Corrigendum: Transcriptional and epigenetic response to sedentary behavior and physical activity in children and adolescents: A systematic review

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In the original article, we neglected to include the affiliation number 3 for the author Pablo Molina-Garcia. The affiliation added is “3 Instituto de Investigación Biosanitaria (ibs.GRANADA), Granada, Spain.”

In the original article, we neglected to include the affiliation number 9 for the author Signe Altmäe. The affiliation added is “9 Competence Centre on Health Technologies, Tartu, Estonia.”

In the original article, the reference “37. Radom-Aizik S, Zaldívar F, Leu SY, Cooper DM. Brief bout of exercise alters gene expression in peripheral blood mononuclear cells of early- and late-pubertal males. Pediatr Res. (2009) 65:447–52. doi: 10.1203/PDR.0b013e3181993473” was missing. The reference list has been updated.

In the original article, the correct reference number “37. Radom-Aizik S, Zaldívar F, Leu SY, Cooper DM. Brief bout of exercise alters gene expression in peripheral blood mononuclear cells of early- and late-pubertal males. Pediatr Res. (2009) 65:447–52. doi: 10.1203/PDR.0b013e3181993473” was not cited in the article.
The citation has now been inserted in the Results section, Paragraph one and Paragraph three, and the Discussion section, Paragraph one and Paragraph nine. These paragraphs appear below.

In the original article, there was an error in Table 1. “Histone acetylation” and “Microarray” are different terms and were combined in the table row. "qPCR" and “transcriptome” are different terms and were combined in the table row. The corrected Table 1 appears below.

In the original article, there was an error in Table 2, the reference number 37 was indicated for different manuscripts as follows “Radom-Aizik et al. (37)” and "de Souza e Silva et al. (37).” The correct Table 2 appears below.

In the original article, there was an error in the legend of Figure 3, the reference number 37 was missing. The correct legend appears below.

In the original article, we neglected to include the funders The Estonian Research Council (grant PRG1076), and the European Commission and Enterprise Estonia (grant EU48695). The correct Funding statement appears below.

In the original article, the Conflict of Interest statement was incomplete. Author Signe Altmäe was collaborating with Competence Centre on Health Technologies, Estonia. The corrected statement appears below.

Results, Paragraph one

“PRISMA checklist 2020 shows the appropriateness of the methods performed in our systematic review (Supplementary Tables 2, 3). Figure 1 illustrates the PRISMA 2020 flow diagram for the selection process of the studies: a total of 1,473 articles were included from the three databases, and after removing the duplicates and non-eligible studies, 15 articles remained eligible for this review (6 cross-sectional articles, 5 studies reported the acute effects of physical activity, and 5 articles showed the chronic effects of physical activity). The sample size ranged from 12 to 369 participants (27–41). The age of participants ranged from 9 to 18 years old (27–41). Thirteen studies used blood samples (27, 29–32, 34–41) while 2 saliva (33) and buccal swabs (28) respectively. Regarding disease, four studies included children with obesity (27, 34, 38, 41) and 1 study children with HIV infection (29). Concerning countries/regions, 4 studies were performed in the United States of America (28, 31, 36, 37), 2 in Brazil (30,38), 4 in Europe (27, 33, 35, 39), 3 in Asia (32, 34, 41), 1 in Mexico (40), and 1 in India (29). All the relevant information extracted from each article is presented in Table 2. In addition, a graphical summary of the mains results is presented in Figure 2. Specific genes and related pathways found in the studies are interpreted and discussed in the context of existing knowledge in the Discussion section.”

Results, Paragraph three

“Five out of the twelve articles presented in Table 2 reported significant effects of acute bout of physical activity on gene expression (31, 35–37, 39). Among the five studies, three reported the effects of acute bout of physical activity using candidate gene analyses (i.e., mRNA or miRNA expression) (31, 35, 39), while two studies performed high-throughput transcriptomics analyses using microarrays (36, 37). Four studies used circulating peripheral blood mononuclear cells (PBMCs) to quantify gene expression (31, 36, 37, 39), while one study used capillary blood samples from the earlobe (35).”

Discussion, Paragraph one

“This study aimed to provide current knowledge on the effect of sedentary behavior and physical activity on gene expression and epigenetic mechanisms in the pediatric population. The main findings and gaps identified by this systematic review in children and adolescents were: (1) there is very limited information of the molecular mechanisms of sedentary behavior and/or physical activity on gene expression and its regulation in pediatric population; (2) most of the studies showed that sedentary behavior and physical activity (acute and chronic effects) alter gene and MicroRNA expression, and DNA methylation of candidate genes related to obesity, asthma, immune function, and cardiovascular disease; (3) the studies are hardly comparable due to different candidate genes selected, characteristics of the exposure, health and training status of the participants, and study designs; (4) only two studies performed high-throughput transcriptomics analyses and detected thousands of genes differentially altered by acute bout of physical activity in boys and girls at different pubertal stages (36, 37). The relatively small number of studies, the heterogeneity in the methodology, different study designs, and most of the studies were performed in Europe and/or the United States of America (8/15) limit the extrapolation of our findings to the general pediatric population. Studies using high-throughput techniques (i.e., sequencing) and longitudinal study approach and/or randomized controlled trials on bigger cohorts are lacking in children and adolescents.”

Discussion, Paragraph nine

“In regards to high-throughput analyses, two studies reported the acute effects of physical activity (cycle ergometer test, 10 × 2 min bouts, ∼90% of HRpeak with 1-min rest intervals) on gene expression profile in PBMCs of healthy boys and girls at different pubertal stages using microarrays analysis (36, 37). The expression of 1,246 genes were altered following the acute physical activity bout in late-pubertal boys (37), while the expression level of 109 genes was found to be altered in early-pubertal boys (37). 13 gene pathways related to immune function and type 1 diabetes, among others were enriched (37). Contrary to boys, the difference in the number of genes their expression was altered following the same acute bout of physical activity was much smaller; 877 genes in late-pubertal girls (36) and 1,320 genes in early-pubertal girls (36). 622 genes overlapped between the groups. These genes enriched gene pathways involved in inflammation, stress, and apoptosis (36). These pioneering studies highlight the need to account for sex and pubertal stage when interpreting genomic data in response to acute bout of physical activity (36, 37), and the
need to apply high-throughput approach to better understand the molecular mechanisms involved in the response to physical activity.”

Figure 3. The complex integration of “omics” data (i.e., multi-omics analysis) might contribute to a better understanding of the molecular mechanisms underlying the health-related benefits of physical activity in children and adolescents. The human genome is essentially invariant and comprises more than 25,000 genes, which encode ∼100,000–200,000 transcripts and 1 million proteins, and a smaller number of metabolites (2,500–3,000) make up the human metabolome (71). The epigenome, which can be influenced by physical activity in adults (15), shows a low/moderate temporal variance and influences both transcriptome and proteome. The transcriptome can be affected by a single bout of physical activity (36, 37) in children and presents a high temporal variance and is translated into the proteome, influencing the metabolome in a tissue-specific manner. Figure modified from Altmäe et al. (72) with permission of the Publisher. This figure was created with BioRender.com.

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Conflict of interest

The author SA is collaborating with the Competence Centre on Health Technologies (Estonia) and is not employed by the entity.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The authors apologize for these errors and state that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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TABLE 1  Definition of the main molecular biology-related terms used in this systematic review.

| Term          | Definition                                                                                                                                   |
|---------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| mRNA          | Messenger RNA (mRNA) carries the genetic information from nucleus to ribosomes necessary to synthesize proteins. Gene expression analysis is based on analysing mRNA molecules. |
| Epigenetics   | Epigenetic modifications (i.e., DNA methylation, histone acetylation) that act on DNA structure. These mechanisms can activate or repress transcription (i.e., gene expression). miRNA is also considered a form of epigenetic regulation, see description below. |
| CpG site      | DNA region prone to methylation where a cytosine nucleotide is followed by a guanine nucleotide linked by a phosphate group.                      |
| DNA methylation | One of the most studied epigenetic modifications that consists in adding a methyl group to C nucleotide in DNA.                                |
| Histone acetylation | Epigenetic modification that involves the addition of an acetyl group to the histone proteins.                                             |
| Microarray    | Microarray is a technology that detects the expression levels of thousands of genes at the same time. Briefly, thousands of genetic sequences are located on a chip, and based on the complementary sequences of the transcripts in a biological sample the hybridization takes place, allowing the detection of gene expression levels. |
| miRNA         | Non-coding micro RNA (miRNA) molecule that is small in length, 18–24 pair of bases. These small RNA molecules are able to regulate gene expression by influencing the half-life of the mRNA or its availability for translation. |
| omics         | Refers to analyses of entire set of molecules such as proteins (i.e., proteomics), metabolites (i.e., metabolomics), DNA sequence variants (i.e., genomics), mRNA expression (i.e., transcriptomics), or DNA methylation profile (i.e., epigenomics) within the sample. |
| RNA-seq       | RNA sequencing technique to quantify the gene expression profile (i.e., transcriptome) in a biological sample.                                  |
| qPCR          | Laboratory technique based on polymerase chain reaction (PCR), which is widely used in molecular biology to amplify a specific nucleic acid sequence and obtain millions to billions of copies. This technique is able to quantify gene expression levels. |
| Transcriptome | Analysis of transcripts (typically mRNA molecules) in order to assess the gene expression levels. Both microarray and RNA-seq approaches are used. The difference between these methods is that in the array a set of possible genes is defined by the set of probes that are present, while RNA-seq allows detection of known and unknown genes. |
# TABLE 2  Summary of study characteristics of articles included in this review.

### Sedentary behavior and physical activity: cross-sectional evidence

| References       | Study design | Target population [Sample size (N)]; Sex (boys %); Age (SD or range in years); Ethnicity/Race (%) | Characteristics of the exposure (SB, PA) or PA intervention | Tissue | Dependent outcome and analytical method | Main findings |
|------------------|--------------|-----------------------------------------------------------------------------------------------|------------------------------------------------------------|--------|----------------------------------------|---------------|
| Wu et al. (34)   | Cross-sectional | Group 1: Children with obesity (N = 59); Boys + Girls (45.8%); 13.8 ± 3.0 y; Chinese (100%) Group 2: Normal-weight children (N = 39); Boys + Girls (61.5%); 10.3 ± 1.1 y; Chinese (100%) | SB and PA across 6 months (questionnaire completed by parents or guardians) | Leukocytes | DNA methylation at FAIM2 promoter (Sequenom MassARRAY platform) | Differentially methylation levels at FAIM2 promoter between obese and normal-weight children according to SB and PA levels. Results were not significant after multiple hypothesis testing corrections |
| Lovinsky-Desir et al. (28) | Cross-sectional | Group 1: Active children (N = 77); Boys + Girls (45%); 12.2 y (9.2–14.0 y); Hispanic (60%), African American (40%) Group 2: Non-active children (N = 58); Boys + Girls (55%); 12.7 y (10.5–14.0 y); Hispanic (72%), African American (28%) | PA across 6 days (accelerometer on the non-dominant wrist) | Buccal swabs (squamous epithelial cells) | DNA methylation at FOXP3 promoter (pyrosequencing) and gene expression | Active children had lower FOXP3 promoter methylation compared to Non-active children exposed to high air pollutant black carbon concentrations. No significant association was reported between FOXP3 promoter methylation and gene expression |
| Vriens et al. (33) | Cross-sectional | Children with normal-weight 70%, overweight 12.5%, and underweight 17.5% (N = 80); Boys + Girls (46.3%); 10.44 ± 0.97 y; Caucasian (91.3%) | SB and PA across ~2 years (out-of-school sport activities and screen time use questionnaires filled out by the parents) | Extracellular fraction of saliva | Expression levels of miRNA-222 and miRNA-146a (qPCR) | SB, represented by screen time use, was positively associated with miRNA-222 and miRNA-146a levels. PA was not significantly associated with either miRNA-222 or miRNA-146a |
| Wu et al. (40)   | Cross-sectional | Adolescents (N = 369); Boys + Girls (47.2%); 14.22 ± 1.99 y for boys/13.95 ± 2.04 y for girls, Mexican (100 %) | SB and PA across 7 days (accelerometer on the non-dominant wrist) | Leukocytes | DNA methylation at PPARG, H19, LINE-1, and HSD11B2 (pyrosequencing) | Substituting 30-min of vigorous PA for 30-min of SB daily was associated with higher methylation at HSD11B2 promoter in boys |

(Continued)
| References                        | Study design       | Target population [Sample size (N)]; Sex (boys %); Age (SD or range in years); Ethnicity/Race (%) | Characteristics of the exposure (SB, PA) or PA intervention | Tissue | Dependent outcome and analytical method | Main findings                                                                 |
|----------------------------------|-------------------|------------------------------------------------------------------------------------------------|----------------------------------------------------------------|--------|------------------------------------------|--------------------------------------------------------------------------------|
| Gopalan et al. (29)              | Cross-sectional   | Group 1: Exercisers (N = 20); Boys + Girls with HIV infection (75%); 10.5 y; Indian (100%)      | Children who practiced 20–45 min/day, 4 times per week from year 0 to year 2 were categorized as “exercisers” (physical activity questionnaire suited for Indian children) | PBMC   | IL-2 and BDNF gene expression (qPCR)     | The gene expression of IL-2 and BDNF was not significantly different between exercisers and non-exercisers groups |
| Dos Santos Haber et al. (30)     | Cross-sectional   | Children and adolescents (N = 108) divided into 4 groups (type I diabetes with ketoacidosis; decompensated type I diabetes; Compensated type I diabetes and healthy control); Boys + girls (NR), 10-18 years old, NR | Frequency and duration of PA activities recorded during the last 3 months by questionnaires. Children were classified as low active (<150 min/week), active (150–250 min/week), and very active (>250 min/week) | Blood samples | IL-10 and TNF-α (qPCR) | A higher PA level (very active compared to active and control groups) was associated with increased IL-10 and decreased TNF-α expression in children with type I diabetes/ketoacidosis and decompensated type I diabetes |
| Acute effects of physical activity | Within-subjects experiment | Group 1: Early-pubertal boys (N = 10); Boys; 10.5 + 0.4 y; NR Group 2: Late-pubertal boys (N = 10); Boys; 17.4 + 0.4 y; NR | Cycle ergometer test, 10 × 2 min bouts, the work rate was individualized for each boy (~90% of HRpeak) with 1-min rest intervals | PBMC   | Microarray gene expression (Affymetrix U133+2 arrays) | A single bout of PA induced changes in PBMC gene expression in both groups, particularly 1,246 genes (517 up, 729 down) in late-pubertal boys and 109 (79 up, 30 down) in early-pubertal boys. 13 gene pathways involved in immune function and type I diabetes, were altered by acute PA in both early- and late-pubertal boys |

(Continued)
### TABLE 2 Continued

| References | Study design | Target population [Sample size (N)]; Sex (boys %); Age (SD or range in years); Ethnicity/Race (%) | Characteristics of the exposure (SB, PA) or PA intervention | Tissue | Dependent outcome and analytical method | Main findings |
|------------|--------------|--------------------------------------------------------------------------------------------------|-----------------------------------------------------------|--------|----------------------------------------|--------------|
| Radom-Aizik et al. (36) | Within-subjects experiment | Group 1: Early-pubertal girls (N = 10); Girls; 10.0 ± 0.3 y; NR Group 2: Late-pubertal girls (N = 10); Girls; 16.1 ± 0.4y; NR | Cycle ergometer test, 10 × 2 min bouts, the work rate was individualized for each girl (~90% of HRpeak) with 1-min rest intervals | PBMC | Microarray gene Expression (Affymetrix U133 + 2 arrays) | A single bout of PA induced changes in PBMC gene expression in both groups, particularly, 877 genes (611 up, 266 down) in late-pubertal girls and 1,320 (829 up, 491 down) in early-pubertal girls. 5 gene pathways related to inflammation, stress, and apoptosis, were altered by acute PA in both early- and late-pubertal girls. |
| Kochanska-Dziurowicz et al. (39) | Within-subjects experiment | Youth ice hockey players (N = 19); Boys; 17.1 ± 0.5 y; Polish (100%) | Cycle ergometer test until voluntary exhaustion (starting with 1.0 W•kg⁻¹ load and increasing the intensity by 0.5 W•kg⁻¹ each 3 min) | PBMC | ADRB2 and ACTB gene expression (qPCR) | ADRB2 and ACTB (internal control) gene expression increased in 74% of players after the PA test |
| Kilian et al. (35) | Cross-over experiment | Competitive young cyclists (N = 12); Boys; 14.4 ± 0.8 y; NR | Session 1: HIIT, 4 × 4 min at 90-95% PPO with 3-min active recovery intervals at 45% PPO Session 2: HVT, 90 min at 60% PPO | Capillary blood samples | Expression levels of miRNA-16, miRNA-21, miRNA-126, and VEGF mRNA (qPCR) | HVT significantly increased miRNA-16 and miRNA-126 during and after the PA test, whereas HIIT showed no significant influence on the miRNAs. VEGF gene expression significantly increased during and after HIIT and HVT |

(Continued)
| References           | Study design               | Target population | Characteristics of the exposure (SB, PA) or PA intervention | Tissue | Dependent outcome and analytical method | Main findings                                                                                                                                                                                                 |
|----------------------|---------------------------|-------------------|-------------------------------------------------------------|--------|----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Lu et al. (31)        | Within-subjects experiment| Group 1: Asthmatics adolescents ($N = 12$); Boys + Girls (33.3%); 15.7 y (14.0–17.0 y); White (50%), Asian (42%), more than one ethnicity (1%) Group 2: Healthy adolescents ($N = 14$); Boys + Girls (57.1%); 15.0 y (14.0–17.0 y); White (71%), Asian (21%), more than one ethnicity (7%) | Acute effects of PA: Cycle ergometer test, $10 \times 2$ min at $\sim 75\%$ of VO$_{2\text{max}}$ with 1-min rest intervals Chronic effects of PA: 8-weeks, 3 days/week (1 h-session) | PBMC   | GR (NR3C1), GRβ, HSP70, TGFβ1, and TGFβ2 gene expression (qPCR) | No effect on PBMC gene expression of NR3C1, GRβ, TGFβ1, and TGFβ2 in both healthy and asthmatic adolescents. In addition, HSP70 gene expression was increased after acute PA while was decreased after chronic PA intervention |
| Woo et al. (32)       | Non-randomized controlled trial | Group 1: Children with overweight ($N = 20$); Boys; 11.30 ± 1.17 y; Korean (100%) Group 2: Normal-weight children ($N = 19$); Boys; 11.32 ± 1.06 y; Korean (100%) | 12-weeks PA intervention. The characteristics of the PA intervention were unclear (i.e., intensity, frequency, among others) | PBMC   | SOD and GPx gene expression (qPCR) | SOD and GPx gene expression was up-regulated after 12-weeks of PA in both groups. In addition, SOD and GPx gene expression was up-regulated after 24-weeks of PA in children with overweight |
| Blüher et al. (27)    | Non-randomized controlled trial | Adolescents with overweight/obesity ($N = 28$); Boys + Girls (46.5%); 15.5 ± 1.4 y; NR | HIIT, 6-months, 2 sessions/week, 60 min/session at 80–95% HR$_{\text{max}}$ with active breaks at 50–60% of HR$_{\text{max}}$ | Blood samples | DNA methylation at RALBP1 (pyrosequencing) | No significant changes in levels of methylation at RALBP1 were observed after 6-months of PA intervention in children with overweight/obesity |
| Zhao et al. (41)      | Non-randomized controlled trial | Children and adolescents with obesity (PA intervention group $N = 40$; control group $N = 20$); Boys + Girls (68.3%); 8-16 y; NR | 12-weeks PA intervention. Frequency of 5 sessions/week, 50 min each session, intensity 60–70% of HR$_{\text{max}}$ | Blood samples | Long non-coding RNA MALAT1 and miR-320a expression (qPCR) | PA intervention decreased MALAT1 and increased miR-320a expression |
| De Souza E Silva et al. (38) | Non-randomized controlled trial | Children and adolescents with overweight/obesity (PA intervention group $N = 17$; control group $N = 18$); Boys + Girls (53.0%); 10–16 y; Euro-Brazilian (self-reported) | 12-weeks PA intervention (indoor cycling), 3 sessions/week (60 min/session) | Blood samples | ADRR2 gene expression (qPCR) | No significant changes in levels of ADRR2 expression were reported after 12-weeks of PA intervention in children with overweight/obesity |