Toki T, Kanezaki R, Kobayashi E, Kaneko H, Suzuki M, Wang R, Terui K, Kanegane H, Maeda M, Endo M, Mizuochi T, Adachi S, Hayashi Y, Yamamoto M, Shimizu R, Ito E (2013) Naturally occurring oncogenic GATA1 mutants with internal deletions in transient abnormal myelopoiesis in Down syndrome. *Blood* **121**(16): 3181–3184.

Vojtechova P, Martin RM (2009) The association of atopic diseases with breast, prostate, and colorectal cancers: a meta-analysis. *Cancer Causes Control* **20**(7): 1091–1105.

Weijerman ME, Brand PL, van Furth MA, Broers CJ, Gemke RJ (2011) Recurrent wheeze in children with Down syndrome: is it asthma? *Acta Paediatrica* **100**(11): e194–e197.

BJC

British Journal of Cancer (2013) 109, 1388–1390 | doi: 10.1038/bjc.2013.436

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

J C Núñez-Enríquez[1], A Fajardo-Gutiérrez[1], E P Buchán-Durán[1], E Jiménez-Hernández[2] and J M Mejía-Aranguré*[,1,3]

[1]Unidad de Investigación Médica en Epidemiologia Clínica, Hospital de Pediatría, Centro Médico Nacional 'Siglo XXI', Instituto Mexicano del Seguro Social, Av. Cuauhtémoc 330, Delegación Cuauhtémoc, México D.F. 06720, México; [2]Servicio de Hematología Pediátrica, Hospital General 'Gaudencio González Garza', Centro Médico Nacional 'La Raza', Instituto Mexicano del Seguro Social, Calzada Vallejo y Jacarandas S/N Col. La Raza, Delegación Azcapotzalco, México D.F. 02990, México and [3]Coordinación de Investigación en Salud, Instituto Mexicano del Seguro Social, Torre Academia Nacional de Medicina 4to piso, Av. Cuauhtémoc 330, Delegación Cuauhtémoc, México D.F. 06720, México

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.

*Correspondence: Dr JM Mejía-Aranguré; E-mail: juan.mejiaa@imss.gob.mx
Published online 1 August 2013

Regarding the allergies as protective factors for the development of cancer, Aryan and Rezaei (2013b) referred to research carried out in adult populations with general cancer. Each cancer has different manifestations and risk factors, and the hypotheses that emerge are very heterogeneous. Additionally, the biological mechanisms involved in adulthood cancer are very different from those observed in childhood cancer; therefore, it is not possible to extrapolate conclusions, particularly in children with acute leukaemia (Ahlbom *et al*, 2001; Lightfoot and Roman, 2004; Raab and Gartner, 2009; Morisot *et al*, 2010).

Our study is not the first to show that asthma may be a risk factor for the development of acute leukaemia in children; in our paper we cited the research conducted by Spector *et al* (2004) and Chang *et al* (2012) who also reported a positive association between asthma and the development of leukaemia in children.

The question addressed by Aryan and Rezaei (2013b) 'why was asthma found as a risk factor of acute leukaemia development?' and their comments can be summarised in four points:

1. The allergy diagnosis and definition of allergic conditions could affect categorisation of patients that in turn influenced our results.
2. Misclassification of asthma in children with Down syndrome.
3. Congenital heart defects would confound the association between asthma and acute leukaemia.
4. Down syndrome may be a cause of asthma and acute leukaemia.

Following are the answers to the above points:

1. Asthma is related to other allergic conditions such as comorbidities, including rhinitis, skin allergy or food allergies, as argued by Aryan and Rezaei (2013b). However, Aryan and Rezaei (2013b) reported the prevalence of comorbidities observed in studies (Aryan *et al*, 2013a; Bousquet *et al*, 2012) carried out in general populations, whereas our study was conducted in children with Down syndrome which is a population characterised by immunological impairment. Previous studies in Down syndrome children have suggested that the mechanisms involved for the development of allergy of a specific allergen and its clinical manifestations differ from those observed in the general population (Muñoz-López, 2011). Indeed, the number of studies reporting the prevalence of allergic conditions in Down syndrome children is limited; thus, the real prevalence of allergies in this population is controversial. The frequencies in relation to asthma and other allergies as comorbidities are displayed in Table 1a. In the logistic regression analysis and correlation matrix analysis we observed a high correlation (above 0.3) among the different type of allergies; in this situation it has been suggested to choose one of the following options: (1) to eliminate any correlated variable or (2) to carry out a separate analysis (Kleinbaum and Klein, 2002). Taking into account that the analysis that ignores the correlations may lead to incorrect inferences, and in order to avoid the homoscedasticity phenomenon we opted for the second option, to carry out a separate analysis according to each allergic condition (Kleinbaum and Klein, 2002). Concerning the diagnosis of allergic diseases in Down syndrome children, there is neither a 'gold standard' laboratory test nor specific criteria to diagnose allergies, particularly in asthma where it is not possible to confirm the diagnosis through pulmonary function test due to generalised muscle hypotonia characteristic of Down syndrome patients. Additionally, the pulmonary function test requires patient's collaboration that includes exhalations which are not feasible in Down syndrome children (Weijerman *et al*, 2011). Therefore, the diagnosis of asthma is based on heterogeneous signs and symptoms, radiologic studies and the exclusion of other diseases that could manifest similarly to asthma such as respiratory infections, cardiopathies, etc. (Madan *et al*, 2006; Weijerman *et al*, 2011).
2. Aryan and Rezaei (2013b) do not understand our case–control study (Down syndrome children with and without leukaemia). If Down syndrome children's parents confounded wheezing with asthma this bias could be also expected in Down syndrome children with acute leukaemia and without acute leukaemia. Generating a non-differential misclassification bias would cause an underestimation of odds ratios (ORs); thus, the association between asthma and acute leukaemia would be higher than the observed in this study.
3. As we showed in our article, the presence of cardiopathies in Down syndrome children was inversely associated with the risk of acute leukaemia (OR 0.35; CI 95%: 0.18–0.67). In this reply letter, we show the stratified analysis by cardiopathies (Table 1b) and the calculated differences between the Mantel–Haenszel and the crude OR for both bronchial asthma and skin allergy, which were minimal. These results do not support the argument by Aryan and Rezaei (2013b) that in our population the general practitioners confounded cardiopathies with asthma.
4. Aryan and Rezaei (2013b) manifest a poor understanding of epidemiological methodology because the cases and controls recruited in our research have Down syndrome. As a matter of fact, our question has been 'why do some Down syndrome children develop leukaemia and others do not?' We have named

Table 1a. Frequencies in relation to asthma and other allergies as comorbidities

	Bronchial asthma		Skin allergy	
Allergic condition	***n***	**%**	***n***	**%**
Bronchial asthma	—	—	6	11.5
Skin allergy	6	37.5	—	—
Rhinitis	3	20	8	15.7
Other allergies	2	12.5	14	26.9

Table 1b. Results of stratified analysis according to cardiopathies (yes/no) for the association between bronchial asthma or skin allergy and the development of acute leukaemia in children with Down syndrome

Allergic condition	Cardiopathy (yes) OR (95% CI)	Cardiopathy (no) OR (95% CI)	$_{MH}$OR (95% CI)	Difference between $_{MH}$OR and $_{C}$OR and (%)
Bronchial asthma	6.00 (0.76–47.14)	4.00 (1.17–13.71)	4.35 (1.49–12.70)	4
Skin allergy	1.05 (0.20–5.49)	0.33 (0.14–0.79)	0.42 (0.19–0.89)	0.9

Abbreviations: CI = confidence interval; COR = crude odds ratio; $_{M}$HOR = Mantel–Haenszel odds ratio; OR = odds ratio.

this design 'case–control study matched for susceptibility' (Mejía-Aranguré, 2013). This design does not allow us to think that Down syndrome produces asthma and acute leukaemia. The conclusion is that children with Down syndrome who developed leukaemia had higher frequency of asthma than Down syndrome children who did not developed leukaemia.

We are thankful to Aryan and Rezaei (2013b) because their letter has nourished the explanation of why we included in our studies cases and controls with a high susceptibility to developing childhood acute leukaemia.

REFERENCES

Ahlbom IC, Cardis E, Green A, Linet M, Savitz D, Swerdlow A (2001) Review of the epidemiologic literature on EMF and health. *Environ Health Perspect* **109**: 911–933.

Aryan Z, Comapalati E, Canonica GW, Rezaei N (2013a) Allergen-specific immunotherapy in asthmatic children: from the basis to clinical applications. *Expert Rev Vaccines* **12**: 639–659.

Aryan Z, Rezaei N (2013b) 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? *Br J Cancer* **109**(5): 1386–1388.

Bousquet J, Schunemann HJ, Samolinski B, Demoly P, Baena-Cagnani CE, Bachert C, Bonini S, Boulet LP, Bousquet PJ, Brozek JL, Canonica GW, Casale TB, Cruz AA, Fokkens WJ, Fonseca JA, van Wijk RG, Grouse L, Haahtela T, Khaltaev N, Kuna P, Lockey RF, Lodrup Carlsen KC, Mullol J, Naclerio R, O'Hehir RE, Ohta K, Palkonen S, Papadopoulos NG, Passalacqua G, Pawankar R, Price D, Ryan D, Simons FE, Togias A, Williams D, Yorgancioglu A, Yusuf OM, Aberer W, Adachi M, Agache I, Ait-Khaled N, Akdis CA, Andrianarisoa A, Annesi-Maesano I, Ansotegui IJ, Baiardini I, Bateman ED, Bedbrook A, Beghe B, Beji M, Bel EH, Ben Kheder A, Bennoor KS, Bergmann KC, Berrissoul F, Bieber T, Bindslev Jensen C, Blaiss MS, Boner AL, Bouchard J, Braido F, Brightling CE, Bush A, Caballero F, Calderon MA, Calvo MA, Camargos PA, Caraballo LR, Carlsen KH, Carr W, Cepeda AM, Cesario A, Chavannes NH, Chen YZ, Chiriac AM, Chivato Perez T, Chkhartishvili E, Ciprandi G, Costa DJ, Cox L, Custovic A, Dahl R, Darsow U, De Blay F, Deleanu D, Denburg JA, Devillier P, Didi T, Dokic D, Dolen WK, Douagui H, Dubakiene R, Durham SR, Dykewicz MS, El-Gamal Y, El-Meziane A, Emuzyte R, Fiocchi A, Fletcher M, Fukuda T, Gamkrelidze A, Gereda JE, Gonzalez Diaz S, Gotua M, Guzman MA, Hellings PW, Hellquist-Dahl B, Horak F, Hourihane JO, Howarth P, Humbert M, Ivancevich JC, Jackson C, Just J, Kalayci O, Kaliner MA, Kalyoncu AF, Keil T, Keith PK, Khayat G, Kim YY, Koffi N'goran B, Koppelman GH, Kowalski ML, Kull I, Kvedariene V, Larenas-Linnemann D, Le LT, Lemiere C, Li J, Lieberman P, Lipworth B, Mahboub B, Makela MJ, Martin F, Marshall GD, Martinez FD, Masjedi MR, Maurer M, Mavale-Manuel S, Mazon A, Melen E, Meltzer EO, Mendez NH, Merk H, Mihaltan F, Mohammad Y, Morais-Almeida M, Muraro A, Nafti S, Namazova-Baranova L, Nekam K, Neou A, Niggemann B, Nizankowska-Mogilnicka E, Nyembue TD, Okamoto Y, Okubo K, Orru MP, Ouedraogo S, Ozdemir C, Panzner P, Pali-Scholl I, Park HS, Pigearias B, Pohl W, Popov TA, Postma DS, Potter P, Rabe KF, Ratomaharo J, Reitamo S, Ring J, Roberts R, Rogala B, Romano A, Roman Rodriguez M, Rosado-Pinto J, Rosenwasser L, Rottem M, Sanchez-Borges M, Scadding GK, Schmid-Grendelmeier P, Sheikh A, Sisul JC, Sole D, Sooronbaev T, Spicak V, Spranger O, Stein RT, Stoloff SW, Sunyer J, Szczeklik A, Todo-Bom A, Toskala E, Tremblay Y, Valenta R, Valero AL, Valeyre D, Valiulis A, Valovirta E, Van Cauwenberge P, Vandenplas O, van Weel C, Vichyanond P, Viegi G, Wang DY, Wickman M, Wohrl S, Wright J, Yawn BP, Yiallouros PK, Zar HJ, Zernotti ME, Zhong N, Zidarn M, Zuberbier T (2012) Allergic rhinitis and its impact on asthma (ARIA): achievements in 10 years and future needs. *J Allergy Clin Immunol* **130**: 1049–1062.

Chang J, Tsai Y, Tsai CR, Wiemels JL (2012) Allergy and risk of childhood acute lymphoblastic leukemia: a population-based and record-based study. *Am J Epidemiol* **176**: 970–978.

Kleinbaum DG, Klein M (2002) Logistic regression. *A Self-Learning Text*. Springer: New York, America.

Lightfoot TJ, Roman E (2004) Causes of childhood leukaemia and lymphoma. *Toxicol Appl Pharmacol* **199**: 104–117.

Madan V, Williams J, Lear JT (2006) Dermatological manifestations of Down's syndrome. *Clin Exp Dermatol* **31**: 623–629.

Mejía-Aranguré JM (2013) Model for identifying the etiology of acute lymphoblastic leukemia in children. In *Clinical Epidemiology of Acute Lymphoblastic Leukemia – From the Molecules to the Clinic*, pp 3–17. InTech: Rijeka.

Morisot S, Wayne AS, Bohana-Kashtan O, Kaplan IM, Gocke CD, Hildreth R, Stetler-Stevenson M, Walker RL, Davis S, Meltzer PS, Wheelan SJ, Brown P, Jones RJ, Shultz LD, Civin CI (2010) High frequencies of leukemia stem cells in poor-outcome childhood precursor-B acute lymphoblastic leukemias. *Leukemia* **24**: 1859–1866.

Muñoz-López F (2011) Pediatrics, Down's syndrome and allergic disease. *Rev Med Int Sindr Down* **15**: 8–13.

Raab CP, Gartner Jr JC (2009) Diagnosis of childhood cancer. *Prim Care* **36**: 671–684.

Spector L, Groves F, DeStefano F, Liff J, Klein M, Mullooly J, Black S, Shinefield H, Ward J, Marcy M (2004) Medically recorded allergies and the risk of childhood acute lymphoblastic leukaemia. *Eur J Cancer* **40**: 579–584.

Weijerman ME, Brand PLP, Van Furth Ma, Broers CJM, Gemke RJBJ (2011) Recurrent wheeze in children with Down syndrome: is it asthma? *Acta Paediatr* **100**: e194–e197.