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Reply

From the Authors:



We are grateful for the interest Dr. Gupta and colleagues have shown in our manuscript and its implications (1). We of course agree that minimal clinically important difference estimates are context dependent. In this study, we reported differences based on 6-minute walk (6MW) 1 year apart without treatment change, because ECLIPSE was a prospective observational study (2). This context is of course explicit in the METHODS. We believe our work is a useful addition to the literature because prior studies have been context dependent in a different sense, specifically around improvement rather than natural progression and around a treatment intervention, typically rehabilitation and/or surgery, to which the patient cannot be blinded.

The question as to whether different thresholds for change in 6-minute-walk distance (Δ 6MWD) produce different odds ratios for mortality is interesting. In the original article, we had already given data for -30 and -39.6 m. As one would expect, lowering this threshold adds patients who don't die to the group, with the larger Δ 6MWD thus diminishing the hazard ratios (HRs) and weakening statistical significances, though these are retained by virtue of the very large sample size (-20 m: HR = 1.87, 95% confidence interval, 1.24–2.81, $P = 0.003$; -25 m: HR = 1.90, 95% confidence interval, 1.27–2.85; $P = 0.002$). Nevertheless this question fails to appreciate the origin of the -30 m, which is the difference in Δ 6MWD, rounded from -29.7 m, between those who died and those who did not.

Lastly, we accept that in a literal sense, death cannot be considered a minimal change. However death is clearly a categorical variable; like pregnancy, one cannot be “slightly” dead. Against that background and in the context of the work, we believe the use of the word is justified. We do agree that minimal clinically important difference for perceptible improvement in symptoms, as Gupta and colleagues propose, has value in relation to some therapeutic interventions, and particularly for conditions where death is infrequent. Nevertheless, because subtypes of COPD do have a poor prognosis (3–5) and COPD is not just a disease affecting the symptoms domain, we also submit that a clinical assessment tool, like 6MW, that detects mortality risk will be of value both to clinicians and those designing clinical trials.

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Allergic Sensitization and Airway Inflammation after Early Swimming



To the Editor:

There is increasing evidence that irritant chlorination products in swimming pools can cause respiratory problems in pool workers and competitive swimmers (1, 2). Whether these risks may extend to recreational swimmers is an important question which to date remains unresolved. Several studies of adults and adolescents (3–8) have shown that recreational swimming in outdoor or indoor chlorinated pools is associated with increased risks of allergic diseases, in particular asthma. In adolescents, the asthma risk associated with chlorinated pool attendance appears to largely be the consequence of an interaction with atopy, increasing only among subjects sensitized to aeroallergens (6, 7). Other studies found no increase of asthma risk with swimming pool attendance (8, 10). These studies, however, were more focused on children who perhaps were too young for detecting among them associations with atopic asthma, a chronic disease developing mostly during late childhood (11). Further complicating the matter, some observations suggest that early exposure to chlorinated pools might promote allergic sensitization and thus contribute to the development of atopy itself. Attendance at chlorinated pools during infancy or early childhood has indeed been associated with an increased risk of eczema (9) and house dust mite (HDM) sensitization (12, 13), two outcomes that are predictive of rhinitis and asthma later in life.

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Author Contributions: C.V. recruited the children, organized their examination in schools, performed the collection and analysis of data, and contributed to the writing of the manuscript. A.S. was responsible for the screening of aeroallergen-specific IgE in nasal mucosa. A.B. provided the scientific guidance of the project, participating in the study design, the data analysis and interpretation, and the writing of the manuscript.

TABLE 1. NEW-ONSET CASES OF SENSITIZATION TO HDM AND OF INCREASED EXHALED NO ACCORDING TO THE TOTAL TIME SPENT IN INDOOR OR OUTDOOR CHLORINATED SWIMMING POOLS BEFORE THE AGE OF 3 YEARS

	Cumulative attendance at chlorinated pools before the age of 3 yr (h)				
	Never	1–30	>30	1–60	>60
New-onset HDM sensitization*					
n/N (%)	7/48 (14.6)	15/57 (26.3)	20/64 (31.3)	21/76 (27.6)	14/45 (31.1)
Crude OR (95% CI)	1.00	2.09 (0.77–5.66)	2.66 (1.02–6.96)	2.24 (0.87–5.76)	2.65 (0.95–5.76)
Adjusted OR (95% CI)	1.00	2.60 (0.91–7.38)	3.27 (1.18–9.07)	2.63 (0.98–7.12)	3.60 (1.21–10.7)
P for trend			0.047		0.06
New-onset exhaled NO > 15 ppb†					
n/N (%)	5/43 (11.6)	17/59 (28.8)	20/64 (31.3)	21/78 (26.9)	16/45 (35.6)
Crude OR (95% CI)	1.00	3.08 (1.04–9.15)	3.46 (1.18–10.1)	2.80 (0.97–8.07)	4.19 (1.38–12.8)
Adjusted OR (95% CI)	1.00	4.41 (1.33–14.7)	4.66 (1.42–15.2)	3.88 (1.21–12.4)	5.92 (1.72–20.5)
P for trend			0.03		0.01

Definition of abbreviation: CI = confidence interval; HDM = house dust mite.

N represents the number of subjects in the different groups that at baseline were not sensitized to HDM or were negative in the exhaled nitric oxide test.

*Adjusted for preterm birth, mold in bedroom.

† Adjusted for preterm birth, number of older siblings, mold in bedroom, use of bleach for house cleaning, smoking during pregnancy, parental allergies and parental smoking.

We here report the results of a 2-year prospective study comparing the development of new-onset allergic sensitization and diseases and increased exhaled nitric oxide (eNO) between children who started to swim in early life and those who did not.

The study was conducted among 196 schoolchildren in 30 schools located in the areas of Brussels and Liège in Belgium. The first examination took place between December 2007 and March 2008 when children were all in the third year of kindergarten (mean age, 5.7 yr; SD, 0.37). The children were then reexamined 2 years later by visiting the schools in the same order between December 2009 and March 2010. The baseline group included 431 children, but 2 years later, 128 of them had left the schools. Among the remaining children, 236 (77.9%) participated in the study with the agreement of their parents and 196 of them successfully performed all of the tests. Subjects and nonsubjects did not differ significantly regarding studied outcomes, chlorinated pool attendance, and the main risk factors of allergies. Parents filled out a self-administered questionnaire about the health of their child and factors likely to influence the development of respiratory and allergic diseases. The questionnaire included questions intended to calculate the total time (cumulative pool attendance [CPA]) the child had spent in indoor or outdoor chlorinated pools before the age of 3 (referred to hereinafter as “early swimmers”), during the 2-year follow-up, and over their lifetime. The examination of children, performed in schools between 9:00 A.M. and 1:00 P.M., included a screening of aeroallergen-specific IgE in nasal mucosa by the Rhinostick test (14) and the measurement of eNO (NIOX analyzer; Aerocrine AB, Solna, Sweden). The Rhinostick test was calibrated with serum standards and was considered positive at specific IgE $\geq$ 0.35 kIU/L (14). For eNO, we used a cutoff of 15 ppb (15), which in our study corresponded to the 95th percentile of baseline values in children who were nonatopic. The study protocol was approved by the Institutional Review Board of the Catholic University of Louvain. We used backward logistic regression analyses to calculate the crude and adjusted odds ratios (aORs) of outcomes according to increasing CPA while adjusting for confounders that remained in the model at a P value $<$ 0.20. For these analyses, we used children who never attended chlorinated pools before the age of 3 as referents and we dichotomized early swimmers at CPA cutoff values (30 or 60 h) that corresponded approximately to the median (32 h) or twice the median of their CPA. Because there were only 10 children who never visited chlorinated pools, the CPA during the follow-up or over the child's lifetime was stratified in tertiles. Results were considered statistically significant at a P value $<$ 0.05.

Early swimmers and their controls were well matched with respect to gender, parental history of allergies, and other traditional risk factors of atopic diseases. At baseline, the two groups did not show any significant difference in the prevalence of increased eNO and of allergic sensitization or diseases, except for eczema, which was much more frequent in early swimmers (aOR, 3.17; 95% confidence interval [CI], 1.29–7.81; P = 0.01). When children were reexamined 2 years later, we found no significant differences in the prevalence of new-onset allergic diseases between the two groups. By contrast, there was a marked increase in the prevalence of new-onset sensitization to HDM (aOR, 2.93; 95% CI, 1.14–7.55; P = 0.03) and new-onset increased eNO (aOR, 4.54; 95% CI, 1.48–13.9; P = 0.008) among early swimmers as compared with controls. As shown in Table 1, the adjusted ORs for these two outcomes increased dose dependently with the time spent in indoor or outdoor chlorinated pools before the age of 3. These associations were independent of each other, of parental allergies, and of preexisting diseases, including eczema. Such associations were not seen with IgE sensitization to pollen or cat allergens. Whether tested alone or with the CPA before the age of 3, the CPA during the follow-up (median [h] in early swimmers, 161; in controls, 77) or over the child's lifetime (early swimmers, 309; controls, 99) was never retained as a significant predictor for any of the studied outcomes.

This prospective study shows that children who regularly attended indoor or outdoor chlorinated pools during their infancy were more likely to develop airway inflammation and a sensitization to HDM. Attendance at chlorinated pools later during childhood did not emerge as a significant predictor for these risks. These specific associations with early swimming, also observed in cross-sectional studies (12, 13), suggest, not surprisingly, that developing airways of young children are highly vulnerable to injury by chlorination products. Our study has some limitations, in particular regarding the exposure assessment on the basis of the questionnaire and the lack of a control group attending nonchlorinated pools. However, because at the age of 3, and even later, children cannot really swim and do not actively practice a sport, physical exercise is unlikely to be the cause of our findings. The most plausible explanation is that the exposure to chlorine-based irritants in swimming pools causes defects in epithelial barriers predisposing children to allergic sensitization and airway inflammation (11, 12). To enhance sensitization, these epithelial defects logically require a concomitant and sufficient exposure to allergens, a condition more easily met with perennial allergens like HDM than with seasonal allergens linked to pollination. This probably explains why sensitization

to pollen was not increased in early swimmers and also why the risk of HDM sensitization increased only after a time lag of a few years. Combined with data from previous studies showing that pool chlorine can interact with atopic status to increase the risks of allergic rhinitis or asthma (6, 7), our findings suggest that chlorine used to disinfect swimming pools is a significant driver of the atopic march, promoting allergic sensitization at an early stage and later the clinical manifestations of atopy.

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Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery Presenting as Sudden Death in a Young Woman



To the Editor:

Sports-related sudden death is a specific nosological entity, occurring in the vast majority of cases without prodrome. Its incidence in France is currently 4.6 per million per year, affecting males in 95% of cases (1). In addition, under the age of 35, ventricular arrhythmia is the leading cause of sudden death, followed by coronary artery diseases and cardiomyopathy (2).

We present the case of a 16-year-old woman admitted for a sports-related sudden cardiac arrest leading to diagnosis of abnormal implantation of the coronary arteries.

A 16-year-old woman, measuring 1.65 m and weighing 56 kg, with no previous abnormal medical history collapsed during school running practice without prodromal symptoms. A diagnosis of cardiac arrest was made and cardiopulmonary resuscitation (CPR) was performed by the sports teacher (2 min of mouth-to-mouth breathing followed by external cardiac massage). The emergency services arrived 5 minutes after collapse. Their semi-automatic defibrillator advised an external electric shock (pace recovered *a posteriori* showed ventricular fibrillation), which was successful with return to sinus rhythm and spontaneous circulation. Due to persistent coma (Glasgow Coma Score = 5) and after initial CPR, the patient was intubated by the Mobile Emergency and Resuscitation Service's physician, who arrived 20 minutes after the initial loss of consciousness. The patient was then transferred to the intensive care unit for further care and etiological appraisal. Computed tomography (CT) of the brain showed no abnormality, echocardiography didn't find any systolic–diastolic dysfunction, and ECG revealed anterior and lateral ST segment elevation associated with a high maximum peak of troponin Tc of 150 ng/L (n < 14 ng/L) to H6. No metabolic abnormality was found except for lactic acidosis (lactates, 3.44 mmol/L; pH 7.24), which was quickly reversible. Evolution was favorable in the intensive care unit with an adapted revival without neurological deficit (Cerebral Performance Category score = 1) after 24 hours of therapeutic hypothermia at 33°C with a CoolGuard device (IST Cardiology, Saint-Contest, France). The patient was extubated 3 days after admission (D3) and then transferred to the cardiology department for etiological appraisal at D4.

Cardiac CT angiography showed agenesis of the common trunk of the left coronary artery with fistula between the proximal left anterior descending artery and pulmonary artery. This was associated with dilatation of the coronary arteries, constituting a significant distal and intraseptal left–right anastomotic network (Figure 1). Cardiac magnetic resonance imaging (MRI) showed a left-to-right shunt (via an anastomosis between the right coronary artery and the left coronary artery) of 1.4 L/minute and a subendocardial infarction in the lateral wall of the left ventricle. Left ventricular ejection fraction was maintained at 63%. The diagnosis was anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) (also known as Bland-White-Garland syndrome). The patient underwent cardiac surgery with reimplantation of the left coronary artery into the aorta. The postoperative course was uneventful, allowing hospital discharge at D18 with β -blocker and angiotensin-converting enzyme inhibitor. Six months after initial admission, the patient suffered no neurological or cardiac sequelae, enabling resumption of sports with no restrictions.

ALCAPA, which corresponds to implantation of the left coronary artery into the pulmonary artery, is a rare congenital heart