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Comment on 'Allergy and acute leukaemia in children with Down syndrome: a population study. Report from the Mexican Inter Institutional Group for the Identification of the Causes of Childhood Leukaemia (MIGICCL)' – Is increased surveillance by hypersensitive immune system a reality or myth?

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Sir,

We read with great interest the study by Nunez-Enriquez *et al* (2013)' recently published in this journal. They conducted a multi-institutional population-based case–control study on children with Down syndrome and found that asthma is a risk factor of acute leukaemia development (odds ratio: 4.18 and 95% confidence interval: 1.47–11.87). However, other allergies had no effect on acute leukaemia development or were protective, in their experience. This study has revived an old question about effect of having allergies and chance of cancer development. Previous studies in this regard unveiled that allergies usually do not increase the risk of cancers, and in contrast, might be protective from cancer development (Vojtechova and Martin, 2009; Chen *et al*, 2011; Dikalioti *et al*, 2012). In allergic subjects, there is bone marrow involvement with reprogramming of bone marrow stem cells, regarded as 'reflex nature of allergic disease' (Holt and Strickland, 2010). Allergic phenotype in an atopic child may lead to epigenetic reprogramming that in turn affects immune surveillance by increasing antigen-presenting cell activity (Holt and Strickland, 2010). In addition, recent studies have demonstrated that serum eosinophil count is inversely associated with colorectal cancer development (Prizment *et al*, 2011). Hence, it seems that increased surveillance by hyperactive immune system of allergic patients is a reality. Here, the main question is 'why was asthma found as a risk factor of acute leukaemia development?'.

The method of allergy diagnosis and definition of allergic conditions affect categorisation of patients into different allergic groups, particularly with regard to recruitment of patients from different institutions. Moreover, considerable proportion of asthmatic patients might also have rhinitis, skin allergies or food allergies. Asthma and allergic rhinitis are too close in which more than half of asthmatic patients have also allergic rhinitis and up to 40% of allergic rhinitis patients experience asthma (Bousquet *et al*, 2012; Aryan *et al*, 2013). Skin allergies and food allergies are other allergic conditions that are common in asthmatics, in such a way up to 15% of asthmatics have food allergies (Fiocchi *et al*, 2013). It is not clear in this study that how investigators categorised patients who had several allergic conditions and it might affect their results.

Another point is that wheezing in Down syndrome children is not likely to be asthma and asthma misclassification is possible to be occurred. It has been shown that Down syndrome children

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might experience episodes of wheezing mimicking asthma phenotype. Weijerman *et al* (2011) studied recurrent wheeze in 173 Down syndrome children and found that none of Down syndrome children below 4 years of age had asthma according to international guidelines, and only 3.1% of overall Down syndrome children were actually asthmatic. Weijerman *et al* (2011) demonstrated that 46% of wheezes in Down syndrome children were due to congenital heart defects. In addition, neither of increased immunoglobulin-E level nor evidence of aeroallergen sensitisation was found in these children (Weijerman *et al*, 2011). Hence, the diagnosis of asthma should be made more carefully in Down syndrome patients and only reliance of parent's memory might probably lead to misclassification of asthma in Down syndrome children. Moreover, not all asthmatic Down syndrome children have allergy, and in contrast, asthma in Down syndrome patients seem to be non-allergic (Weijerman *et al*, 2011). Collectively, the results of this study regarding asthma might be affected by misdiagnosis and misclassification of asthma as an allergic condition.

On the other hand, Down syndrome is a primary immune deficiency characterised by lymphopenia, thrombocytopenia, and vulnerability to autoimmune and infectious diseases. Down syndrome children have increased susceptibility to respiratory syncytial virus infections, a known risk factor of asthma, thus they may experience manifestations quasi-asthma or actually develop asthma (Bloemers *et al*, 2010). Down syndrome patients have also inherited risk of acute leukaemia development. Accumulating evidences show that several genes on chromosome 21 have relevant functions in haematopoiesis and their qualitative or quantitative changes affect blood cells. Transient abnormal haematopoiesis and acute myeloid leukaemia are more likely to develop in Down syndrome children with *GATA1* mutation (Maclean *et al*, 2012; Toki *et al*, 2013). It indicates that regardless of role of environmental factors, inborn genetic defects in Down syndrome children affect haematopoietic cell biology and cause leukaemogenesis. Down syndrome might be a confounder in relation between asthma and acute leukemia. Altogether, Down syndrome may be considered as a cause of both asthma and acute leukaemia and drawing a causative link from asthma to acute leukaemia in this setting seems a raw conclusion.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Reply: Comment on 'Allergy and acute leukaemia in children with Down syndrome: a population study. Report from the Mexican Inter-Institutional Group for the Identification of the Causes of Childhood Leukaemia (MIGICCL)' – A reality or myth or two viewpoints about the association between allergies and acute leukaemia in Down syndrome children

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Sir,

We are very grateful to Drs Aryan and Rezaei (2013b) for their interest in our manuscript; their letter is interesting as it reveals the differences between a reductionist and a population viewpoint with regard to the relationship between allergies and the development of leukaemia in children with Down syndrome.

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