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ORIGINAL RESEARCH

Mechanisms of stress, energy homeostasis, and insulin resistance in European adolescents - the HELENA study - Evidence review

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1. ABSTRACT

The HELENA study examined, in 723 adolescents from ten European cities, the relationship between fasting cortisol, certain indicators of energy balance, and the HOMA-IR index, an indirect estimate of insulin resistance calculated from fasting glycemia and insulin. In boys, higher cortisol concentrations were associated with higher insulin, glucose, and HOMA-IR; in girls, with higher leptin, insulin, and HOMA-IR, but not with higher glucose.The research contributes to the narrative of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi regarding the possible link between metabolic stress and reduced insulin sensitivity. However, it did not measure the insulin receptor or the IRS-1 and IRS-2 proteins. Independent studies indicate that excess glucocorticoids can alter insulin signaling in muscle, but such effects are tissue- and experimental model-dependent. Confirmation of the book's specific narrative is therefore primarily mechanistic and indirect.

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MISSION

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2. ANALYZED STUDY

The research question was whether the activity of the stress system, represented by fasting blood cortisol concentration, was associated with signs of impaired energy control and lower insulin sensitivity in European adolescents. The authors' hypothesis was that higher cortisol levels could be accompanied by higher values of insulin, glucose, leptin, and HOMA-IR.The reason for the citation in paragraphs 4.1 and 4.2 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi is the general link between metabolic stress, altered energy balance, and reduced insulin sensitivity. The study documents this link at an observational level: it detects associations between biomarkers measured at the same time, but it does not prove that cortisol causes insulin resistance.A clarification is important: the publication did not measure insulin receptor expression in peripheral tissues, its activity, the cellular distribution of IRS-1 and IRS-2 proteins, nor markers of chronic inflammation. Consequently, its contribution to the book's text concerns the more general segment of the chain, i.e., metabolic stress associated with lower insulin sensitivity, not the direct demonstration of molecular modifications of the receptor or IRS proteins.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The study used data from the HELENA-CSS project with a cross-sectional observational design: exposures and outcomes were measured during the same period, without follow-up. A total of 723 adolescents aged between 12.5 and 17.5 years from ten European cities were included. This information does not allow for the determination of which variable appeared first.Fasting blood samples were collected to measure cortisol, leptin, insulin, and glucose. Leptin is a hormone produced primarily by adipose tissue that signals the body's available energy reserves. The HOMA-IR, or the homeostatic model assessment for insulin resistance, was calculated using fasting insulin and glucose concentrations; it is an indirect estimate rather than a direct measure of insulin action in tissues.The authors also evaluated age, body fat percentage, and duration of exclusive breastfeeding. Analyses were conducted separately for boys and girls. Pearson correlations and hierarchical linear models were calculated, considering the city as a clustering unit and adjusting the results for age, body fat, and duration of exclusive breastfeeding. Detailed inclusion and exclusion criteria, the data collection period, absolute biomarker values, and laboratory analytical procedures are not reported in the available material, which consists only of the abstract.

4. RESULTS

In boys, higher cortisol was associated with higher insulin, higher glucose ($r = 0.315$; $p < 0.001$), and higher HOMA-IR. The r coefficient indicates the direction and strength of a linear relationship: all these values were positive, meaning that as cortisol levels increased, the indicators considered also increased on average. The strength of the association was small for insulin and HOMA-IR and more pronounced, though not high, for glucose.In girls, higher cortisol was associated with higher leptin, higher insulin, and higher HOMA-IR. No statistically significant association was observed between cortisol and glucose. In simple terms, in girls with higher cortisol, glucose was not systematically higher in the analyzed sample.According to the abstract, the observed associations remained independent of age, body fat percentage, and duration of exclusive breastfeeding after applying hierarchical models. However, the corrected coefficients of the models, the relative confidence intervals, and the P-values of the adjusted analyses are not reported in the available material.The result most relevant to the book's narrative is that higher cortisol was associated with higher HOMA-IR in both sexes. This is compatible with lower insulin sensitivity, but HOMA-IR does not identify the specific point in the insulin pathway that might be involved: it therefore does not allow the phenomenon to be attributed to the insulin receptor, IRS-1, IRS-2, or a single tissue.

5. INTERPRETATION

In plain language, the data indicate that adolescents with higher cortisol levels showed, on average, blood markers consistent with a greater difficulty for the body to maintain an efficient insulin response. This does not mean that every boy or girl with higher cortisol will develop a metabolic disease, nor that cortisol is the sole cause of the alteration.The potential

biological significance is consistent with the role of glucocorticoids, a family of hormones that includes cortisol and coordinates the stress response and energy availability. When the glucocorticoid signal is excessive or persistent, it can promote a reduced tissue response to insulin. The study analyzed, however, only observed blood concentrations and metabolic estimates; it did not evaluate the phosphorylation of the insulin receptor—that is, the initial chemical activation of the receptor—nor the quantity or localization of IRS.Regarding the book's sections, the publication therefore supports an indirect link: conditions associated with metabolic stress can be accompanied by lower insulin sensitivity. The subsequent part of the narrative, which suggests that insulin receptor activity and IRS proteins in peripheral tissues may be involved, requires specific experimental evidence. Studies on rodents, muscle cells, and adipose cells show that the effect of glucocorticoids can indeed involve these nodes of the insulin pathway, but also that the direction of the effect changes based on the cell type and the experimental condition.

6. INDEPENDENT CONFIRMING EVIDENCE

Observational confirmation in the young population comes from a study conducted on 205 overweight Latin American children and adolescents, aged between 8 and 13, who were at risk for type 2 diabetes. Higher morning cortisol was associated with lower insulin sensitivity as measured by dynamic metabolic tests, both in the cross-sectional analysis and during the observation period. This result confirms the narrative segment regarding higher cortisol and lower insulin response, using a more direct measure of insulin action than HOMA-IR. However, the sample was selected based on being overweight and ethnic origin, and therefore does not represent all adolescents [1].The molecular step involving the receptor and IRS-1 is supported by an experiment in male rats treated for five days with cortisone and compared with pair-fed controls. In skeletal muscle, cortisone increased the amount of insulin receptor by 36%, but reduced its tyrosine phosphorylation to 69% of the control and reduced the IRS-1 content by 50%. In other words, having more receptors did not mean a more efficient signal: a smaller proportion of receptors was activated by insulin. The study experimentally confirms that glucocorticoids can reduce the efficiency of the receptor-IRS signal in muscle, but it does not prove that the same occurs in healthy adolescents [2].A subsequent study strengthened the link between glucocorticoids and IRS-1 in muscle. In human and rodent muscle cell cultures, dexamethasone reduced insulin-stimulated glucose uptake, reduced IRS-1 messenger RNA and protein, and increased the inactivating phosphorylation of IRS-1 at serine 307. In mouse models, inhibition of the 11β-HSD1 enzyme, which locally increases the availability of active glucocorticoids, improved insulin sensitivity and reduced this inactivating signal. This evidence supports the possible pathway of hormonal stress alteration of IRS-1 lower insulin signaling, but it remains predominantly cellular and animal-based [3].The three publications are independent of the HELENA study and form a coherent chain: in young humans, higher cortisol can be associated with lower insulin sensitivity; in experimental models, excess glucocorticoids can reduce the efficiency of the insulin receptor and IRS-1. None of these findings, however, proves that the associations observed in the HELENA sample depended specifically on a change in the receptor or the cellular distribution of IRS.

7. CONFLICTING EVIDENCE

Directly relevant evidence shows that the effect of glucocorticoids is not uniform. In primary human preadipocytes, which are precursor cells to fat cells, pretreatment with glucocorticoids increased the expression of the insulin receptor, IRS-1, and IRS-2, and increased the activation of AKT, a protein that transmits the insulin signal within the cell. In this specific model, therefore, glucocorticoids increased rather than reduced insulin sensitivity, preparing the cells for adipose differentiation [4].This conflicting result does not invalidate the observations regarding muscle or metabolic markers in adolescents. However, it indicates that it is incorrect to describe glucocorticoids as invariable inhibitors of the insulin receptor or IRS. Cell type, duration of exposure, hormone concentration, the cell's differentiation state, and the metabolic context can all modify the response. No further directly conflicting evidence of sufficient relevance has been identified in the general adolescent population; this does not prove the absence of contrary findings.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the observational study under review from independent research that confirms or defines the individual steps of the narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cross-sectional observational	723 European adolescents, 12.5-17.5 years	Higher cortisol associated with higher HOMA-IR; differences between boys and girls	biologically consistent evidence	moderate
[1]	Longitudinal and cross-sectional observational	205 overweight Latin American children and adolescents, 8-13 years	Higher morning cortisol associated with lower insulin sensitivity	direct confirmation	moderate
[2]	Experimental animal	Male Sprague-Dawley rats, skeletal muscle	Cortisone reduces insulin receptor phosphorylation and IRS-1 content	indirect confirmation	moderate
[3]	Cellular and animal	Human and rodent myotubes, muscle and murine models	Glucocorticoids reduce IRS-1 and insulin-stimulated glucose utilization	indirect confirmation	moderate
[4]	Cellular	Primary human preadipocytes	Glucocorticoids increase insulin receptor, IRS-1, and insulin sensitivity in the model	discordant evidence	preliminary

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The HELENA study shows that, in European adolescents, higher cortisol concentrations were associated with indicators of lower insulin sensitivity, with differences between boys and girls. This result is consistent with the general section of the book regarding metabolic stress and the insulin response.However, the publication does not demonstrate that the insulin receptor is less expressed or less active, nor that IRS proteins are redistributed in the cells of adolescents. Independent evidence makes a link between glucocorticoids and alterations in receptor-IRS signaling plausible, especially in muscle, but this link is tissue-dependent and requires direct validation in young humans. The narrative is therefore supported at an observational and mechanistic level, without a complete causal demonstration.

Aggiornato al 17/11/2026. Questo contenuto riflette una sintesi divulgativa delle evidenze scientifiche al momento della pubblicazione e non sostituisce il parere medico.

10. TRANSPARENCY AND SCIENTIFIC RESPONSIBILITY

Artificial Intelligence was used solely as a tool for editorial and documentary support. All content, interpretations, bibliographic citations and conclusions have been verified, reviewed and approved by the author, who assumes full scientific responsibility for them.

The manuscript was also subjected to independent peer review prior to publication.

To ensure the greatest transparency, the complete history of the article, including the dates of submission, revision, acceptance and publication, as well as information on the peer review process, is available on the dedicated Article History page.

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