users, the odds ratios (ORs) and corresponding 95% confidence

111 intervals (CIs) were estimated by using univariate and multivariate logistic regression models.

112 We also measured the cumulative incidence of AE in acetaminophen and ibuprofen users by

113 using the Kaplan–Meier method and tested differences in the curves by using the log-rank test.

114 The incidence curves were drawn using R software (R Foundation for Statistical Computing,

115 Vienna, Austria), and data management and statistical analyses were performed using SAS 9.4

116 (SAS Institute, Cary, NC, USA). A 2-sided *P* value of <.05 was set as the significance level.

117

118 **Results**

119 Table 1 summarizes the demographic characteristics of the 2 groups. After excluding patients

120   who had no asthma-related prescription (n = 69), those with severe systemic diseases (n = 74),

121   mixed antipyretic users (n = 3181), and those with no acetaminophen or ibuprofen prescription

122   (n = 137), 591 children with acetaminophen prescription alone and 392 with ibuprofen

123   prescription alone remained. The mean age of the patients in the ibuprofen group was lower than

124   that in the acetaminophen group (4.0 ± 0.9 vs 4.2±0.9 y, *P*=0.008), and the ibuprofen group had a

125   higher percentage of boys (67.1% vs 59.7%, *P* = 0.02). There were no between-group differences

126   in age of asthma onset, severe AE (ER visit or hospitalization), frequency of upper RTI, or

127   asthma-related prescriptions including ICSs, LTRAs, and systemic corticosteroids.

128   We first analyzed some possible risk factors for AE after adjusting for age, sex, and patient

129   asthma and medication status in the previous year (Table 2). An ER visit or hospitalization in the

130   previous year was associated with a high risk (OR = 10.6, 95% CI= 5.90–18.9, *P* <0.0001). In

131   addition, the ibuprofen group had a higher risk of AE than did the acetaminophen group after

132   adjustment for sex, age, and patient status in the previous year (OR = 2.10, 95% CI = 1.17–3.16,

133   *P* = 0.01). The ibuprofen group exhibited a significantly higher cumulative risk of AE from early

134   weeks to the end of the study period (Figure 2, *P* = 0.04).

135   We then compared the risk of AE between patients in the acetaminophen and ibuprofen groups

136   who had systemic corticosteroid prescription and an asthma-related ER visit or hospitalization in

137   the previous year (Table 3). Among children who had an asthma-related ER visit or

138   hospitalization in the previous year, those in the ibuprofen group had a higher risk of AE than did

139   those in the acetaminophen group (OR = 3.28, 95% CI = 1.30–8.29, P = 0.01). In children with

140   no asthma-related ER visitor or hospitalization in the previous year, the risks of AE in both the

141   acetaminophen and ibuprofen groups were similar (P = 0.28). For children who had systemic

142   corticosteroid prescription in the previous year, the ibuprofen group had a higher risk of AE than

143   the acetaminophen group (OR = 2.30, 95% CI = 1.61–4.54, P = 0.02). When we further analyzed

144   our results according to the patients' sex, we found that among female children (Table 3-1) with

145   asthma who had an asthma-related ER visit or hospitalization in the previous year, those in the

146   ibuprofen group had a higher risk of AE than did those in the acetaminophen group (OR = 5.15,

147   95% CI = 1.03–25.7, P = 0.05). Among female children who had systemic corticosteroid

148   prescription in the previous year, the ibuprofen group had a higher risk of AE than the

149   acetaminophen group (OR = 3.6, 95% CI = 1.14–11.43, P = 0.03). However, there were no

150   significant findings among male children with asthma (Table 3-2).

151   When we subdivided systemic corticosteroid prescription into OPD visits and ER visits or

152   hospitalization for asthma (Table 4), children receiving systemic corticosteroids in the OPD

153   showed similar risks of AE in the acetaminophen and ibuprofen groups (P = 0.55), whereas

154   among those receiving systemic corticosteroids in an ER visit or hospitalization, the risk was

155   higher in the ibuprofen group than in the acetaminophen group (OR = 3.15, 95% CI = 1.32–3.52,

156 $P = 0.01$).

157

158 **Discussion**

159 In this study, we identified children aged 1–5 years with asthma who received acetaminophen or

160 ibuprofen prescription alone for 52 weeks from the NHIRD to compare the rate of AE and

161 analyze the potential risks. We identified AE on the basis of an ER visit or hospitalization due to

162 asthma. The ibuprofen group exhibited a higher risk of an ER visit or hospitalization for asthma

163 and had significantly higher cumulative AEs over 52 weeks in our study. Among children who

164 had an ER visit or hospitalization in the previous year, the ibuprofen group carried a higher risk

165 of severe AE than the acetaminophen group. This difference was not evident in children who had

166 no ER visit or hospitalization for asthma in the previous year, regardless of whether they used

167 systemic corticosteroids.

168 We focused on antipyretics because they are the most frequently prescribed pediatric drugs.(L.

169 Vernacchio et al. 2009) From the data in the NHIRD, acetaminophen and ibuprofen account for

170 98.62% of antipyretic prescriptions in children 1–5 years old (unpublished data), and respiratory

171 infection is the most common condition associated with antipyretic use.(J. E. Sordillo et al. 2015)

172 The impacts of antipyretic prescription and respiratory infection on asthma control are a concern.

173 However, it is difficult and almost impossible not to use antipyretics when a child has a fever,

174   and there are ethical concerns related to designing a clinical study to compare asthma control

175   between children using and not using antipyretics under such a condition. Studies comparing the

176   effects of different antipyretics on asthma control may provide valuable information for medical

177   decisions in clinical practice.

178   A few randomized, double-blind trials have compared acetaminophen and ibuprofen use for

179   asthma control.(S. M. Lesko et al. 2002; I. Matok et al. 2017; W. J. Sheehan et al. 2016) The

180   Boston University Fever Study evaluated the rates of hospitalization and outpatient visits for

181   asthma among children who had asthma and a febrile illness within 4 weeks after receiving

182   acetaminophen or ibuprofen. Compared with the acetaminophen group, the ibuprofen group had

183   fewer outpatient visits but no difference in asthma-related hospitalization.(S. M. Lesko et al.

184   2002) The Acetaminophen versus Ibuprofen in Children with Asthma (AVICA) trial was a long-

185   term study that followed children aged 1–5 years for 52 weeks; it found no difference in AE, as

186   evaluated by the intake of systemic corticosteroids, in groups receiving acetaminophen or

187   ibuprofen alone.(W. J. Sheehan et al. 2016) Riley and colleagues are recruiting for a randomized

188   controlled trial of acetaminophen versus ibuprofen use during infancy and its association with

189   the risk of asthma.(J. Riley et al. 2016) In the present NHIRD study, which also examined

190   children with asthma taking ibuprofen or acetaminophen over 52 weeks in 2010, no difference in

191   AE between the 2 groups was found with respect to systemic corticosteroid use. However, we

192   found that the ibuprofen group had a higher rate of asthma ER visits or hospitalization, which

193   frequently occurred within 4 weeks of taking the antipyretic during our study period.

194   Sordillo et al demonstrated that RTIs might confound the relationship between infant antipyretic

195   use and early childhood asthma.(J. E. Sordillo et al. 2015) Other studies adjusting for RTIs when

196   analyzing early-life acetaminophen use and asthma have showed similar results.(A. J. Lowe et al.

197   2010; E. Schnabel & J. Heinrich 2010) The AVICA trial found that RTIs carry higher risks of

198   antipyretic use and AE.(W. J. Sheehan et al. 2016) The Boston University Fever Study(S. M.

199   Lesko et al. 2002) also considered RTIs. In our study, the frequencies of RTI in the study period

200   and the previous year were similar between the acetaminophen and ibuprofen groups.

201   Factors contributing to AE include poor asthma control, severe exacerbation in the past year,

202   viral infection, allergen exposure, virus–allergen interaction, smoking, and air pollution. Among

203   these factors, severe exacerbation in the past year is the strongest independent factor.(L. S. Fu &

204   M. C. Tsai 2014; A. Fuhlbrigge et al. 2012) Our study focused on severe AE as indicated by

205   asthma-related ER visits or hospitalization in the previous year, which was not analyzed in

206   previous studies. There is no "urgent OPD care" in the current health care system in Taiwan;

207   therefore, we included only ER visits and hospitalization. Concerning the need for systemic

208   corticosteroids, the AVICA trial had 4 scenarios for initiating systemic corticosteroids—poor

209   asthma control, an unscheduled visit to the OPD or ER due to asthma, hospitalization, and

210   physicians' discretion. The present study could identify systemic corticosteroid use only in OPD

211   visits, ER visits, and hospitalization.

212   Several studies have investigated the effects of acetaminophen on lung function. Ioannides et al

213   showed no significant effect of 12-week-long acetaminophen intake (1g bid) on bronchial

214   hyperresponsiveness in adults with asthma.(S. J. Ioannides et al. 2014) Soferman et al

215   administered children with asthma 15mg/kg acetaminophen and then performed spirometry and

216   measured fractional exhaled nitric oxide 60 minutes later. The results were not different from

217   those of the control group.(R. Soferman et al. 2013) Matok and colleagues conducted a cross-

218   sectional study on the association between antipyretics and wheezing in children with febrile

219   illness(I. Matok et al. 2017); in multivariate analysis, they found that ibuprofen was associated

220   with a lower risk of wheezing.

221   Several biological mechanisms underlying acetaminophen-induced asthma development and

222   acute attack have been proposed.(A. J. Henderson & S. O. Shaheen 2013) In vitro and animal

223   studies have revealed that N-acetyl-p-benzoquinone imine (NAPQI), one of the metabolites of

224   acetaminophen, leads to the depletion of glutathione, which acts as an important antioxidant in

225   the airways; further epithelial damage and airway inflammation may occur. Acetaminophen may

226   also lead to preferential Th2 cytokine responses as it decreases intracellular glutathione levels

227   and modulates cytokine production in human alveolar macrophages and type II pneumocytes in

228   vitro.(S. Dimova et al. 2005) Furthermore, aspirin and most non-steroid anti-inflammatory drugs,

229   including ibuprofen, inhibit cyclo-oxygenase-1 (COX-1) activity. This may lead to dysregulation

230   of arachidonic acid metabolism and eventually the clinical symptoms of non-steroid anti-

231   inflammatory drug–exacerbated respiratory diseases (NERDs),(R. A. Simon et al. 2015)

232   previously known as aspirin-exacerbated respiratory diseases. A meta-analysis for NERD

233   showed its prevalence to be 9% in adults.(D. R. Morales et al. 2015) Studies have found ROS-

234   related and TL4 gene polymorphisms to be significantly associated with the effects of

235   acetaminophen use in asthma.(S. H. Kang et al. 2013; S. H. Lee et al. 2014) In this study, we

236   found a stronger effect of ibuprofen in the children with asthma.

237   This study has some limitations. In clinical practices, there are no golden standards in diagnosing

238   asthma among patients under 5 years old except for recurrent symptoms and physicians'

239   judgement; however, the methodology used in this study was similar and even more rigorous

240   than previous published literatures (Y. C. Hung et al. 2014; J. Y. Wang et al. 2013; W. C. Wang

241   et al. 2017). There was a lack of data on the immunoglobulin E level, total eosinophil count, and

242   aeroallergen sensitization; however, no study has shown that the atopic condition influences the

243   effect of antipyretics on asthma control. This study is a retrospective database analysis, and we

244   could not be clear if the patients did take the antipyretics or evaluate the cumulative antipyretic

245   dose; however, the AVICA trial found that the cumulative antipyretic dose is not related to

246   asthma control.(W. J. Sheehan et al. 2016) This study focused on children with persistent asthma

247   aged 1–5 years old, so the results may not be applied to other age groups or children with

248   intermittent to mild asthma.

249   **Conclusions**

250   In conclusion, this study using the NHIRD showed that an ER visit or hospitalization for asthma

251   is a major risk factor for AE. Ibuprofen carries a higher risk of AE than acetaminophen in

252   children with asthma, especially for those who have severe AE with an ER visit or

253   hospitalization, or systemic corticosteroid prescription in the previous year. We suggest that

254   studies analyzing the risk of antipyretics in asthma control consider severe AE in the previous

255   year. In clinical practice, it is difficult to avoid prescribing antipyretics to febrile children, but

256   pediatricians should use antipyretics after full evaluation of children with asthma and be cautious

257   of the risk of AE.

258

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388

Flowchart of patient inclusion in the study

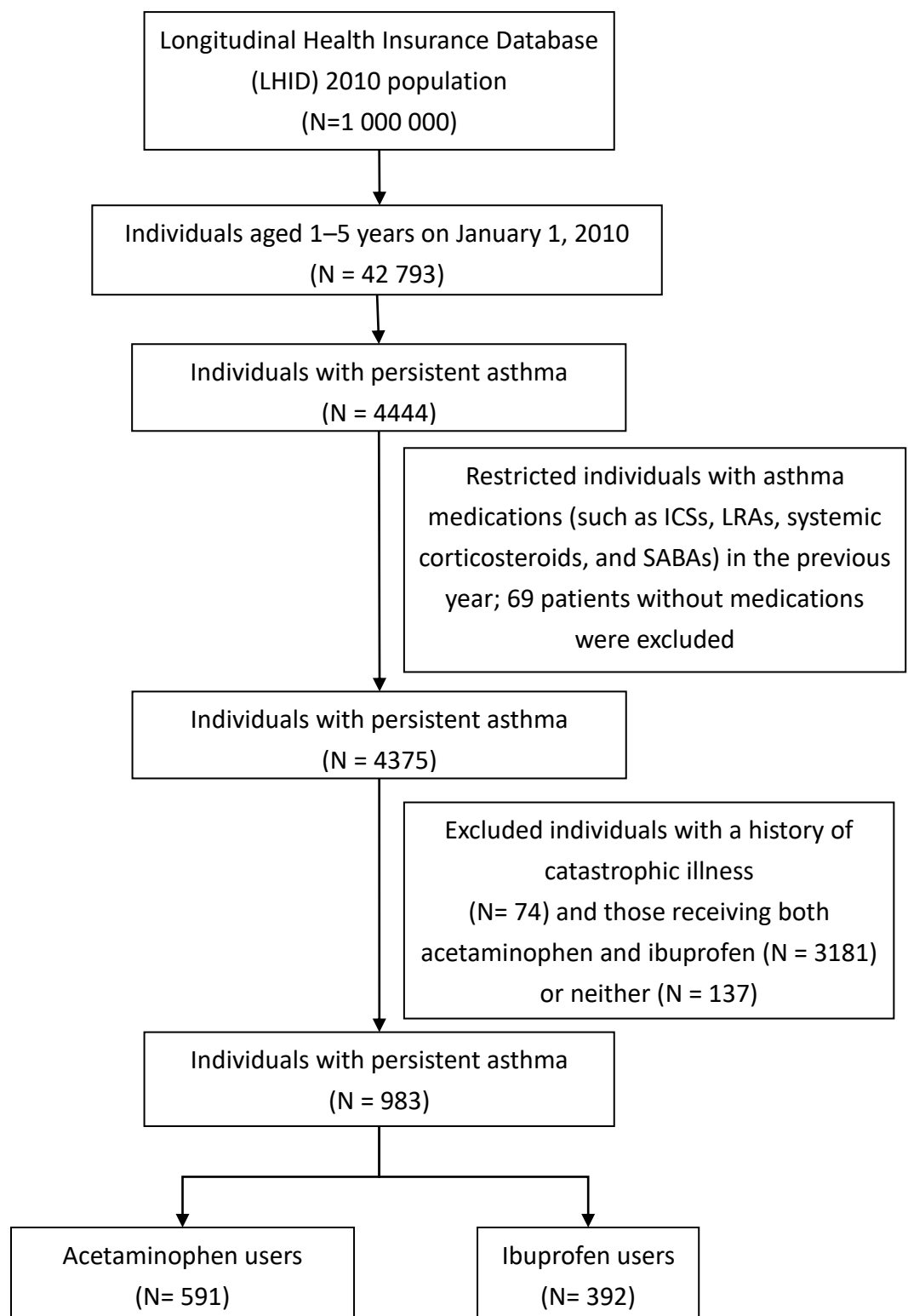
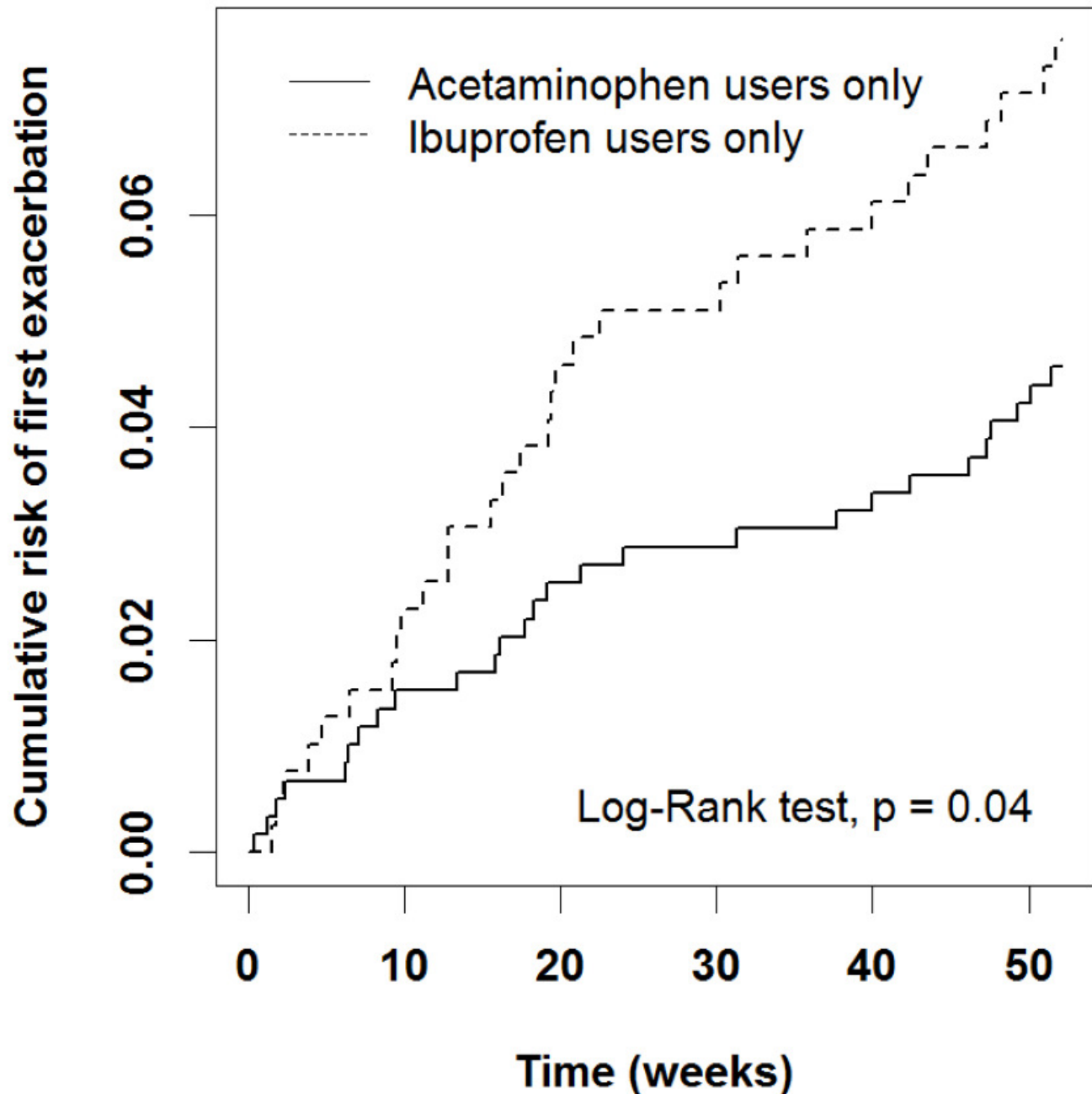



Figure 2

Cumulative risk of first AE in acetaminophen and ibuprofen users

Baseline Characteristics of Subgroups of Patients with Asthma

1   Table 1: Baseline Characteristics of Subgroups of Patients with Asthma

Variables	Acetaminophen users N = 591	Ibuprofen users N = 392	*p*-value
Age, year (SD)	4.2 (0.9)	4.0 (0.9)	0.008
Sex			0.02
Female (%)	238 (40.3)	129 (32.9)	
Male (%)	353 (59.7)	263 (67.1)	
Age at onset of asthma, month (SD)	26.5 (13.2)	25.3 (13.3)	0.15
Asthma exacerbation status in the previous year (%)	71 (12.0)	37 (9.4)	0.21
Emergency visits for asthma (%)	37 (6.3)	18 (4.6)	0.27
Hospitalizations for asthma (%)	43 (7.3)	23 (5.9)	0.39
Medication status in the previous year			
Use of ICS (%)	116 (19.6)	61 (15.6)	0.10
Use of leukotriene receptor antagonist (%)	150 (25.4)	115 (29.3)	0.17
Use of systemic corticosteroids (%)	267 (45.2)	156 (39.8)	0.10
Diagnosed upper respiratory tract infection			
In the previous year (%)	589(99.7)	388(99.0)	0.18
In 2010 (%)	582(98.5)	378(96.4)	0.04

2   SD: standard deviation

3   ICS: inhaled corticosteroids

Analysis of Risk Factors for AE

1   Table 2: Analysis of Risk Factors for AE

Variables	Asthma exacerbation		Adjusted OR	
	No (%)	Yes (%)	(95% CI)	*p*-value
Antipyretics*				
Acetaminophen	564 (60.9)	27 (47.4)	Reference	
Ibuprofen	362 (39.1)	30 (52.6)	2.10 (1.17-3.76)	0.01
Age, year [SD]	4.1 [0.9]	3.8 [0.9]	0.80 (0.60-1.07)	0.13
Sex				
Female	346 (37.4)	21 (36.8)	Reference	
Male	580 (62.6)	36 (63.2)	1.03 (0.57-1.86)	0.93
Patient status in the previous year				
Asthma AE‡				
No	846 (91.4)	29 (50.9)	Reference	
Yes	80 (8.6)	28 (49.1)	10.6 (5.90-18.9)	<0.0001
Use of systemic corticosteroids#				
No	547 (59.1)	13 (22.8)	Reference	
Yes	379 (40.9)	44 (77.2)	3.07 (1.56-6.05)	0.001

2   * adjusted for age, sex, and patient status in the previous year (AE and use of systemic
3   corticosteroids)
4   ‡ adjusted for age, sex, and AE in the previous year
5   # adjusted for age, sex, and use of systemic corticosteroids in the previous year
6   OR: odds ratios
7   CI: confidence intervals

Risk of Acetaminophen and Ibuprofen Use in Subgroups of Children with Asthma

1   Table 3: Risk of Acetaminophen and Ibuprofen Use in Subgroups of Children with Asthma

	Without Asthma exacerbation in the previous year				Asthma exacerbation in the previous year			
	Asthma exacerbation		Adjusted OR		Asthma exacerbation		Adjusted OR	
Antipyretics	No (%)	Yes (%)	(95% CI)	*p*-value	No (%)	Yes (%)	(95% CI)	*p*-value
Acetaminophen	506 (97.3)	14 (2.7)	Reference		58 (81.7)	13 (18.3)	Reference	
Ibuprofen	340 (95.8)	15 (4.2)	1.52 (0.71-3.25)	0.28	22 (59.5)	15 (40.5)	3.28 (1.30-8.29)	0.01
	Non-use of systemic corticosteroids in the previous year				Use of systemic corticosteroids in the previous year			
	Asthma exacerbation		Adjusted OR		Asthma exacerbation		Adjusted OR	
	No (%)	Yes (%)	(95% CI)	*p*-value	No (%)	Yes (%)	(95% CI)	*p*-value
Acetaminophen	318 (98.1)	6 (1.9)	Reference		246 (92.1)	21 (7.9)	Reference	
Ibuprofen	229 (97.0)	7 (3.0)	1.71 (0.56-5.29)	0.35	133 (85.3)	23 (14.7)	2.30 (1.16-4.54)	0.02

2   Model adjusted for age, sex, and patient status in the previous year (AE and use of systemic corticosteroids)

3   OR: odds ratios

4   CI: confidence intervals

8   Table 3-1: Risk of Acetaminophen and Ibuprofen Use in Subgroups of Female Children with Asthma

	Without Asthma exacerbation in the previous year				Asthma exacerbation in the previous year			
	Asthma exacerbation		Adjusted OR		Asthma exacerbation		Adjusted OR	
Antipyretics	No (%)	Yes (%)	(95% CI)	*p*-value	No (%)	Yes (%)	(95% CI)	*p*-value
Acetaminophen	204 (65.0)	7 (63.6)	Reference		24 (75.0)	3 (30.0)	Reference	
Ibuprofen	110 (35.0)	4 (36.4)	1.01 (0.28-3.66)	0.98	8 (25.0)	7 (70.0)	5.15 (1.03-25.7)	0.05

	Non-use of systemic corticosteroids in the previous year				Use of systemic corticosteroids in the previous year			
	Asthma exacerbation		Adjusted OR		Asthma exacerbation		Adjusted OR	
	No (%)	Yes (%)	(95% CI)	*p*-value	No (%)	Yes (%)	(95% CI)	*p*-value
Acetaminophen	130 (62.8)	4 (80.0)	Reference		98 (70.5)	6 (37.5)	Reference	
Ibuprofen	77 (37.2)	1 (20.0)	0.40 (0.04-3.66)	0.42	41 (29.5)	10 (62.5)	3.6 (1.14-11.43)	0.03

9   Model adjusted for age, sex, and patient status in the previous year (AE and use of systemic corticosteroids)

10   OR: odds ratios

11   CI: confidence intervals

13   Table 3-2: Risk of Acetaminophen and Ibuprofen Use in Subgroups of Male Children with Asthma

	Without Asthma exacerbation in the previous year				Asthma exacerbation in the previous year			
	Asthma exacerbation		Adjusted OR		Asthma exacerbation		Adjusted OR	
Antipyretics	No (%)	Yes (%)	(95% CI)	*p*-value	No (%)	Yes (%)	(95% CI)	*p*-value
Acetaminophen	302(56.8)	7 (38.9)	Reference		34 (70.8)	10 (55.6)	Reference	
Ibuprofen	230(43.2)	11(61.1)	1.93 (0.72-5.14)	0.19	14 (29.2)	8 (44.4)	2.49 (0.76-8.18)	0.13
	Non-use of systemic corticosteroids in the previous year				Use of systemic corticosteroids in the previous year			
	Asthma exacerbation		Adjusted OR		Asthma exacerbation		Adjusted OR	
	No (%)	Yes (%)	(95% CI)	*p*-value	No (%)	Yes (%)	(95% CI)	*p*-value
Acetaminophen	188 (55.3)	2 (25.0)	Reference		148 (61.7)	15 (53.6)	Reference	
Ibuprofen	152 (44.7)	6 (75.0)	3.67 (0.72-18.8)	0.12	92 (38.3)	13(46.4)	1.86 (0.78-4.43)	0.16

14   Model adjusted for age, sex, and patient status in the previous year (AE and use of systemic corticosteroids)

15   OR: odds ratios

16   CI: confidence intervals

Analysis of Patients with Systemic Corticosteroid Prescription in the Previous Year

1   Table 4: Analysis of Patients with Systemic Corticosteroid Prescription in the Previous Year

	Only in OPD				In ER/hospitalization (with or without OPD)			
	Asthma exacerbation		Adjusted OR		Asthma exacerbation		Adjusted OR	
	No (%)	Yes (%)	(95% CI)	*p*-value	No (%)	Yes (%)	(95% CI)	*p*-value
Acetaminophen	190 (96.9)	6 (3.1)	Reference		56 (78.9)	15 (21.1)	Reference	
Ibuprofen	113 (95.0)	6 (5.0)	1.44 (0.43-4.83)	0.55	20 (54.1)	17 (45.9)	3.15 (1.32-7.52)	0.01

2   Model adjusted for age, sex, and patient status in the previous year (AE and use of systemic corticosteroids)

3   OR: odds ratios

4   CI: confidence intervals

5   OPD: outpatient department