The present study has several methodological strengths; the evaluation of a large prospective cohort enrolled from the Japanese general population and the exclusion of persons with known cardiovascular or cancer disease at baseline reduce potential for recall bias and bias from dietary changes due to known diseases. Also, the results from a cohort of community residents are more relevant to generalizability than those of occupational employees, hospital-based patients, or volunteers. Close follow-up, comprehensive review of potential events, and centralized judgment reduced the potential for missed or misclassified outcomes.

The mean intake of TDF in our study was 10–11 g/d for both sexes, although this figure may have been underestimated by as much as 40% according to our validation study (19). Thus, the actual mean fiber intake was probably ~15 g/d, which is compatible with data from the Japan National Nutrition Survey (11), yet this figure is much lower than that for Western countries (7–9,23–33). The low dietary fiber content of refined rice, frequently consumed by Japanese, may have resulted in the low intake of fiber compared with Western populations. Sources of dietary fiber differ from one population to another. The major sources of dietary fiber for the participants in this study were miso soup (18%), rice (14%), fruits other than citrus fruit (9%), and green leafy vegetables (7%). In most Western countries, the sources are mainly whole grains, cereals, vegetables, and fruit (3–9,22,23); e.g., sources of fiber reported in the Zutphen Study were bread and other cereal products (29–34%), vegetables (20–28%), and fruits (15–23%) (34), and that of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study was rye bread (33).

Limitations of this study include the lack of multiple measurements of dietary variables. During the long follow-up period, both the participants' diet and food composition may have changed, so multiple evaluations of diet over time are important to reduce measurement errors and to better assess the temporal relationship between dietary fiber intake and mortality from CVD. Moreover, the ratios of mean intakes estimated by the FFQ to those calculated from the DR were 0.60, 0.58, and 0.51 for TDF, IDF, and SDF, respectively, which is probably due to the limited number of foods in the FFQ. However, the rank correlations for fiber intake between the FFQ and DR were fairly good: 0.46 for TDF, 0.47 for IDF, and 0.42 for SDF, which supports the validity of our FFQ. Lastly, the apparent protective effect of fiber on risk of CHD may be due to other health-related habits, such as regular exercise, no smoking, and a high fish intake by persons who consume greater amounts of dietary fiber. Although we made adjustments for all of these potential confounders, some confounding and other unexamined health habits may remain unaccounted for.

In conclusion, our results constitute supporting evidence that higher intake of both insoluble and soluble fiber, especially fruit and cereal fibers may contribute to the prevention of CHD in Japanese men and women.


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REGULAR ARTICLE

# History of blood transfusion before 1990 is associated with increased risk for cancer mortality independently of liver disease: a prospective long-term follow-up study

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**Abstract**
*Objectives* The aim of this work is to investigate the association between transfusion history and cancer mortality in a prospective follow-up study.
*Methods* We conducted a prospective cohort study in four areas of Akita Prefecture, Japan, in 10,451 individuals (4,401 men and 6,050 women, aged 40–79 years) without history of cancer. The subjects were followed until 31 December 2003 and the number of deaths from cancer was recorded.
*Results* After mean follow-up of 12.76 years (140,259 person–years), 520 individuals (333 men and 187 women) died of cancer. History of blood transfusion before 1990 was mildly but significantly associated with overall cancer mortality (hazard ratio = 1.75, 95% confidence interval: 1.32–2.18) and nonliver cancer mortality (HR = 1.68, 95% CI: 1.25–2.26). This significant association remained unchanged after excluding deaths that occurred within 5 years of baseline for overall cancer mortality (HR = 1.47, 95% CI: 1.04–2.09) and for nonliver cancer mortality (HR = 1.43, 95% CI: 1.00–2.04). The significant association for nonliver cancer mortality was confirmed in subjects with no smoking history and/or alcohol consumption (HR = 2.01, 95% CI: 1.35–3.00). Site-specific analysis showed a possible association between transfusion history and death from pancreatic cancer.
*Conclusions* History of blood transfusion before 1990 was found to be associated with increased risk for cancer mortality and was independent of liver diseases. The mechanism of the association between blood transfusion and cancer mortality warrants further research.

**Keywords** Cancer · Cohort studies · Residence characteristics · Blood transfusion

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## Introduction

Although allogeneic blood transfusion is an established mode of therapy, it has several recognized risks. In this study, we aimed to test the hypothesis of a long-term biological influence of past transfusion on overall cancer mortality. Although many epidemiological studies have suggested that allogeneic blood transfusion is associated with increased risk for postoperative cancer recurrence [1–12], few studies have investigated the association between transfusion history and cancer mortality. One preliminary study has suggested that past transfusion might increase the risk for overall cancer mortality [13]. Therefore, further studies are needed to confirm this association, with adjustment for related lifestyle factors or past medical histories that might confound the association between cancer mortality and transfusion history.

We conducted a 14-year follow-up cohort study of middle-aged and elderly general population in Japan using self-report questionnaires on transfusion history and other factors that might confound analysis of the association between transfusion history and cancer mortality.

## Materials and methods

### Study cohort

The cohort was established in four areas (areas A–D) in Akita Prefecture as part of the Japan Collaborative Cohort Study for evaluation of Cancer Risk (JACC study), which was ongoing for 14 years (from 1990 to 2003); the details of the study have been described in more detail elsewhere [14, 15]. In brief, a total of 11,631 individuals (4,865 men and 6,766 women, aged 40–79 years) in the four areas participated in municipal health screening examinations between 1988 and 1991, which were conducted in accordance with Japan's law on health services for elderly people. All of the participants completed a self-administered questionnaire. The cohort study was set up in accordance with the ethical standards of the Helsinki Declaration, and the protocol and the data usage for this research was approved by the Research Ethics Committee of Kyoto University.

### Follow-up

Date and cause of death were confirmed biannually, with the permission of the Director-General of the Prime Minister's Office (Ministry of Public Management, Home Affairs, Post, and Telecommunications). The date of moving away from the study area was also annually verified by the investigator in each area by reviewing the population register sheets of the cohort members. The time of follow-up for each subject was calculated from the day of enrollment in the study to the day of death from cancer or any other cause, the time of moving away from the study area or the end of 2003, whichever occurred first. By the end of 2003, 14.2% (944 men and 621 women) of the participants had died and 3.4% (131 men and 241 women) were lost to follow-up because they had moved away from the study areas.

### Questionnaire

At baseline, all participants completed self-administered questionnaires containing the following items: sex, age, birth date, medical history (transfusion, liver diseases, external injury that required hospitalization, and abdominal surgery), smoking status, alcohol consumption, and history of pregnancy. Medical histories and history of pregnancy were inquired about, using a yes/no question regarding whether the participant had a particular medical or pregnancy history. For example, for transfusion history, participants were asked, "Have you ever been treated with blood transfusion by the time of this survey?" For alcohol consumption, individuals chose their status from three categories: those who had never consumed alcohol, current drinkers or ex-drinkers. For smoking status, individuals chose from three categories: those who had never smoked, current smokers or ex-smokers. Those with unmarked or missing data in the questionnaire were not used in the analyses.

### Data retrieval and analysis

We restricted the present analysis to include only those participants who provided information about their age, sex, and transfusion history, and who did not have history of cancer. Of the 11,631 participants, those with history of cancer ($n = 638$) and those with missing questionnaire data about their age, sex or transfusion history ($n = 759$) were not used in this analysis. A total of 1,180 individuals were excluded, and our final dataset comprised data from 10,451 individuals (4,401 men and 6,050 women, aged 40–79 years). For deceased subjects, cause of death was recorded from death certificates and coded according to the International Classification of Diseases and Related Health Problems (ICD) tenth revision for deaths occurred after 1995, or the ninth version for deaths that occurred between baseline and 1994; the latter were then recoded according to the tenth revision. Deaths due to malignant neoplasms were coded as 140–208 according to the ICD ninth revision (for deaths between baseline and 1994) and as C00-C97 according to the tenth revision (for deaths after 1995).

### Statistical analysis

The Cox proportional-hazards model was used to calculate the age-adjusted and multivariate hazard ratio (HR) of history of blood transfusion for cancer mortality, along with the 95% confidence interval (CI). The risk of cancer mortality in patients with liver disease was also estimated. All calculations were performed using SAS version 8.2 software (SAS Inc., Cary, NC, USA). Differences at $P < 0.05$ were considered statistically significant.

The multivariate HR of transfusion history for cancer mortality was estimated after adjusting for baseline age, sex, and typical risk factors of total cancer mortality (smoking status and alcohol consumption), and history of external injury, abdominal surgery, liver disease, and pregnancy, which were factors related to transfusion, or factors showing a significant association in age-adjusted univariate analysis.

## Results

During average follow-up of 12.76 years (140,259 person–years), a total of 520 individuals (333 men and 187 women)

died of cancer: 26 (15 men and 11 women) from liver cancer and 494 (318 men and 176 women) from nonliver cancer. Baseline characteristics are presented in Table 1. The prevalence of external injury (41.0%), abdominal surgery (73.7%), and liver disease (8.2%) among subjects with history of blood transfusion was more than twice that of those without history of transfusion (17.6%, 29.6%, and 2.9%, respectively) ($P < 0.001$, $\chi^2$ test). On the other hand, there was no significant difference in smoking status or alcohol intake between those with and those without history of blood transfusion.

**Table 1** Demographic and clinical data of the study cohort

| | History of transfusion | |
|---|---|---|
| | Yes ($n$ = 972) | No ($n$ = 9,479) |
| Age | | |
| Mean (SD), years | 56.7 (9.5) | 58.1 (9.3) |
| | $n$ (%) | $n$ (%) |
| Area | | |
| A | 221 (22.7) | 1,826 (19.3) |
| B | 247 (25.4) | 1,834 (19.3) |
| C | 202 (20.8) | 2,827 (29.8) |
| D | 302 (31.1) | 2,992 (31.6) |
| Number | | |
| Men | 352 (36.2) | 4,049 (42.7) |
| Women | 620 (63.8) | 5,430 (57.3) |
| Smoking status | | |
| Never | 555 (57.1) | 5,433 (57.3) |
| Smoker | 183 (18.8) | 2,086 (22.0) |
| Ex-smoker | 103 (10.6) | 726 (7.7) |
| Unknown | 131 (13.5) | 1,234 (13.0) |
| Alcohol intake | | |
| Never | 433 (44.5) | 4,246 (44.8) |
| Drinker | 396 (40.7) | 4,278 (45.1) |
| Ex-drinker | 64 (6.6) | 287 (3.0) |
| Unknown | 79 (8.1) | 667 (7.0) |
| History of external injury | | |
| Yes | 399 (41.0) | 1,673 (17.7) |
| No | 495 (50.9) | 7,497 (79.1) |
| Unknown | 78 (8.0) | 308 (3.2) |
| History of abdominal surgery | | |
| Yes | 716 (73.7) | 2,805 (29.6) |
| No | 229 (23.6) | 6,588 (69.5) |
| Unknown | 27 (2.8) | 85 (0.9) |
| History of liver disease | | |
| Yes | 80 (8.2) | 272 (2.9) |
| No | 821 (84.5) | 8,777 (92.6) |
| Unknown | 71 (7.3) | 429 (4.5) |
| History of pregnancy[a] | | |
| Yes | 565 (98.8) | 5,055 (99.3) |
| No | 7 (1.2) | 37 (0.7) |

People with history of cancer before participation in the cohort were excluded from this analysis

*SD* standard derivation

[a] Females only

Table 2 shows the age-adjusted HRs for cancer mortality for the sex-specific and sex-stratified analyses. Generally, history of blood transfusion was significantly associated with increased risk of cancer death, regardless of whether death was associated with liver cancer or nonliver cancer. Smoking status was also significantly associated with increased risk of cancer death. Current smoking and ex-smoking statuses were, respectively, associated with cancer mortality, for overall cancer and nonliver cancer. History of liver disease was significantly associated with increased risk for liver cancer mortality, although this association was not confirmed for mortality due to other cancers. In women, ex-drinking habit and history of external injury were also significantly associated with increased risk of cancer mortality. History of abdominal surgery and pregnancy were not significantly associated with cancer mortality.

On multivariate analysis, the significant association between cancer mortality and history of transfusion remained unchanged (Table 3). We also tested this association after excluding deaths in the first 5 years (totally 511 cases were excluded, including 120 cancer deaths), because such deaths might have resulted from unidentified factors that engendered a spurious association between transfusion and cancer mortality risk. Even after excluding deaths in the first 5 years, the significant association remained unchanged; the HR (95% CI) was 1.47 (1.04–2.09) for overall cancer mortality and 1.43 (1.00–2.04) for nonliver cancer mortality. Furthermore, we confirmed the significant associations between history of transfusion and risk for cancer mortality in subjects with no history of smoking and/or drinking; the HR (95% CI) was 2.04 (1.39–3.00) for overall cancer mortality and 2.01 (1.35–3.00) for nonliver cancer mortality.

Based on the site-specific analysis, we found a significant association between transfusion history and mortality due to cancer in the stomach, liver, and pancreas. After excluding deaths in the first 5 years, there remained significant associations for cancer in liver (HR = 1.75, 95% CI: 1.32–2.33) and pancreas (3.20, 1.02–10.07).

## Discussion

We found that history of blood transfusion before 1990 was mildly but significantly associated with elevated cancer mortality risk among middle-aged and elderly general

**Table 2** Age-adjusted analysis for factors associated with cancer mortality: all cancers, nonliver cancers, and liver cancers

| | Men | | | Women | | | All | |
|---|---|---|---|---|---|---|---|---|
| | *n* | HR (95% CI) | *P* value | *n* | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Cancer (all) | | | | | | | | |
| Smoking status | | | | | | | | |
| Never | 61 | 1.00 | | 147 | 1.00 | | 1.00 | |
| Smoker | 194 | 2.01 (1.51–2.69) | <0.0001 | 8 | 1.75 (0.86–3.57) | 0.12 | 1.97 (1.51–2.57) | <0.0001 |
| Ex-smoker | 71 | 1.43 (1.09–1.89) | 0.0107 | 2 | 1.61 (0.33–7.74) | 0.55 | 1.44 (1.10–1.89) | 0.0089 |
| Alcohol intake | | | | | | | | |
| Never | 59 | 1.00 | | 124 | 1.00 | | 1.00 | |
| Drinker | 243 | 0.77 (0.52–1.13) | 0.18 | 49 | 0.60 (0.28–1.26) | 0.18 | 0.74 (0.53–1.05) | 0.0888 |
| Ex-drinker | 29 | 1.16 (0.75–1.82) | 0.51 | 8 | 2.23 (1.09–4.56) | 0.0279 | 1.36 (0.92–2.02) | 0.12 |
| History of external injury | | | | | | | | |
| No | 256 | 1.00 | | 140 | 1.00 | | 1.00 | |
| Yes | 72 | 0.87 (0.67–1.13) | 0.3 | 49 | 1.42 (1.02–1.96) | 0.0369 | 1.04 (0.85–1.27) | 0.72 |
| History of abdominal surgery | | | | | | | | |
| No | 250 | 1.00 | | 113 | 1.00 | | 1.00 | |
| Yes | 90 | 1.08 (0.85–1.37) | 0.55 | 82 | 1.09 (0.82–1.45) | 0.55 | 1.08 (0.90–1.30) | 0.41 |
| History of liver disease | | | | | | | | |
| No | 308 | 1.00 | | 177 | 1.00 | | 1.00 | |
| Yes | 17 | 1.28 (0.79–2.09) | 0.32 | 8 | 1.47 (0.72–2.99) | 0.29 | 1.34 (0.89–2.00) | 0.16 |
| History of blood transfusion | | | | | | | | |
| No | 296 | 1.00 | | 153 | 1.00 | | 1.00 | |
| Yes | 37 | 1.33 (0.94–1.87) | 0.11 | 34 | 1.91 (1.32–2.77) | 0.0007 | 1.55 (1.20–1.99) | 0.0006 |
| History of pregnancy | | | | | | | | |
| No | | | | 5 | 1.00 | | | |
| Yes | | | | 169 | 0.42 (0.17–1.02) | 0.0562 | | |
| Cancer (nonliver) | | | | | | | | |
| Smoking status | | | | | | | | |
| Never | 58 | 1.00 | | 137 | 1.00 | | 1.00 | |
| Smoker | 185 | 2.02 (1.50–2.71) | <0.0001 | 8 | 1.88 (0.92–3.84) | 0.0827 | 2.00 (1.52–2.62) | <0.0001 |
| Ex-smoker | 68 | 1.44 (1.08–1.91) | 0.0116 | 2 | 1.61 (0.33–7.74) | 0.55 | 1.44 (1.09–1.90) | 0.0096 |
| Alcohol intake | | | | | | | | |
| Never | 58 | 1.00 | | 116 | 1.00 | | 1.00 | |
| Drinker | 233 | 0.86 (0.56–1.30) | 0.46 | 48 | 0.67 (0.30–1.48) | 0.32 | 0.83 (0.57–1.20) | 0.31 |
| Ex-drinker | 25 | 1.02 (0.64–1.63) | 0.95 | 7 | 2.09 (0.98–4.49) | 0.0575 | 1.21 (0.80–1.82) | 0.37 |
| History of external injury | | | | | | | | |
| No | 249 | 1.00 | | 133 | 1.00 | | 1.00 | |
| Yes | 64 | 0.80 (0.60–1.05) | 0.1 | 45 | 1.37 (0.97–1.92) | 0.0711 | 0.97 (0.78–1.20) | 0.77 |
| History of abdominal surgery | | | | | | | | |
| No | 239 | 1.00 | | 108 | 1.00 | | 1.00 | |
| Yes | 86 | 1.08 (0.84–1.38) | 0.56 | 74 | 1.03 (0.77–1.39) | 0.85 | 1.06 (0.87–1.28) | 0.57 |
| History of liver disease | | | | | | | | |
| No | 297 | 1.00 | | 168 | 1.00 | | 1.00 | |
| Yes | 13 | 1.02 (0.58–1.77) | 0.96 | 6 | 1.16 (0.52–2.63) | 0.72 | 1.06 (0.67–1.68) | 0.81 |
| History of blood transfusion | | | | | | | | |
| No | 286 | 1.00 | | 144 | 1.00 | | 1.00 | |
| Yes | 32 | 1.19 (0.82–1.71) | 0.36 | 32 | 1.91 (1.30–2.80) | 0.0009 | 1.46 (1.12–1.90) | 0.005 |

**Table 2** continued

| | Men | | | Women | | | All | |
|---|---|---|---|---|---|---|---|---|
| | *n* | HR (95% CI) | *P* value | *n* | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| History of pregnancy | | | | | | | | |
| No | | | | 4 | 1.00 | | | |
| Yes | | | | 159 | 0.49 (0.18–1.33) | 0.1615 | | |
| Cancer (liver) | | | | | | | | |
| History of liver disease | | | | | | | | |
| No | 11 | 1.00 | | 9 | 1.00 | | 1.00 | |
| Yes | 4 | 8.27 (2.63–26.05) | 0.0003 | 2 | 7.21 (1.55–33.51) | 0.0117 | 7.93 (3.18–19.81) | <0.0001 |
| History of blood transfusion | | | | | | | | |
| No | 10 | 1.00 | | 9 | 1.00 | | 1.00 | |
| Yes | 5 | 5.41 (1.84–15.88) | 0.0021 | 2 | 1.88 (0.41–8.70) | 0.42 | 3.56 (1.49–8.50) | 0.0042 |

People with history of cancer before participation in the cohort were excluded from this analysis

*HR* hazard ratio, *CI* confidence interval

population in Japan who had no history of cancer. These significant associations were maintained even after excluding deaths in the first 5 years, and in subjects who reported no history of smoking and/or drinking.

Site-specific analysis showed a significant association between transfusion history and death from pancreatic cancer. Pancreatic cancer has an extremely low survival rate [16] and is the fifth leading cause of cancer death in Japan [17]. Its incidence and mortality have increased markedly over the past four decades in Japan [18]. Nevertheless, few epidemiological studies have been conducted to identify the environmental/genetic risk factors that contribute to the development of pancreatic cancer, and its etiology remains unclear. Consistent evidence of an association with pancreatic cancer mortality has so far been limited to cigarette smoking [19]. The association between transfusion history and pancreatic cancer in this study needs to be assessed in future studies containing a larger number of cases.

Although this investigation had some limitations, as described below, two main possibilities should be considered if we assume that transfusion history per se leads to an increase in cancer mortality. First, the oncogenic potential of infectious agents transmitted by transfusion is possible. For example, transfusion-transmitted hepatitis virus infection may carry an increased risk for developing a wide range of tumors [20, 21]. Second, the white blood cells and platelets in allogeneic blood transfusion have been suggested to cause transfusion-related immunomodulation (TRIM) [22, 23]. In Japan, until 1988, blood transfusion was performed without filtration or irradiation of white blood cells, or screening for bacterial or viral infections. Whole blood or packed red blood cells were used after matching the allogeneic antigens [24].

In terms of the oncogenic potential of infectious agents, previous studies have suggested that hepatitis C virus (HCV) might have an oncogenic role in a wide range of cancers [21]. Therefore, an association between history of liver disease and cancer mortality might be an important indicator of whether infectious agents are responsible for the significant association between transfusion history and cancer mortality, because blood transfusion is an important transmission route for HCV in Japan [25, 26]. We found that history of liver disease was associated with history of transfusion, and was significantly associated with increased risk for liver cancer mortality. On the other hand, overall cancer and nonliver cancer mortality were not significantly associated with history of liver disease, but were associated with history of transfusion. This suggests that the increased risk for overall cancer mortality was associated with phenomena induced by pathogens other than infectious agents, which occurs in liver disease.

In terms of the second possibility, TRIM might be directly or indirectly associated with the incidence or promotion of fatal cancer. Clinical and experimental results have shown that allogeneic blood transfusion leads to immunomodulation in the recipient [27–29]. There is epidemiological evidence that TRIM facilitates the recurrence of malignancy or the occurrence of postoperative infections [30–32], although an association with fatal cancer occurrence has not been demonstrated. This condition might be similar to the phenomenon that high-dose immunosuppressive regimens, such as cyclosporine, in transplant recipients lead to a higher frequency of cancer mortality [33]. Therefore, further evidence of the immunosuppressive effect of transfusion on cancer mortality is needed in other populations.

The present study has several limitations. We could not determine the incidence of diseases or other events that

**Table 3** Multivariate analyses for the association between history of transfusion or liver disease and cancer mortality: cancer (specific site), all cancer, and nonliver cancer

| | History of transfusion | | | History of liver disease | | |
|---|---|---|---|---|---|---|
| | *n* | Adjusted HR (95% CI) | *P* value | *n* | Adjusted HR (95% CI) | *P* value |
| Cancer (all) | | | | | | |
| All | 71 | 1.75 (1.32–2.33) | 0.0001 | 25 | 1.26 (0.83–1.91) | 0.27 |
| Men | 37 | 1.47 (1.00–2.18) | 0.0522 | 17 | 1.26 (0.76–2.09) | 0.38 |
| Women | 34 | 2.18 (1.39–3.43) | 0.0007 | 8 | 1.39 (0.67–2.84) | 0.37 |
| Cancer (nonliver) | | | | | | |
| All | 64 | 1.68 (1.25–2.26) | 0.0007 | 19 | 1.00 (0.62–1.61) | 0.99 |
| Men | 32 | 1.33 (0.87–2.02) | 0.18 | 13 | 1.01 (0.56–1.81) | 0.98 |
| Women | 32 | 2.20 (1.38–3.51) | 0.0009 | 6 | 1.08 (0.47–2.45) | 0.86 |
| Cancer (specific site) | | | | | | |
| Lung | | | | | | |
| All | 12 | 1.54 (0.78–3.06) | 0.22 | 4 | 1.06 (0.39–2.91) | 0.91 |
| Men | 7 | 1.12 (0.46–2.75) | 0.8 | 3 | 1.09 (0.34–3.50) | 0.88 |
| Women | 5 | 2.87 (0.90–9.14) | 0.07 | 1 | 1.31 (0.17–10.18) | 0.79 |
| Stomach | | | | | | |
| All | 13 | 1.99 (1.01–3.91) | 0.0462 | 4 | 1.17 (0.42–3.23) | 0.76 |
| Men | 7 | 1.35 (0.55–3.34) | 0.51 | 3 | 0.78 (0.19–3.22) | 0.73 |
| Women | 6 | 3.24 (0.91–11.52) | 0.0698 | 1 | 2.32 (0.53–10.11) | 0.26 |
| Colorectum | | | | | | |
| All | 6 | 1.27 (0.46–3.46) | 0.65 | 1 | 0.68 (0.09–5.02) | 0.71 |
| Men | 1 | n/a | n/a | 1 | 2.40 (0.31–18.60) | 0.4 |
| Women | 5 | 1.25 (0.34–4.59) | 0.7334 | 0 | n/a | n/a |
| Liver | | | | | | |
| All | 7 | 3.07 (1.14–8.31) | 0.0269 | 6 | 6.57 (2.51–17.23) | 0.0001 |
| Men | 5 | 3.94 (1.19–13.08) | 0.025 | 4 | 5.45 (1.65–17.93) | 0.0053 |
| Women | 2 | 2.15 (0.35–11.89) | 0.4259 | 2 | 9.04 (1.80–45.40) | 0.0075 |
| Pancreas | | | | | | |
| All | 7 | 3.34 (1.28–8.72) | 0.014 | 0 | n/a | n/a |
| Men | 4 | 4.10 (1.12–14.98) | 0.0328 | 0 | n/a | n/a |
| Women | 3 | 2.57 (0.63–10.60) | 0.1905 | 0 | n/a | n/a |
| Other | | | | | | |
| All | 26 | 1.47 (0.89–2.42) | 0.13 | 9 | 1.26 (0.61–2.59) | 0.53 |
| Men | 13 | 1.32 (0.67–2.57) | 0.42 | 6 | 1.12 (0.45–2.77) | 0.81 |
| Women | 13 | 1.70 (0.80–3.61) | 0.16 | 3 | 1.58 (0.49–5.13) | 0.45 |

Adjusted HR for cancer mortality was estimated after adjustment for age, sex, and typical risk factors for overall cancer mortality [smoking status (never smokers, current smokers or ex-smokers) and alcohol consumption (never drinkers, current drinkers or ex–drinkers)], history of pregnancy (yes or no), and other factors that may have been related to transfusion or that showed a significant association in the age-adjusted univariate analysis (history of external injury, abdominal surgery, and liver disease). People with history of cancer before participation in the cohort were excluded from this analysis. Each specific site of cancer was defined from ICD, tenth revision, as lung (C34), stomach (C16), colorectum (C18), liver (C22), pancreas (C25)

*n/a* not applicable

might have been related to cancer mortality following entry to the study, and therefore it is possible that unrecognized confounding factors might be related to the association between history of transfusion and cancer mortality.

Another limitation is that this survey collected self-reported transfusion history, which may have reduced the objectivity of the study. It is also possible that some cancer deaths were not recorded in the cohort, specifically those who left their original communities to undergo long-term hospitalization. These factors may have hindered accurate calculation of the association between transfusion history and cancer mortality. On the other hand, we could not use background information on the transfusion procedure. Therefore, the possibility of biased selection of persons

receiving blood transfusions cannot be ignored. Finally, because this study contained relatively small numbers of cancer mortality for each site, it is possible that statistical errors may have had an adverse influence on the results.

In this study, we found that history of blood transfusion prior to 1990 in middle-aged and elderly general population in Japan was mildly but significantly associated with cancer mortality, in terms of overall cancer and nonliver cancer. The strength of our study was that we tested and confirmed the association between transfusion history and overall or site-specific cancer mortality, by conducting a long-term follow-up cohort study. In addition, the significant association remained even after adjusting for known major cancer mortality factors such as alcohol intake and smoking, and after excluding early deaths, which might have been related to unidentified factors that may engender a spurious association between transfusion history and cancer mortality, and our results showed that this association seemed to be independent from the oncogenic action induced by infectious agents from transfusion. Since 1990, the system and procedures used for transfusion in Japan have evolved dramatically; therefore, we need to evaluate whether current regimens have reduced the risk for major disease such as cancer.

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# Insulin Resistance in Children: Consensus, Perspective, and Future Directions

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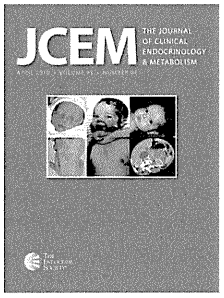



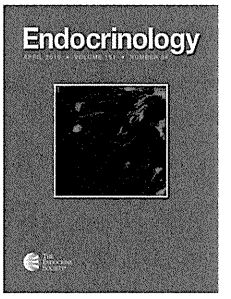


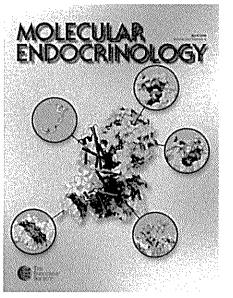


THE ENDOCRINE SOCIETY®

# Insulin Resistance in Children: Consensus, Perspective, and Future Directions

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**Objective:** Emerging data indicate that insulin resistance is common among children and adolescents and is related to cardiometabolic risk, therefore requiring consideration early in life. However, there is still confusion on how to define insulin resistance, how to measure it, what its risk factors are, and whether there are effective strategies to prevent and treat it. A consensus conference was organized in order to clarify these points.

**Participants:** The consensus was internationally supported by all the major scientific societies in pediatric endocrinology and 37 participants.

**Evidence:** An independent and systematic search of the literature was conducted to identify key articles relating to insulin resistance in children.

**Consensus Process:** The conference was divided into five themes and working groups: background and definition; methods of measurement and screening; risk factors and consequences; prevention; and treatment. Each group selected key issues, searched the literature, and developed a draft document. During a 3-d meeting, these papers were debated and finalized by each group before presenting them to the full forum for further discussion and agreement.

**Conclusions:** Given the current childhood obesity epidemic, insulin resistance in children is an important issue confronting health care professionals. There are no clear criteria to define insulin resistance in children, and surrogate markers such as fasting insulin are poor measures of insulin sensitivity. Based on current screening criteria and methodology, there is no justification for screening children for insulin resistance. Lifestyle interventions including diet and exercise can improve insulin sensitivity, whereas drugs should be implemented only in selected cases. ***J Clin Endocrinol Metab* 95: 5189–5198, 2010)**

Insulin resistance in adults has been recognized for decades as a cardinal feature in the development of type 2 diabetes (T2D) and has been associated with obesity, the metabolic syndrome, hypertension, and heart disease (1). It is also clear that insulin resistance is significantly related to obesity and cardiometabolic risk in children (2). However, there is a lack of clarity as to how insulin resistance in childhood is best assessed, in what clinical disorders it occurs, and whether it can be treated or prevented.

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Abbreviations: DM, Diabetes mellitus; FSIVGTT, frequently sampled iv glucose tolerance test; GDM, gestational DM; HOMA, homeostasis model assessment; IGT, impaired glucose tolerance; LOE, level of evidence; NAFLD, nonalcoholic fatty liver disease; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; SSPP, steady-state plasma glucose; T2D, type 2 diabetes.

To address the current state of the art related to insulin resistance in children, the European Society for Pediatric Endocrinology (ESPE), the Lawson Wilkins Pediatric Endocrine Society (LWPES), the International Society for Pediatric and Adolescent Diabetes (ISPAD), the Asia Pacific Pediatric Endocrine Society (APPES), the Australasia Pediatric Endocrine Society (APEG), the Sociedad Latino-Americana de Endocrinologia Pediatrica (SLEP), and the Japanese Society for Pediatric Endocrinology (JSPE) convened a panel of experts for a consensus conference on childhood insulin resistance.

## Methods

The conference used an evidence-based approach. An independent and systematic search of the literature was conducted through EMBASE and PubMed based on MeSH terms. Grading of the evidence was based on previously published American Diabetes Association standards (3). See Supplemental Data, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org.

## Definition and Background

### 1. Insulin resistance refers to reduced whole body glucose uptake [level of evidence (LOE) A; mostly in adults]

Insulin resistance is defined as the decreased tissue response to insulin-mediated cellular actions and is the inverse of insulin sensitivity. The term "insulin resistance," as generally applied, refers to whole-body reduced glucose uptake in response to physiological insulin levels and its consequent effects on glucose and insulin metabolism. Euglycemic hyperinsulinemic clamp studies have shown that insulin resistance is determined primarily by the response of skeletal muscle, with over 75% of infused glucose taken up by muscle and only 2–3% by adipose tissue (4).

### 2. Insulin resistance is a continuum (LOE A in adults)

Insulin sensitivity is a continuum from very low levels in individuals with high insulin resistance to very high levels in individuals without insulin resistance.

### 3. Insulin resistance is commonly associated with obesity (LOE A in adults and children)

Insulin resistance is most commonly associated with obesity, although not all obese people are insulin resistant and insulin resistance may occur in nonobese children and adults (5–7). Insulin resistance can also occur during normal physiological conditions, such as pregnancy or puberty (8).

### 4. One of the consequences of insulin resistance is chronic compensatory hyperinsulinemia (LOE A in adults, B in children)

Although the primary interest has been in insulin resistance, the adverse effects related to insulin resistance are more likely mediated via compensatory hyperinsulinemia (9). Despite the hyperinsulinemic response to insulin resistance, the current LOE does not support development of a definition of insulin resistance based on fasting insulin.

### 5. Standards for insulin resistance in children, with definitions for normal and abnormal levels, are nonexistent (LOE C in children)

Standards for insulin resistance in children have not been established. This is due, in part, to the use of a variety of techniques to measure insulin sensitivity, lack of sufficient cohort sizes to establish normative distributions for insulin sensitivity, and lack of adequate longitudinal studies to relate definitions for insulin resistance to long-term outcomes. Clinical features, such as acanthosis nigricans, can point to the likelihood of insulin resistance but cannot define it. Fasting insulin is not an optimal tool for individual assessment of peripheral insulin sensitivity, but it may provide information regarding compensatory hyperinsulinemia and liver insulin metabolism. Depending on the study population, fasting insulin is not always well correlated with insulin resistance in children (10), and differences exist between the heritability of fasting insulin and insulin resistance (11). Many studies have used fasting insulin alone or in combination with fasting glucose as surrogates for insulin resistance, but these are poor substitutes for the direct measures, thus limiting their precision. Fasting insulin as an index of insulin resistance may be applicable in epidemiological studies using large populations of children and/or well-defined cohorts.

## Methods of Measurement

### 6. The euglycemic hyperinsulinemic clamp is the "gold standard" for measuring insulin sensitivity; the frequently sampled iv glucose tolerance test (FSIVGTT) and steady-state plasma glucose (SSPG) methods are also valid measurements (LOE A in adults, C in children)

The hyperinsulinemic euglycemic clamp, the FSIVGTT with modeling, and the SSPG are generally accepted as valid and reliable for measurement of insulin sensitivity. However, each of these methods is time consuming, requires iv infusions and frequent blood sampling, is bur-

densome for participants, is costly, and requires a research setting.

Less intensive methods, such as measurement of insulin during the oral glucose tolerance test (OGTT), offer the advantage of a smaller number of blood samples. High correlations were reported in adult studies comparing the OGTT with the euglycemic hyperinsulinemic clamp (12). The OGTT has not been studied as well in children. In a group of 38 obese 8–18 yr olds, the correlation between the OGTT (whole-body insulin sensitivity index) and the euglycemic hyperinsulinemic clamp was 0.78 (13).

### 7. The homeostasis model assessment (HOMA) and the quantitative insulin-sensitivity check index do not offer any advantages over fasting insulin in euglycemic children (LOE A in adults, B in children)

In an attempt to further simplify the measurement of insulin sensitivity, a number of methods using single simultaneously obtained samples of fasting insulin and glucose have been developed. Each of these uses a mathematical formula that adjusts for individual variability in insulin and glucose secretion and clearance. Although the goal for these methods was to improve the accuracy of fasting insulin alone by the addition of fasting glucose, it is now agreed that they yield similar results to fasting insulin. For instance, HOMA, the most widely used of the surrogate measures in children, is highly correlated with fasting insulin ($r \geq 0.95$) in children (10) and adults. These high correlations can be attributed to the narrow range of fasting glucose even among obese children and those with abnormal glucose tolerance (14, 15), whereas there is a 53-fold variation in fasting insulin in children (10).

### 8. Fasting insulin is a poor measure of whole body insulin sensitivity in an individual child (LOE A)

The accuracy of fasting insulin as a measure of insulin sensitivity has been assessed through correlation analyses with the euglycemic hyperinsulinemic clamp, FSIVGTT, or SSPG and found to be disappointingly low (16). Studies of cohorts (with more than 50 participants for this consensus statement) containing both grade school-aged and high school-aged children have reported correlations from 0.42–0.91 between fasting insulin and the clamp (10, 17) and from 0.18–0.8 between fasting insulin and FSIVGTT (18–21). In the largest cohort reported to date, the correlation between fasting insulin and the clamp was 0.42 at mean age of 13 yr ($n = 323$) and 0.29 at mean age of 15 yr ($n = 300$), with slightly higher correlations in obese than thin children (10). It can be concluded from these studies that fasting insulin is a poor measure of whole body insulin sensitivity in an individual child, and it should not be used for clinical decision making in daily clinical practice.

Although fasting insulin is a poor surrogate, much of the data relating to prevalence, intervention, and prevention are based on it or other surrogates, bringing into question the precision of the results from those studies.

## Methods of Screening

### 9. Based on current screening criteria and methodology, there is no justification for screening children for insulin resistance, including obese children (LOE A)

The prevalence of insulin resistance is unknown, but it is clear that insulin-resistant obese children have significantly greater cardiovascular risk profiles, and childhood insulin resistance appears to predict future cardiovascular risk (21). Although this suggests that screening has the potential to identify at-risk children, the key issue for any screening program is availability of an accurate, reliable, reproducible, and easily applicable method of measurement. It is impractical to use any lengthy methods requiring multiple samples because of the complexity, time, and cost of individual testing. In the clinical setting, fasting insulin is an unreliable measure of insulin sensitivity, and testing of aliquots of a common sample assayed in different laboratories has shown disparate results (22). Even if a uniformly reliable insulin assay became available, separate standards would need to be developed by genders, ethnic groups, and pubertal stages (8, 23, 24). Currently, there is no recommended pharmacological treatment for isolated insulin resistance. Therefore, screening for insulin resistance is not justified in the clinical setting for children, including those with obesity. The mere presence of obesity should call for intervention to lower weight and consequently improve insulin sensitivity without a need to measure insulin levels.

## Assessment of Risk Factors of Childhood Insulin Resistance

### 10. The two most important biological conditions associated with insulin resistance in childhood are ethnicity and puberty (LOE A)

Using a variety of methods, studies show that African-American, Hispanic, Pima Indian, and Asian children are less insulin sensitive compared with Caucasian children (25–27). The insulin resistance in minority ethnic groups is manifested as lower insulin-stimulated glucose uptake, concomitant with hyperinsulinemia, evidence of increased insulin secretion from the $\beta$-cell and decreased insulin clearance (25–27).

During puberty there is ~25–50% decline in insulin sensitivity with recovery when pubertal development is

complete (8). The compensatory increase in insulin secretion during puberty may be blunted in African-American and Hispanic youth, thus increasing their risk for T2D around the time of puberty (28, 29).

### 11. Obesity, particularly increased abdominal visceral adiposity, and nonalcoholic fatty liver disease (NAFLD) are associated with insulin resistance in children (LOE A)

Obesity is the most prevalent pathophysiological cause of insulin resistance. Insulin sensitivity is inversely associated with body mass index and percentage body fat, and obese youth have lower insulin sensitivity than their normal-weight peers (30, 31). Independent of the relation between total body fat and insulin resistance, increased abdominal visceral adipose tissue in obese youth is associated with lower insulin sensitivity and higher acute insulin response (23). Limited studies show that ectopic fat deposition such as intramyocellular lipid in obese adolescents is also associated with decreased peripheral insulin sensitivity (32).

Studies using the clamp methodology demonstrate that NAFLD is associated with hepatic and peripheral insulin resistance (33). The relation between insulin sensitivity and NAFLD seems to be, in part, driven by abdominal fat content (34).

The relationship between lifestyle factors, *e.g.* nutrition and physical activity, and insulin sensitivity is poorly defined in children.

Increased caloric intake leading to obesity, rather than the dietary macronutrient composition, is associated with insulin resistance and hyperinsulinemia. Limited cross-sectional data suggest that dietary saturated fat and sugar-sweetened beverages may be associated with alterations in insulin sensitivity and secretion (35).

The effect of physical activity on insulin sensitivity, independent of changes in weight and adiposity, remains controversial.

### 12. Polycystic ovary syndrome (PCOS), independent of weight, is characterized by insulin resistance in childhood (LOE B)

Adolescent girls with PCOS can have severe insulin resistance with increased risk for impaired glucose tolerance (IGT) and T2D, and the impairment in insulin sensitivity is more pronounced in obese than lean PCOS girls (36, 37). In some ethnic groups, girls with premature pubarche, a potential antecedent of PCOS, have increased insulin levels, and a causal relation between hyperinsulinemia and adrenal and/or ovarian androgen hypersecretion has been hypothesized (38, 39). However, population studies of normal girls have shown that rapid weight gain is associated with higher adrenal androgens and body fatness, and that insulinemia was related to early menarche (40). Thus, the association of higher insulin levels with premature pubarche and subsequent PCOS may be driven, at least in part, by obesity.

### 13. Genetics and heritability play a role in childhood insulin resistance (LOE B)

In studies of adult twins, approximately half of the variance in insulin sensitivity and secretion can be attributed to genetic factors (41, 42). Healthy children with a family history of T2D are more insulin resistant, with an impaired balance between insulin sensitivity and secretion (43, 44). Recently, common genetic variants have emerged that identify heritable components of insulin sensitivity (45). The T2D protective variant Pro12Ala in PPAR-$\gamma$ is associated with higher insulin sensitivity in Caucasian children (46).

### 14. Intrauterine exposure to poorly controlled maternal diabetes increases the risk of obesity, insulin resistance, and IGT in childhood (LOE B)

Epidemiological and clinical studies have demonstrated that offspring of mothers with preexisting diabetes mellitus (DM) or gestational DM (GDM) have an increased risk of obesity and altered glucose metabolism (47). Small size at birth or being large for gestational age is independently associated with increased risk of childhood obesity (and possibly altered glucose metabolism) (48), but the risk of obesity and IGT/diabetes is also higher in normal-weight offspring of mothers with DM or GDM (49). Infants of mothers with GDM have more body fat than infants born to mothers with normal glucose tolerance (50), but less is known about whether excess adiposity in these infants is a risk factor for obesity or insulin resistance in later life.

Higher levels of maternal glucose during pregnancy, with or without meeting criteria for the diagnosis of GDM, might play a role in the future risk of childhood obesity and insulin resistance in the offspring (51).

### 15. Postnatal and childhood weight gain increase the risk of insulin resistance in normal-birth-weight and small-for-gestational-age children (LOE B)

Rapid postnatal weight gain has consistently been associated with risk of insulin resistance and greater adiposity in children and young adults (52–56) and predicts insulin resistance-related outcomes in adults (57, 58). However, the timing of rapid weight gain with respect to future insulin resistance remains controversial, with some

studies relating it to early infancy (0–6 months) and others between ages 2 and 11 yr (54–56).

The association between small-for-gestational-age infants and an increased risk of obesity, insulin resistance, and T2D is accentuated by weight gain during early life with increased percentage body fat (52, 59, 60).

Preterm children have reduced insulin sensitivity, which persists in adulthood and is associated with truncal obesity (61).

## Consequences of Childhood Insulin Resistance

### 16. Insulin resistance is a risk factor for prediabetes and T2D in childhood (LOE B)

Insulin resistance and impaired β-cell function are the two key components in the pathogenesis of T2D in youth (62). Despite limited and conflicting cross-sectional data, it is well accepted that youth with IGT have impairment in insulin secretion compared with equally obese youths with normal glucose tolerance (63–65). In some studies, this has been associated with similar levels of insulin sensitivity (63, 65), whereas in others obese adolescents with IGT were more insulin resistant than adolescents with normal glucose tolerance and a similar degree of adiposity (32, 66). However, there are very limited longitudinal data on whether insulin resistance predicts the development of IGT and T2D. A recent longitudinal study has shown that obese adolescents progressing to IGT manifest primary defects in β-cell function, which are aggravated by a progressive decline in insulin sensitivity (67).

### 17. Insulin resistance is associated with the metabolic syndrome and cardiometabolic risk factors (LOE A)

Regardless of the metabolic syndrome definition used, insulin resistance and high insulin levels are associated with the clustering of cardiometabolic risks associated with metabolic syndrome in a variety of ethnic groups (7, 68, 69).

There are no studies that directly measure *in vivo* insulin sensitivity and its relationship to atherosclerotic abnormalities in children. Very limited observations suggest a relationship between HOMA and arterial stiffness and fasting insulin levels in youth (70). However, a role for insulin resistance in the early abnormalities of vascular smooth muscles is proposed based on the observation that circulating biomarkers of endothelial dysfunction (intercellular adhesion molecule and E-selectin) are highest, whereas the antiatherogenic adipocytokine adiponectin is lowest among the most insulin-resistant youths (71).

## Treatment

### 18. Diet and weight loss drugs improve insulin sensitivity in adolescents through weight loss and other mechanisms (LOE B)

Dietary fat intake influences insulin sensitivity, with the most consistent effect related to increased fat intake lowering insulin sensitivity rather than reduced fat intake increasing insulin sensitivity (35, 72). However, a consistent effect of fat quality on insulin sensitivity could not be found across 41 adult studies, largely because of design flaws limiting interpretation (73).

A high whole-grain or dietary fiber intake is associated with higher insulin sensitivity and weight loss, and a low intake is associated with lower insulin sensitivity, based upon a questionnaire study in adolescents and prospective crossover studies in adults (74).

Improvement in insulin sensitivity in adolescents on a low glycemic load diet is contradictory to the greater number of studies in adults in which a consistent effect of this diet is not seen on insulin sensitivity (75–77).

Although there are similarities between a low glycemic load and a low-carbohydrate diet, there are no studies evaluating the latter diet's impact on insulin sensitivity in children. In adolescents receiving either a high-fiber or low glycemic load diet, weight loss was observed with improved insulin sensitivity (74–77). It is unclear whether the improvements in insulin sensitivity were due to weight loss, the diet, or a combination of these factors.

Few studies have examined the impact of a hypocaloric diet on insulin sensitivity in children; however, adult studies have found variable weight loss and improvement in insulin sensitivity.

The weight-reducing drugs sibutramine and orlistat led to an improvement in insulin sensitivity with a reduction in weight of approximately 0.6 SD in children and adolescents (78–80).

### 19. Exercise and fitness improve insulin sensitivity through weight loss and also mechanisms independent of weight loss in adolescents (LOE A)

Studies specifically exploring the impact of exercise and mechanism of action on insulin resistance are few.

Lifestyle programs including supervised exercise can improve fasting insulin levels as quickly as 2 wk before measurable weight loss (81, 82). Furthermore, lifestyle intervention improved body composition without a change in body weight (83). Available studies suggest that

fitness may play a more important role than body mass index reduction on improvement in insulin sensitivity in obese adolescents (84).

Adequate studies are not available to differentiate the effect of a single session of exercise on insulin sensitivity, as opposed to the training regimen. There appears to be improvement in insulin sensitivity with prescribed aerobic exercise regimens and combinations of aerobic and resistance training (85, 86). However, there is inadequate evidence about the optimal form of exercise. Exercise intensity has not been shown to be correlated with insulin sensitivity. After the cessation of exercise, improved insulin sensitivity levels revert to preexercise levels, and there may even be a rebound phenomenon with greater insulin resistance (82).

### 20. Multicomponent lifestyle intervention improves insulin sensitivity more than individual lifestyle components in adolescents (LOE B)

There are limited data to show that the effects of nutrition, exercise, and behavioral modification together on insulin sensitivity are more beneficial and sustained than any one component alone (87). Short-term randomized studies of lifestyle and exercise intervention in obese adolescent girls improved insulin sensitivity when compared with no intervention (88).

### 21. Metformin improves insulin sensitivity in adolescence (LOE B)

Metformin has been shown to improve insulin sensitivity in adolescents with T2D and girls with PCOS, justifying consideration of metformin as a therapeutic tool in these disorders (89, 90). There are conflicting reports on the influence of metformin on insulin sensitivity in insulin-treated, insulin-resistant type 2 diabetics (91).

The safety and efficacy of metformin in the management of T2D in children were confirmed using glycemic control as a proxy for improved insulin sensitivity (92). However, other reports have emphasized that lifestyle and dietary measures can be at least as effective as metformin in these patients (91).

Metformin has been shown to be efficacious in improving insulin sensitivity in obese PCOS girls with IGT (90), but not in obese PCOS girls without IGT (96). In nonobese teenage girls with PCOS, combined flutamide-metformin therapy improved insulin sensitivity (97). Both flutamide and metformin seem to be needed to obtain maximal efficacy on parameters of insulin sensitivity and to ameliorate body composition (98).

However, it has to be stressed that metformin has not been approved for the treatment of children with insulin resistance; therefore, appropriate, well-designed, controlled trials are needed.

## Prevention

### 22. Maternal obesity, gestational diabetes, smoking in pregnancy, and maternal undernutrition should be targeted to lessen obesity and insulin resistance in children (LOE A)

All factors affecting fetal growth are potential candidate targets for prevention purposes.

The most common and important among these risk factors are maternal obesity, gestational diabetes, maternal undernutrition, and smoking during pregnancy (49, 99–102).

### 23. Breast-feeding should be promoted through public health interventions as a contributing factor to reduce the prevalence of obesity and potential insulin resistance later in life. In addition, ongoing dietary advice starting from weaning has the potential to prevent insulin resistance in the long term (LOE B)

There are no specific data on a direct relationship between breast-feeding and prevention of insulin resistance, but given the association between obesity and reduced insulin sensitivity, breast-feeding should be promoted (103, 104).

Because of the strong link between obesity and insulin resistance, the impact of dietary interventions used to prevent obesity has been examined for its effect on insulin resistance (104). Increased saturated fat intake has been associated with reduced insulin sensitivity in children (35). A healthy low saturated fat and cholesterol diet, started in 7-month-old infants, showed a positive effect on insulin resistance at the age of 9 yr (105).

### 24. Identification of infants and preschool children at risk for obesity combined with intervention programs to prevent excessive weight gain should be developed and evaluated. Physical activity as a means of increasing insulin sensitivity is an important component of any intervention (LOE B)

Young adults born preterm have lower insulin sensitivity than controls, and weight gain velocity during childhood is associated with lower insulin sensitivity in adulthood (93). Adiposity rebound is a sensitive marker for the risk of developing obesity and its complications, and therefore it should be prevented (55, 94).

Based on available data on the beneficial effect of physical activity on surrogate measures of insulin sensitivity, such as fasting insulin and HOMA for insulin resistance (85, 95), physical activity should be promoted, although further studies using state of the art methodology for insulin sensitivity are required to validate these findings.

## Conclusions

This consensus statement highlights the lack of a clear cutoff to define insulin resistance in children and shows that surrogate measures, such as fasting insulin, are poor estimates of insulin sensitivity. Based on current screening criteria and methodology, there is no justification for screening children for insulin resistance, even those who are obese. However, it appears that prevention strategies should be started early in life and, with regard to treatment, lifestyle interventions should be included, whereas metformin should be limited to selected cases. Future research should aim at assessing the following: how to best measure insulin sensitivity; standardization of insulin measurements; identification of strong surrogate biomarkers of insulin resistance; and the potential role of both lifestyle intervention and medications in the prevention and treatment of insulin resistance.

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