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Genome Instability in Childhood Obesity – a potential role for bariatric surgery in cancer prevention?

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Background

Severe paediatric obesity is associated with a range of metabolic complications and characterised by a chronic meta-inflammatory state. It is postulated that this inflammatory response may result in an excess of systemic reactive oxygen species (ROS) that are well known for inducing DNA damage and reducing the capability of DNA synthesis and repair enzymes. Consequently, chronic inflammation in obesity may promote an accumulation of deleterious DNA mutations, leading to genome instability and driving carcinogenesis.

Aims

This research aims to accrue evidence to consolidate or refute a causative link between genome instability in childhood obesity and the increased risk of developing cancer at a later stage in life. For the purpose of this study, a novel, non-invasive analytical 'tool-kit' for the combined and comprehensive assessment of systemic inflammation and acquired DNA damage has been developed and is being tested on a cohort of severely obese children and healthy weight controls recruited from King's College Hospital and St George's NHS trust. Furthermore, this research aims to propose biomonitoring of the genome to inform prioritization and severity of intervention measures based on the suggested reversibility of DNA damage following early surgical weight-loss treatment.

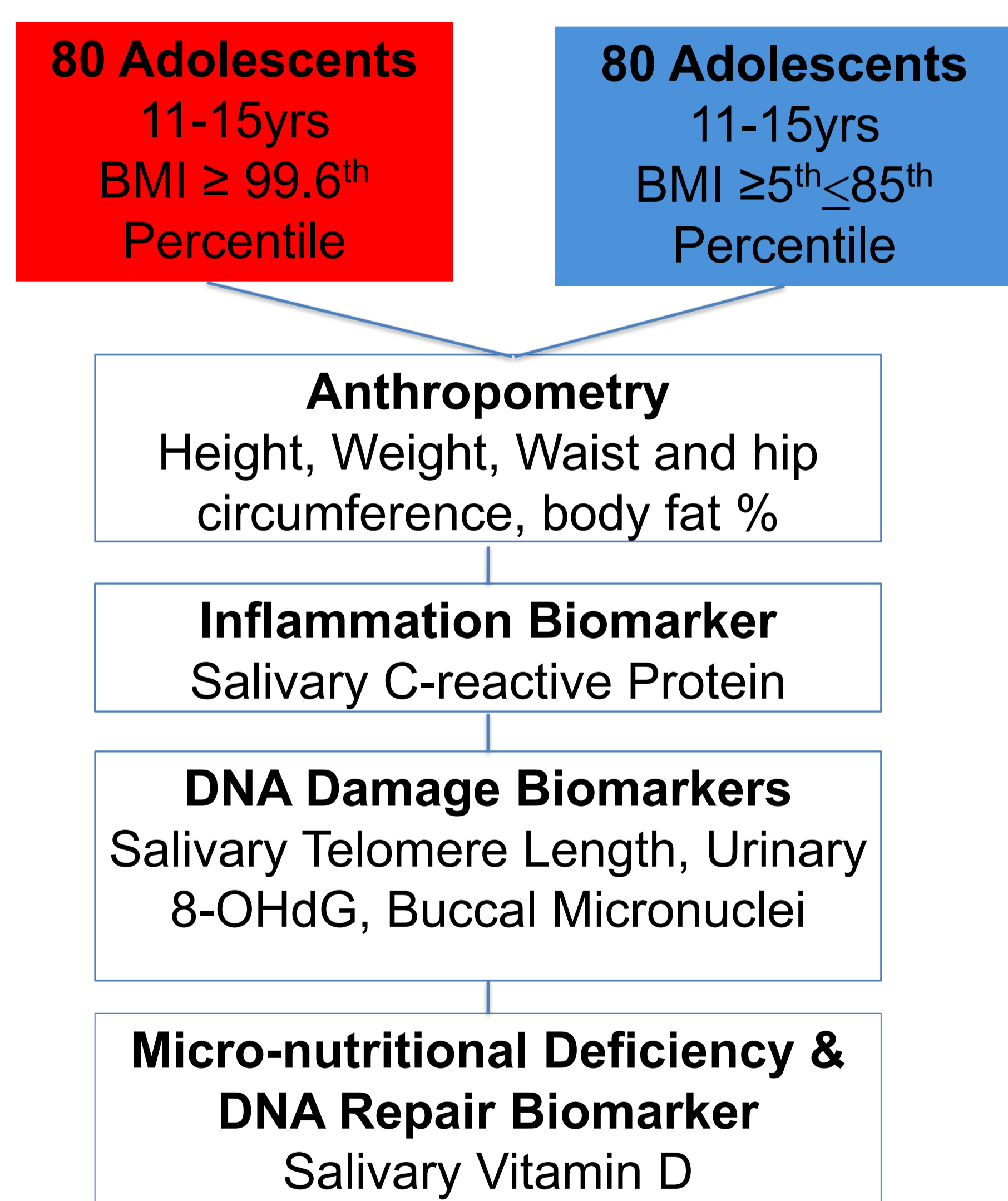


Fig 1. Overview of assessments in the GICO study

Biomarkers of Genome Instability in Obesity

Micronuclei

A micronucleus is a structural body within the cell cytoplasm containing chromosomal fragments or whole chromosomes, which during mitosis have failed to be incorporated into the main nucleus. There is substantial evidence linking the occurrence of micronuclei in peripheral blood lymphocytes with cancer risk¹. Recently, an increased frequency of micronuclei was observed in lymphocytes from obese children². We explore the frequency of micronuclei in differentiated cells of the buccal mucosa by applying a minimally invasive exfoliation technique.

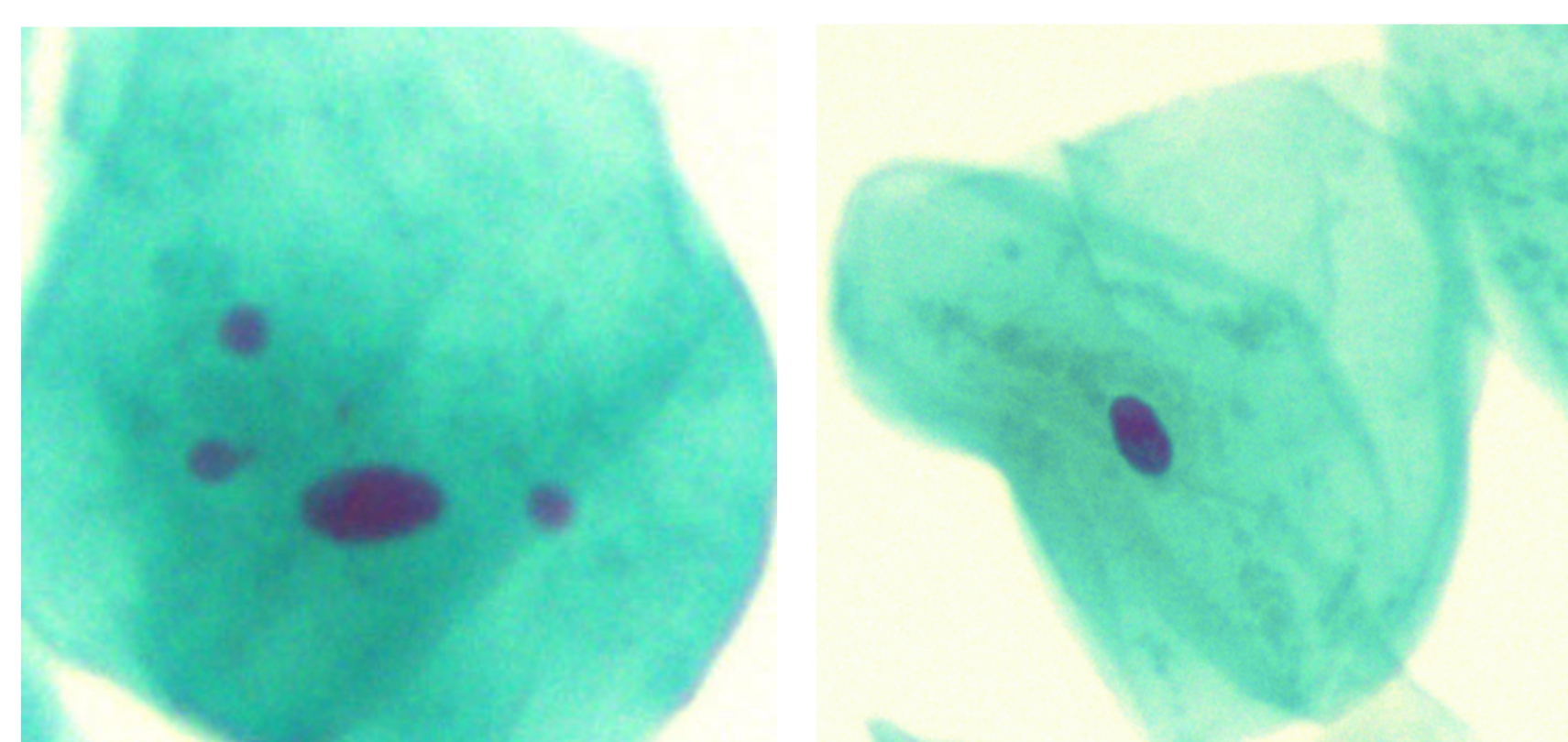


Fig 2. Normal buccal cell and buccal cell containing micronuclei (x1000)

Telomere Length

Telomeres are segments of non-coding DNA repeat sequences (TTAGGG) that are located at the ends of chromosomes, and play a vital role in protecting the integrity of the human genome. In the absence of telomerase – a DNA polymerase enzyme which synthesises telomeric DNA sequences in stem cells, telomeres shorten at every round of the somatic cell cycle. Telomere shortening to a critical length should ultimately result in replicative senescence, hence telomeres shortening have for long been linked to and used as a measure of cellular ageing³. Evidence for telomere shortening in childhood obesity is emerging⁴. A quantitative Polymerase Chain Reaction (qPCR) assay has been optimised to measure telomere length in DNA extracted from saliva.

Bariatric Surgery and the Genome

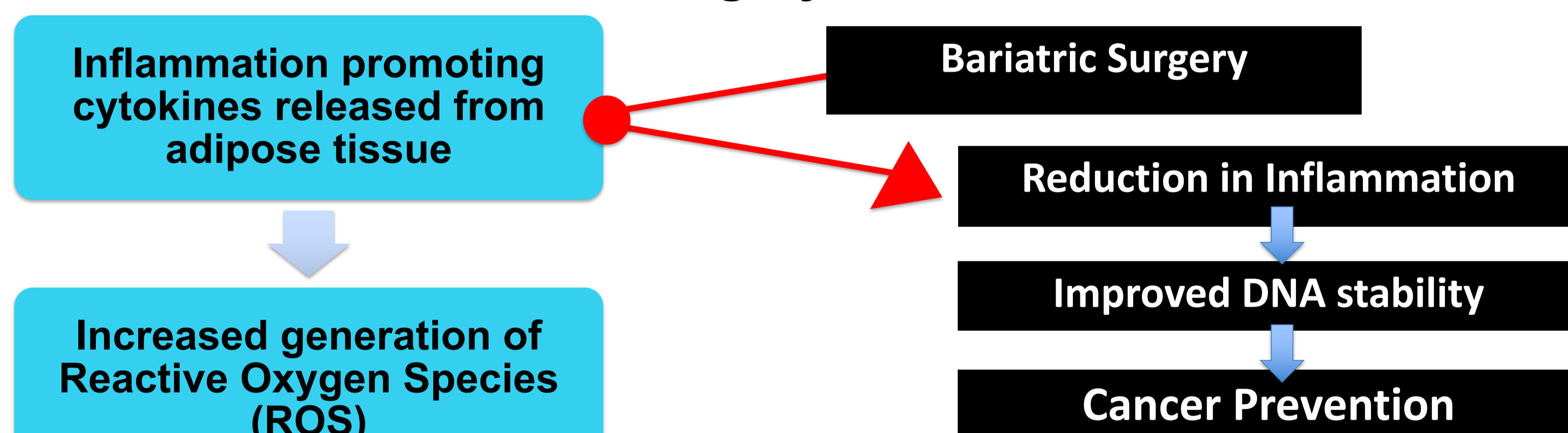


Fig 3. Proposed pathway to cancer in obesity and impact of surgical intervention

Early surgical interventions can have remarkable effects on chronic disorders such as CVD, diabetes and NAFLD in obese children⁵. This could be explained by the evidence for a reduced state of inflammation following Roux-en-Y Gastric Bypass, marked by an increase in adiponectin and decrease in IL-6⁶. A reduction in chronic inflammation may have long-term, positive implications for 'genome health'. Recently, telomere length was found to be increased 10-years following weight loss surgery in a cohort of obese adults⁷. Such findings present novel implications for weight loss surgery in the prevention of cancer associated with severe obesity. Therefore, there is a need to address the status of 'genome health' following surgical intervention in obese adolescents to uncover potential benefits or challenges.

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