determinants of lung function influence susceptibility to asthma" and indicated that their own data "do not support this hypothesis." Because chronic obstructive pulmonary disease (COPD) is defined on the basis of the same spirometric measures of lung function, it is not surprising that some loci associated with measurements of lung function are also associated with COPD — for example, loci containing *HHIP* and *FAM13A*.[3,4] We would not necessarily expect to observe associations between these same loci and asthma. We found that genetic associations with lung function were generally unchanged, despite the reduction in power brought about by excluding persons with asthma or COPD from the analysis.[1] We interpreted this finding as evidence that many of the implicated loci are determinants of lung function in the general population.

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No potential conflict of interest relevant to this letter was reported.

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Smoke-free Legislation and Asthma

TO THE EDITOR: In their article on the observational study of changes in hospital admissions for asthma and the temporal relationship to the Scottish smoking ban, Mackay et al. (Sept. 16 issue)[1] describe other reasons that could explain the observed reduction. On the basis of the crude numbers of admissions, there seems not to be any trend from 2000 to the end of 2008, but there does appear to be a decrease in the first 10 months of 2009. I add two further possible reasons for the decrease in hospital admissions for childhood asthma observed in the study. First, there was bias owing to exclusion of data from November and December 2009 — two important months for childhood asthma[2] and the worst part of the H1N1 influenza pandemic in Scotland.[3] The second reason is a possible reduction in the number of respiratory viral infections, a principal cause of asthma exacerbations in childhood,[4] secondary to the special public health measures taken to reduce the transmission of pandemic influenza in 2009. For clarity, it would be helpful to have the data for all of 2009 and to observe the trend in the years thereafter.

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TO THE EDITOR: As in Scotland, the passage of smoke-free legislation in 2005 was associated with a reduction in the rate of hospitalizations for childhood asthma in the Lombardy region of Italy. We observed a decrease of 30.7% (95% confidence interval, 22.8 to 38.6) in the rate of admissions for asthma; a total of 15,042 children were hospitalized for asthma during the study period (Table 1). We speculate that the law may have had a positive influence on parental smoking, reducing in-home smoking and consequently passive exposure to tobacco smoke. However,

Table 1. Temporal Trends in Hospitalization for Childhood Asthma, According to Subgroup, in the Lombardy Region of Italy.

Subgroup	Annual Change		Net Annual Change after Legislation
	Before Legislation*	After Legislation†	
	percent (95 percent confidence interval)		
Sex			
Male	−4.1 (−24.4 to 16.2)	−31.7 (−80.9 to 17.5)	−35.8 (−63.2 to 27.4)
Female	−9.2 (−31.9 to 13.6)	−28.2 (−73.4 to 17.0)	−37.4 (−57.3 to 19.9)
Age			
0 to <5 yr	−11.5 (−44.2 to 21.3)	−38.4 (−82.9 to 6.1)	−49.9 (−70.8 to 20.9)
≥5 to 14 yr	2.9 (−9.6 to 15.3)	−25.2 (−89.3 to 38.9)	−28.1 (−63.1 to 40.7)
Geographic area			
Urban	−11.0 (−39.3 to 17.2)	−30.0 (−80.6 to 20.6)	−41.0 (−63.4 to 22.3)
Suburban or rural	−1.6 (−23.0 to 19.9)	−30.6 (−76.5 to 15.3)	−32.2 (−61.1 to 28.9)

* The annual change before legislation was the change relative to the rate at baseline, in January 2000.
† The annual change after legislation was the change relative to the rate on January 10, 2005, when the smoke-free legislation was implemented in Italy.

many variables can affect a country's hospitalizations for asthma, such as an increase in sales of antiasthmatic drugs,[1] improved quality of care, and systematic and continuous educational programs and campaigns.[2] The indirect benefit observed for children is an important point against the deleterious effects of tobacco smoking.

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No potential conflict of interest relevant to this letter was reported.

1. Gupta R, Anderson HR, Strachan DP, Maier W, Watson L. International trends in admissions and drug sales for asthma. Int J Tuberc Lung Dis 2006;10:138-45.
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THE AUTHORS REPLY: Moral suggests that exclusion of data from November and December 2009 may have introduced bias because of the seasonal variations that occur each year and the specific effects of HIN1 infections and management in 2009. Our analysis included all the post-legislation data available to us. Complete data on admissions that occurred in November and December 2009 are not yet available. Figure 1 shows the number of admissions according to month in our study cohort. Consistent with the findings of Gergen et al.,[1] the peak in admissions in Scotland occurs in September. Since we included admissions that occurred in September 2009, the exclusion of data from later months is unlikely to have resulted in an overestimate of the effect. Furthermore, we accounted for normal seasonal variations by adjusting for the month of admission in the analysis. In the United Kingdom, the incidence of H1N1 infections peaked in the middle of July 2009, followed by a second smaller peak on October 25, 2009.[2] Both dates occurred before the end of our study. Therefore, if the H1N1 pandemic had a greater effect on childhood asthma than influenza infections in previous years, this would have resulted in an underestimate of the effect of the legislation on underlying trends. The H1N1 vaccination program began on October 21, 2009. Therefore, any protective effect of this program on childhood asthma would have occurred after the period of our study.

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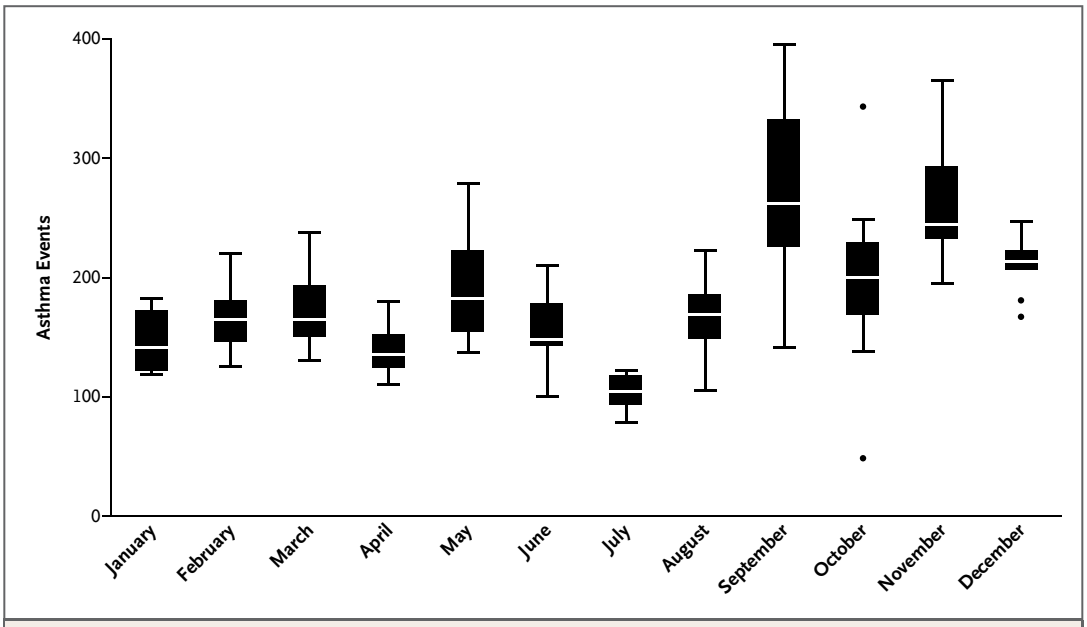

Figure 1. Hospital Admissions for Childhood Asthma in Scotland between January 2000 and October 2009, According to Month.

Boxes indicate the interquartile ranges; the lines within the boxes are medians. The vertical lines represent 1.5 times the interquartile range (above the upper end of the interquartile range and below the lower end of the interquartile range). The dots indicate the lowest and highest values.

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Since publication of their article, the authors report no further potential conflict of interest.

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A Patient with Cubilin Deficiency

TO THE EDITOR: Imerslund–Gräsbeck syndrome, or megaloblastic anemia 1, is a rare autosomal recessive disorder characterized by selective intestinal malabsorption of intrinsic factor–vitamin B_{12}; it is frequently accompanied by tubular proteinuria.[1] The syndrome is caused by mutations in the genes encoding the receptor partners cubilin (*CUBN*) or amnionless (*AMN*),[2] both of which are highly expressed in the absorptive epithelia of the ileum and the proximal tubules of the kidney. Cubilin, which interacts in the proximal tubules with megalin, another receptor with a high molecular weight, is critical to receptor-mediated tubular reabsorption of several important ligands from glomerular ultrafiltrate.[3]

We describe here a patient with a novel homozygous guanine-for-thymine exchange in the conserved donor splice site in exon 23 of *CUBN* (see Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Tests performed on a renal-biopsy specimen showed no immunologic reaction for cubilin and an abnormal cytoplasmic, vesicular distribution of the receptor partner amnionless (Fig. 1), indicating that amnionless depends on cubilin for correct localization in the human