

NZHTA EVIDENCE TABLES

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What clinical features best determine insulin resistance?

A critical appraisal of the literature presented in Evidence Tables

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LIST OF ABBREVIATIONS AND ACRONYMS

95%CI	–	95% confidence interval
AST	–	aspartate aminotransferase
BMI	–	Body Mass Index
BP	–	Blood Pressure
CI	–	Confidence Interval
EC	–	euglycemic (hyperinsulinaemic) clamp
HDL	–	High-Density Lipoprotein
IGT	–	Impaired Glucose Tolerance
IR	–	Insulin Resistance
ISI	–	Insulin Sensitivity Index
M	–	estimate of insulin sensitivity from the hyperinsulinaemic euglycemic clamp
MOH	–	Ministry of Health (NZ)
NGT	–	Normal glucose tolerance
NIDDM	–	non-insulin-dependent diabetes mellitus
ns	–	not significant (i.e., p value > 0.05)
NZGG	–	New Zealand Guidelines Group
NZHTA	–	New Zealand Health Technology Assessment
OGTT	–	Oral Glucose Tolerance Test
PPV	–	Positive Predictive Value
SD	–	Standard Deviation
Se	–	Sensitivity
Sp	–	Specificity
TAG	–	Triglycerides
VLDL	–	Very Low Density Lipoprotein
WHO	–	World Health Organization
WHR	–	Waist-to-hip ratio

GLOSSARY

Cross-sectional study - A study that examines the relationship between diseases (or other health related characteristics), and other variables of interest as they exist in a defined population at one particular time.

Euglycemic insulin clamp - (Also known as the euglycemic clamp, the euglycemic hyperinsulinaemic clamp, and the glucose clamp) provides steady-state measures of insulin action. Exogenous insulin is administered as a prime followed by a constant infusion at a rate designed to maintain a pre-set hyperinsulinemic plateau; simultaneously the plasma glucose concentration is clamped at the normal fasting level by means of an exogenous infusion of glucose. When a steady state is achieved, the exogenous glucose infusion rate equals the amount of glucose disposed of by all the tissues in the body and thus provides a quantitation of overall insulin sensitivity (Ferrannini and Mari, 1998).

Grey literature - That which is produced by all levels of government, academics, business and industry, in print and electronic formats, but which is not controlled by commercial publishers.

Impaired glucose tolerance - Defined by World Health Organization criteria as fasting venous blood glucose level < 6.7 mmol/litre, and 2-hour glucose level as measured by the OGTT of 6.7 - 10.0 mmol/litre.

Insulin Resistance - Insulin resistance is defined clinically as the inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilisation in an individual as much as in a normal population. Insulin resistance occurs as part of a cluster of cardiovascular – metabolic abnormalities commonly referred to as “the Insulin Resistance Syndrome”, “The Metabolic Syndrome” and “Syndrome X”. The cluster of abnormalities may lead to the development of type 2 diabetes, accelerated atherosclerosis, hypertension or polycystic ovarian syndrome depending on the genetic background of the individual developing the insulin resistance (Lebovitz, 2001).

Non-insulin-dependent diabetes mellitus (NIDDM) - Defined by World Health Organization criteria as fasting venous blood glucose level \geq 6.7 mmol/litre, or 2-hour glucose level, > 10.0 mmol/litre.

Positive predictive value - The probability a person actually has the disease when the screening test is positive.

Random sample - A sample that is arrived at by selecting sample units such that each possible unit has a fixed and determinate probability of selection.

Reference standard - An independently applied test that is compared to a screening or diagnostic test being evaluated in order to verify the latter’s accuracy. A reference standard, therefore, provides an accurate or “truth” diagnosis for verification of positive and negative diagnoses. It is sometimes described as providing “final truth determination”.

Risk factor - An exposure or aspect of personal behaviour or lifestyle, which on the basis of epidemiologic evidence is associated with a health-related condition.

Sensitivity - Sensitivity is the proportion of truly diseased persons in a screened population who are identified as diseased by a screening test. Sensitivity is a measure of the probability of correctly diagnosing a case, or the probability that any given case will be identified by the test.

Specificity - The proportion of truly non-diseased persons who are so identified by a screening test. It is a measure of the probability of correctly identifying a non-diseased person with a screening test.

Methodology

BACKGROUND

The Ministry of Health is funding a collaborative venture between the New Zealand Guidelines Group, the Stroke Foundation of New Zealand and the National Heart Foundation to develop an integrated set of best practice, evidence-based guidelines for cardiovascular disease. To inform this work, the New Zealand Health Technology Assessment (NZHTA) unit will produce “evidence tables” reporting on critical appraisals of research studies relevant to specific aspects of the Guideline.

This topic will inform the Guideline relating to how to diagnose the insulin resistance (IR) syndrome, and specifically, what clinical features best determine insulin resistance. Insulin resistance is defined clinically as the inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilisation in an individual as much as in a normal population. Insulin resistance (IR) occurs as part of a cluster of cardiovascular – metabolic abnormalities commonly referred to as “the Insulin Resistance Syndrome”, “The Metabolic Syndrome” and “Syndrome X”. The cluster of abnormalities may lead to the development of type 2 diabetes, accelerated atherosclerosis, hypertension or polycystic ovarian syndrome depending on the genetic background of the individual developing the insulin resistance (Lebovitz, 2001).

Given the importance of insulin resistance for the assessment of cardiovascular risk and response to intervention, there is a need for an accurate and reproducible method of measuring insulin resistance. The euglycemic hyperinsulinaemic clamp is generally considered to be the “gold standard” for measuring insulin resistance (Scheen et al. 1994; Ferrannini, 1998). The euglycemic insulin clamp is the gold standard diagnostic test for insulin resistance, although it is impractical (being expensive and time consuming) to perform in clinical practice, hence the need for identifying simpler diagnostic tests. This topic aims to provide evidence relating to comparisons of various alternative diagnostic tests of insulin resistance applicable in clinical practice compared with the euglycemic insulin clamp.

Most studies in this area tend to consider insulin resistance diagnostic test accuracy for people with impaired glucose tolerance or diabetes. However, there is evidence to suggest that by the time glucose tolerance and fasting glucose become impaired, significant B-cell destruction may have already occurred (DeFronzo and Ferrannini, 1991). Intervention aimed at reducing incidence of type 2 diabetes and cardiovascular disease would be more successful when blood glucose levels are in the normal range (McAuley et al. 2001), and therefore tests for insulin resistance need to be accurate in broad populations including individuals with normal glucose tolerance.

SELECTION CRITERIA

Study inclusion criteria

Publication type

Studies published between 1990 and August, 2002 inclusive in the English language, including primary (original) research (published as full original reports) and secondary research (systematic reviews and meta-analyses) appearing in the published literature.

Study design

Peer reviewed studies will be considered if they used one of the following study designs:

- systematic review or meta-analysis
- cross-sectional study/analyses comparing eligible tests with the reference standard test for insulin sensitivity.

Comparison tests

Studies comparing the reference standard test with one or more of the following tests:

- abdominal obesity (waist girth, waist to hip ratio)
- Body Mass Index (BMI)
- triglycerides
- fasting plasma insulin
- fasting plasma glucose
- Blood Pressure (BP)
- High-Density Lipoprotein (HDL)
- insulin to glucose ratio (at fasting)
- Oral Glucose Tolerance Test (OGTT)
- family history of diabetes
- liver enzymes
- simply ascertained combinations of any of the above.

Reference standard

The euglycemic insulin clamp.

Population

- study population are adults (aged 25-75) from the general population.

Sample size

Studies with samples of at least 20 participants.

Outcomes

Outcomes considered included:

- Sensitivity (Se)
- Specificity (Sp)
- Positive Predictive Value (PPV)

In the absence of the above, other measures of association including correlation coefficients and beta weights were reported.

Study exclusion criteria

Research papers were excluded if they:

- were not published in English
- were “correspondence”, book chapters, conference proceedings, abstracts
- reported studies with fewer than 20 persons included in reported relevant outcomes
- did not clearly describe their methods and results, or had significant discrepancies
- considered any of the following comparison tests (due to difficulties in their application in general practice):
 - hyperglycemic clamp
 - Homeostasis Model Assessment Method (HOMA)
 - insulin sensitivity indices requiring post glucose-load measures during the OGTT, including the ISI (Cederholm), ISI (Belfiore), ISI (Matsuda), ISI (Stumvoll), ISI (Gutt)
 - Quantitative Insulin Sensitivity Check Index (QUICKI)
 - minimal model analysis of data from an Intravenous Glucose Tolerance Test (IVGTT)
 - continuous infusion of glucose with model assessment (CIGMA) test
 - insulin tolerance test
 - use of tracers
 - any other test identified that is impractical for application in clinical practice.

- or concerned:
 - study population, or analyses of sub-groups including, 50% or more of people with diabetes cardiovascular disease, hypertension, impaired glucose tolerance, and/or obesity
 - study population including 50% or more outside the age range of 25 to 75 years
 - study population of a specific, atypical sub-group not broadly generalisable to the NZ general population.

SEARCH STRATEGY

A systematic method of literature searching and selection was employed in the preparation of this review.

Searches were limited to English language material published from 1990 onwards. Dr Kirsten McAuley, a leading New Zealand researcher in this field, verified the search from 1990 as appropriate. The searches were completed on 3 September 2002.

Principal sources of information

The following databases were searched (using the search strategy outlined in **Appendix 1**):

Bibliographic databases

Cochrane Library Controlled Trials Register

Embase

Cinahl

Current Contents

Index New Zealand

Medline

Science/Social Science Citation Index

Review databases

Evidence-based medicine reviews

Cochrane Database of Systematic Reviews

DARE

Health Technology Assessment Database

NHS Economic Evaluation Database

Other sources

Reference lists of eligible papers and narrative reviews retrieved in the course of the research.

Citation searching of key eligible papers. Contact with three experts in the field: Dr Kirsten McAuley, Dr Peter Moore, Professor Russell Scott.

Search terms used

- index terms from Medline (MeSH terms): exp insulin resistance, glucose clamp technique, risk factors, exp ethnic groups
- index terms from Embase: insulin resistance, exp glucose tolerance test
- additional index terms used for insulin resistance syndrome x, metabolic cardiovascular syndrome*, metabolic syndrome*, syndrome X, euglycemic insulin clamp, euglycemic insulin clamp
- the above index terms were used as keywords in databases where they were not available as subject headings and in those databases without controlled vocabulary.

STUDY SELECTION

Studies were selected for appraisal using a two-stage process. Initially, the titles and abstracts (where available) identified from the search strategy, were scanned and excluded as appropriate. The full text articles were retrieved for the remaining studies and these were appraised if they fulfilled the study selection criteria outlined above.

APPRAISAL OF STUDIES

Articles were formally appraised using the NZGG's GATE FRAME checklist for cross sectional studies of diagnostic accuracy and graded using NZGG summary levels of Evidence. There were four gradings applied, as follows:

1. quality of review design (minimising bias)
2. quality of results (understandable, precise, and/or sufficient power)
3. quality of study applicability: could applicability be determined?
4. quality of study applicability: are findings applicable in usual practice/settings?

Each Grade was coded as one of the following: Very well (+), Okay (∅), Poorly (-) or as a combination of these.

EVIDENCE TABLES

Evidence tables for primary research studies present key information summaries described below.

- study source including authors, year published, and country of origin
- study design. Setting, Reference standard including definition of insulin resistance/cut-off score applied. Study comparison tests including definition of insulin resistance/cut-off score applied
- sample including sample size, sample characteristics including demographic variables, any comparisons between intervention groups on these variables at baseline, and inclusion and exclusion criteria
- outcomes including statistically tested comparisons and reporting relevant statistical data. Outcomes will include: Sensitivity (Se), Specificity (Sp), Positive Predictive Value (PPV) and other measures of association including correlation coefficients from analyses comparing tests with reference standard
- authors conclusions
- study quality gradings (applying GATE FRAME criteria as described above)
- comments including specific study limitations.

LIMITATIONS OF THE REVIEW

This study has used a structured approach to review the literature. However, there were some inherent limitations with this approach. Namely, systematic reviews are limited by the quality of the studies included in the review and the review's methodology.

This review has been limited by the restriction to English language studies. Restriction by language may result in study bias, but the direction of this bias cannot be determined. In addition, the review has been limited to the published academic literature, and has not appraised unpublished work. Restriction to the published literature is likely to lead to bias since the unpublished literature tends to consist of studies not identifying a significant result.

Papers published pre-1990 were not considered as these tended to concern outdated practices or poor study designs.

The studies were initially selected by examining the abstracts of these articles. Therefore, it is possible that some studies were inappropriately excluded prior to examination of the full text article. This is

particularly the case for studies if Insulin Sensitivity Indexes (ISIs) where fasting insulin and fasting glucose may have been considered separately in data analysis.

Studies reporting on ISIs have been excluded from appraisal, as the collection of input variables over a two hour OGTT and computer-based calculations required was considered to be impractical for routine clinical practice.

Whilst the euglycemic hyperinsulinaemic clamp is now generally considered to be the “gold standard” for measuring insulin resistance, an absolute index is lacking which makes validation of alternative methods difficult (Scheen et al. 1994).

Studies in this area tend to only report correlation coefficients between the euglycemic clamp and the alternative diagnostic test and few report data enabling test sensitivity and specificity to be determined. Studies reporting correlation coefficients commonly calculate these for many alternative tests and therefore tests are not independent from each other. The correlation coefficient “r” will be overestimated when lack of independence is present.

All but one study included in this review were conducted outside New Zealand, and therefore, their generalisability to the New Zealand population and context may be limited and needs to be considered based on the demographic and clinical features of each sample reported in the tables.

This review was confined to an examination of the diagnostic accuracy of the comparison tests and did not consider ethical, economic or legal considerations associated with these tests. However, alternative tests were selected as those feasible for administering in clinical practice.

Data extraction, critical appraisal and report preparation was performed by a single reviewer.

The review scope was developed with the assistance of NZGG’s Dr Rob Cook.

This review was conducted over a limited timeframe (August, 2002 – November, 2002).

For a detailed description of methods, statistical analyses, and results used in the studies appraised, the reader is referred to the original papers cited.

Results

From the search strategy we identified over 1,900 potentially relevant abstracts. Inclusion and exclusion criteria were applied and 36 were deemed as potentially eligible for appraisal and were retrieved¹. Of the 36 papers retrieved as full text, 31 were excluded for the following reasons: narrative reviews (n=5), reports on a specific, atypical sub-population not generalisable to the general population (n=3), case reports with sample size of fewer than 20 (n=2), did not include eligible outcomes (n=13), did not compare test with the euglycemic clamp (n=3), not relevant to the topic (n=1), correspondence only (n=3), not published in English language (n=1). These excluded papers, annotated with the reason for exclusion are listed in **Appendix 2**.

Five retrieved articles were appraised (listed in **Appendix 3**). Included papers are presented in the evidence tables below. Papers are presented in decreasing order of quality (based on four quality gradings given equal weighting), and papers of equal quality are presented in reverse chronological order (i.e., more recently published first).

¹ Many papers were excluded because the euglycemic clamp was not applied, and because the sample were atypical of the general population (e.g., were diabetic).

Table 1. Evidence table of research studies relating to what clinical features best determine insulin resistance

Authors Country	Study design, setting, comparisons	Sample characteristics, inclusion and exclusion criteria	Methods	Results and authors conclusions	Quality gradings and limitations
McAuley et al. (2001) New Zealand	<p>Cross-sectional study.</p> <p>Study setting Recruited for various previous research projects and with BP, BMI and WHR similar to the general² New Zealand population.</p> <p>Reference standard Hyperinsulinaemic Euglycemic Clamp (EC).</p> <p>Comparison tests</p> <ul style="list-style-type: none"> ▪ fasting insulin (I₀) ▪ insulin to glucose ratio ▪ Body Mass Index (BMI) ▪ waist girth (WG) ▪ waist-to-hip ratio (WHR) ▪ triglycerides (TAG) ▪ HDL cholesterol ▪ family history (FH) ▪ blood pressure (BP) ▪ aspartate aminotransferase (AST). 	<p>Participants N=178 with normal glucose tolerance.</p> <p>Sample characteristics Sex: 17% male (data obtained from author) Insulin resistant: 42% as measured by EC Age range: 25-68, mean=47 years Mean weight: 76 kg Mean BMI: 28 kg/m² Mean WHR (male): 0.97 (n=31) Mean WHR (female): 0.86 (n=68) Mean BP: 125/81 Mean AST: 14.3 (n=73)</p> <p>Inclusion and exclusion criteria None reported.</p>	<p>After a 10 hour overnight fast, weight, height, BP, waist girth and WHR determined.</p> <p>The Euglycemic Clamp procedure was followed with insulin infusion of 40mU/m²/minute and blood glucose clamped at 4.5 mmol/litre for two hours. Glucose disposal rate or M was determined, averaged over 60-120 minute period)(mg/kg/min). The insulin sensitivity index (ISI) corrected for fat-free mass was calculated (Mffm/l). Authors argue that glucose disposal should be corrected for fat free mass as if total body weight is used then insulin resistance is overestimated in overweight individuals.</p> <p>Plasma insulin level determined by the radioimmunoassay.</p> <p>Cholesterol concentrations and triglyceride function tests were also conducted.</p>	<p>Correlations between log-transformed Mffm/l and log-transformed tests: I₀: r=-0.50, p<0.05 Insulin to glucose ratio: r=-0.47, p<0.05 BMI: r=-0.42, p<0.05 WG: r=-0.43, p<0.05 WHR : r=-0.26, p<0.05 TAG : r=-0.45, p<0.05 HDL cholesterol: r=0.35, p<0.05 AST: r=-0.44, p<0.05 FH (not log-transformed): r=0.16, ns BP (not log-transformed): r=-0.13, ns</p> <p>Sensitivity, specificity, and shrinkage analysis for predicting Mffm/l as a continuous variable: Insulin (cutoff=12.2mU/l): Se=0.57; Sp= 0.82 BMI (cutoff=29.3 kg/m²): Se=0.56; Sp= 0.76 TAG (cutoff=1.5 mmol/l): Se=0.53; Sp= 0.75 Insulin and TAG, combined: Se=0.62; Sp= 0.84 Validation estimates: Se=0.64; Sp= 0.83 95% CI: Se=0.53-0.73; Sp:0.74-0.88 Insulin, BMI, and TAG, combined: Se=0.63; Sp= 0.82 Validation estimates: Se=0.64; Sp= 0.81 95% CI: Se=0.53-0.73; Sp:0.74-0.88</p>	<p>Quality gradings</p> <ul style="list-style-type: none"> ▪ quality of design? +/Ø ▪ quality of results? +/Ø ▪ could applicability be determined? + ▪ are findings applicable in usual practice? + <p>Specific limitations</p> <ul style="list-style-type: none"> ▪ unreported (original) participation rate and sample recruitment details ▪ not clear whether the euglycemic clamp and other tests were administered blind to each other ▪ more than one test applied per individual and therefore tests are not independent from each other. Correlation coefficient (r) will be overestimated when lack of independence is present ▪ insufficient data to investigate usefulness of waist circumference and AST as tests.

² Abbreviations and acronyms are defined in the list on page iii.

Table 1. Evidence table of research studies relating to what clinical features best determine insulin resistance (continued)

Authors Country	Study design, setting, comparisons	Sample characteristics, inclusion and exclusion criteria	Methods	Results and authors conclusions	Quality gradings and limitations
McAuley et al. (2001) New Zealand (continued)			<p>Having positive family history (FH) of type 2 diabetes defined as having a first degree relative with diabetes diagnosed after 30 years of age and not requiring insulin during the first 6 months from diagnosis (data for 1010 participants only).</p> <p>Insulin resistance defined as $ISI \leq 6.3 M \cdot mU^{-1} \cdot l^{-1}$ which corresponded to the lowest quartile for the lean population ($BMI < 27 \text{ kg/m}^2$).</p> <p>Regression models were used to devise weights for each variable. The sensitivity (Se) and specificity (Sp) were derived from regressing each key variable alone and in combination, either as continuous or categorical variables (where cut-offs derived from the equations for each predictor variable). A bootstrap procedure was used to carry out internal validation (using median values of Se and Sp).</p>	<p>The authors conclude: fasting insulin of $> 12.2 \text{ mU/l}$ in normoglycemic people is a remarkably specific test for insulin resistance. The addition of triglycerides to fasting insulin increased sensitivity from 0.57 to 0.64 and maintains good specificity, using this score: $Mffm/l = \exp[2.63 - 0.28 \ln(\text{insulin}) - 0.31 \ln(\text{TAG})]$.</p> <p>When glucose disposal is corrected for fat-free mass, BMI does not increase the Se or Sp of this combination.</p> <p>Se and Sp were similar when $Mffm/l$ was used as a categorical variable, however the validation studies showed that there was much more "shrinkage". That is, the score was not able to divide individuals into two groups on a new sample as accurately as it did on the original sample used to establish the score. Authors suggest that a simple computer programme can apply equation using continuous variables as easily as for categorical without loss of information.</p>	

Table 1. Evidence table of research studies relating to what clinical features best determine insulin resistance (continued)

Authors Country	Study design, setting, comparisons	Sample characteristics, inclusion and exclusion criteria	Methods	Results and authors conclusions	Quality gradings and limitations
Donahue et al. (1996) USA	<p>Cross-sectional within a cohort study.</p> <p>Study setting Cohort recruited from populations representing targeted ethnic groups living within 10 miles of the Miami School of Medicine.</p> <p>Reference standard Hyperinsulinaemic Euglycemic Clamp.</p> <p>Comparison tests Blood pressure (systolic and diastolic).</p>	<p>Participants N=58 of 107 (54%) recruited consecutively throughout 1993 participated in sub-study of insulin sensitivity. Five Cuban-Americans were omitted as too few for meaningful comparisons, leaving n=53 (of total cohort of 327 in study).</p> <p>Sample characteristics Sex: 55% male Mean age: 35.4 years Self-identified ethnicity: 53% white non-Hispanic, 47% African-American Family history of high BP: 58% Family history of diabetes: 15% Mean systolic BP: 110 mmHg Mean diastolic BP: 74 mmHg Mean BMI: 27.1 kg/m² Mean fasting glucose 86.3 mg/dl Mean fasting insulin: 11.8 uU/ml</p> <p>There were no differences in these characteristics between study participants and the remainder of the cohort of 327. Attempts were made to recruit equal numbers of males and females within each ethnic group.</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> ▪ aged 24-44 years ▪ self-identified as either African-American, Cuban-American, or white non-Hispanic ▪ volunteered for study ▪ no current/past history of hypertension, diabetes mellitus (according to OGTT), or other CVD risk factors ▪ not receiving medication known to affect glucose or catecholamine metabolism ▪ permanent address in the target area ▪ ability to give informed consent and participate in study. <p>Exclusion criteria Pregnant or lactating women, women within three months post birth or cessation of lactation.</p>	<p>Participants were recruited by telephone call and clinic appointments scheduled in following one to 14 days. Prior to selection for sub-study, all subjects underwent extensive CVD risk factor testing, including an OGTT, to determine eligibility.</p> <p>First phase (systolic) and second phase (diastolic) blood pressure (BP) measured three times using standard mercury manometers by trained technicians using the mean of the second and third measures.</p> <p>After a 10-12 hour fast the night before, the standard Hyperinsulinaemic Euglycemic Clamp procedure was followed over a two hour period as described by DeFronzo et al. (1979). Whole body glucose uptake (averaged over 60-120 minute period) was determined (mg/kg/min), measuring insulin sensitivity (M).</p> <p>Alpha level of 0.05 used for tests of significance.</p>	<p>Multiple linear regressions were conducted to measure the association between insulin sensitivity (mg/kg/min) and systolic and diastolic blood pressure (mmHg) adjusted for age, sex and ethnicity. M (insulin sensitivity) was inversely related to systolic BP (beta = -1.19, p<0.01) and to diastolic BP (beta = -1.10; p<0.01).</p> <p>Therefore, for every unit increase in insulin sensitivity or M (mg/kg/min) there was a 1.19 mmHg decrease in systolic BP, and a 1.10 mmHg decrease in diastolic BP.</p> <p>Analyses were repeated excluding persons with impaired glucose tolerance and the results remained essentially unchanged.</p> <p>The authors argued that the findings support the hypothesis that BP insulin sensitivity is an important determinant of BP level.</p>	<p>Quality gradings</p> <ul style="list-style-type: none"> ▪ quality of design? \emptyset ▪ quality of results? $\emptyset/-$ ▪ could applicability be determined? \emptyset ▪ are findings applicable in usual practice? - <p>Specific limitations</p> <ul style="list-style-type: none"> ▪ the study did not aim to consider BP as an alternative diagnostic test for insulin resistance to the euglycemic clamp ▪ relatively small sample size and poor participation rate ▪ by design recruited people without diabetes, hypertension or CVD resulting in a healthier sample than the general population. Also only considering select ethnic groups and those aged in 24-44 years. This makes the sample of limited generalisability to NZ general population settings ▪ not clear whether BP and euglycemic clamp tests were administered blind to each other's test results ▪ test accuracy including Se, Sp, and Likelihood Ratio's not determined.

Table 1. Evidence table of research studies relating to what clinical features best determine insulin resistance (continued)

Authors Country	Study design, setting, comparisons	Sample characteristics, inclusion and exclusion criteria	Methods	Results and authors conclusions	Quality gradings and limitations
Hanson et al. (2000) USA	<p>Cross-sectional within a longitudinal study.</p> <p>Study setting Subset from a population-based longitudinal study of Pima Indians of the Gila River Indian community of central Arizona, 1982-1997.</p> <p>Reference standard Hyperinsulinaemic Euglycemic Clamp.</p> <p>Comparison tests</p> <ul style="list-style-type: none"> ▪ fasting insulin (I_0) ▪ insulin/glucose ratio at fasting (I_0/G_0) ▪ two hour post load insulin (I_{120}). 	<p>Participants N=457 (subset of wider study).</p> <p>Sample characteristics Without diabetes and normal glucose tolerance = 274 (60%). Characteristics not described. Refers to earlier papers but on retrieval, these only describe much smaller samples.</p> <p>Inclusion criteria</p> <ul style="list-style-type: none"> ▪ aged 20 years or more ▪ persons of full African-American heritage living in target community. <p>Exclusion criteria None described.</p>	<p>Every two years, all community members are invited to have a health examination that includes a 75g OGTT. Fasting and 2 hours post oral glucose load plasma concentrations (G_0 and G_{120}) and fasting and 2 hour post load serum insulin concentrations (I_0 and I_{120}) were determined. Two insulin radioimmunoassays were employed. Diabetic and glucose tolerance status determined according to WHO guidelines based on OGTT.</p> <p>These assessments enabled the following (relevant) tests to be determined: Fasting insulin (I_0), Insulin/glucose ratio at fasting (I_0/G_0), Two hour post load insulin (I_{120}).</p> <p>BMI was measured in light clothing without shoes.</p> <p>After 13 hour fast, the Hyperinsulinaemic Euglycemic Clamp procedure to achieve hyperinsulinemia at 130 μU/ml was used to measure M_{130} as described by Lillioja et al. (1987). The clamp and OGTT tests were conducted within 15 days of each other in the same inpatient visit.</p> <p>In statistical analyses, natural logarithms of the indices were used to reduce skewness. All variables were standardised by sex and assay at a mean of 0 and SD of 1.</p>	<p>Correlations were determined to measure the association between insulin sensitivity (M_{130}) as measured by the euglycemic clamp and the following tests: I_0: $r=-0.60$, $p<0.01$ I_0/G_0: $r=-0.56$, $p<0.01$ I_{120}: $r=-0.56$, $p<0.01$</p> <p>Analyses on subset of 274 persons without diabetes and with normal glucose tolerance were reported separately: I_0: $r=-0.57$, $p<0.01$ I_0/G_0: $r=-0.54$, $p<0.01$ I_{120}: $r=-0.53$, $p<0.01$</p> <p>The authors concluded that insulin sensitivity from these simple OGTT derived indices gave relatively modest correlations with the "more accurate" euglycemic clamp, but nevertheless may be useful surrogates for more sophisticated tests in epidemiological studies.</p> <p>Note that the study also considered the ability of the tests in predicting incidence of diabetes not discussed here.</p>	<p>Quality gradings</p> <ul style="list-style-type: none"> ▪ quality of design? \emptyset ▪ quality of results? $\emptyset/-$ ▪ could applicability be determined? $-$ ▪ are findings applicable in usual practice? $-$ <p>Specific limitations</p> <ul style="list-style-type: none"> ▪ participation rate was not reported ▪ Pima Indians have an extraordinarily high incidence of diabetes, and this makes the sample of limited generalisability to NZ general population settings ▪ not clear whether OGTT and euglycemic clamp tests were administered blind to each other's test results ▪ test accuracy including Se, Sp, and Likelihood Ratio's not determined ▪ the correlation coefficients suggest that I_0, I_0/G_0, and I_{120} explain 32%, 29%, and 28% respectively of the variance in insulin sensitivity (as measured by the euglycemic clamp) ▪ more than one test applied per individual and therefore tests are not independent from each other. Correlation coefficient (r) will be overestimated when lack of independence is present.

Table 1. Evidence table of research studies relating to what clinical features best determine insulin resistance (continued)

Authors Country	Study design, setting, comparisons	Sample characteristics, inclusion and exclusion criteria	Methods	Results and authors conclusions	Quality gradings and limitations
Laakso (1993) Finland	<p>Cross-sectional study.</p> <p>Study setting Participants randomly selected from among subjects with varying degrees of glucose tolerance who participated in previous population studies. These studies recruited people randomly from a city in Finland, Kuopio.</p> <p>Reference standard Hyperinsulinaemic Euglycemic Clamp.</p> <p>Comparison tests <ul style="list-style-type: none"> fasting (I_0) insulin. </p>	<p>Participants N=50 with normal glucose tolerance reported on here (of 132 selected randomly from two large population studies).</p> <p>Sample characteristics Sex: 46% male Age range: 45-74, mean=65 years Mean weight: 76 kg Mean BMI: 28 kg/m² Mean fasting glucose: 4.7 mmol/litre Mean fasting insulin: 13.2 mU/litre Whole-body glucose uptake: 5.9 mg/kg/minute</p> <p>Inclusion criteria <ul style="list-style-type: none"> aged 45-74 years glucose tolerance and diabetic status determined according to WHO criteria. </p> <p>Exclusion criteria None reported.</p>	<p>Participants were admitted to ward for two days. OGTT administered on day 1 (75g glucose in 10% solution) and samples of blood glucose and serum insulin drawn at 0, 1, and 2 hours.</p> <p>The blood glucose level was measured by the glucose oxidase method and the serum insulin level determined by the radioimmunoassay.</p> <p>The Euglycemic Clamp procedure was followed on day 2, as described by Laakso et al. (1990), with insulin infusion of 40mU/m²/minute and blood glucose clamped at 5.5 mmol/litre for two hours. Whole body glucose uptake (averaged over 60-120 minute period) was determined (mg/kg/min).</p>	<p>As there were no differences between men and women, combined data were reported.</p> <p>Correlations were determined to measure the association between insulin resistance (whole body glucose uptake) as measured by the euglycemic clamp and fasting insulin on persons without diabetes and with normal glucose tolerance: I_0: $r=-0.66$, $p<0.01$</p> <p>The authors concluded that insulin levels at fasting (I_0) correlate only moderately with insulin resistance as measured by the euglycemic clamp.</p>	<p>Quality gradings <ul style="list-style-type: none"> quality of design? \emptyset quality of results? $\emptyset/-$ could applicability be determined? $-$ are findings applicable in usual practice? $-$ </p> <p>Specific limitations <ul style="list-style-type: none"> relatively small sample size and unreported (original) participation rate by design, sampled from three groups: normoglycemics, impaired glucose tolerance, and NIDDM, however only the first group's results are reported here, resulting in a healthier sample than in the general population. The sample is also aged 45-74 years. This makes the sample of limited generalisability to NZ general population settings not clear whether the euglycemic clamp was administered blind to the I_0 test results. </p>

Table 1. Evidence table of research studies relating to what clinical features best determine insulin resistance (continued)

Authors Country	Study design, setting, comparisons	Sample characteristics, inclusion and exclusion criteria	Methods	Results and authors conclusions	Quality gradings and limitations
Laakso (1993) Finland (continued)			<p>These assessments enabled the following (relevant) tests to be determined: Fasting insulin (I_0), Two hour post load insulin (I_{120}).</p> <p>Pearsons correlation coefficients (r) reported.</p>	<p>Only very high fasting insulin levels (>18 mU/liter) identified all individuals who were markedly insulin resistant (that is, scoring in the lowest third for whole-body glucose uptake measure by the euglycemic clamp).</p> <p>The authors also conducted the same study at a higher insulin infusion rate ($80\text{mU}/\text{m}^2/\text{minute}$) giving steady state insulin levels of 160 mU/liter and reported similar correlations between I_0 and the euglycemic clamp (-0.70, $p<0.01$).</p> <p>[Note that the study also considered results for glucose intolerant and diabetic sub-groups not discussed here].</p>	<ul style="list-style-type: none"> ▪ test accuracy including Se, Sp, and Likelihood Ratio's not determined as no cut-off score for IR was identified for insulin outcomes ▪ the correlation coefficients suggest that I_0 explain 44% of the variance in insulin resistance (as measured by the euglycemic clamp) ▪ more than one test applied per individual and therefore tests are not independent from each other. Correlation coefficient (r) will be overestimated when lack of independence is present.

Table 1. Evidence table of research studies relating to what clinical features best determine insulin resistance (continued)

Authors Country	Study design, setting, comparisons	Sample characteristics, inclusion and exclusion criteria	Methods	Results and authors conclusions	Quality gradings and limitations
Laakso (1990) Finland Note same study and sample as for Laakso (1993) above with different tests and outcomes	Cross-sectional study. Study setting Participants randomly selected from among subjects with varying degrees of glucose tolerance who participated in previous population studies. These studies recruited people randomly from a city in Finland, Kuopio. Reference standard Hyperinsulinaemic Euglycemic Clamp Comparison tests <ul style="list-style-type: none"> ▪ cholesterol: Total, High density lipoprotein (HDL), low density lipoprotein (LDL), and Very low density lipoprotein (VLDL) ▪ triglycerides: Total, HDL, LDL, and VLDL. 	Participants N=50 with normal glucose tolerance reported on here (of 132 selected randomly from two large population studies). Sample characteristics Sex: 46% male Age range: 50 or over, mean=65 years Mean weight: 76 kg Mean BMI: 28 kg/m ² Mean fasting glucose: 4.7 mmol/litre Mean fasting insulin: 13.2 mU/litre Whole-body glucose uptake: 5.9 mg/kg/minute Inclusion criteria <ul style="list-style-type: none"> ▪ glucose tolerance and diabetic status determined according to WHO criteria. Exclusion criteria None reported.	Participants were admitted to ward for 2-3 days. After a 12 hour fast, OGTT administered (75g glucose in 10% solution) and samples of blood glucose and serum insulin drawn at 0, 1, and 2 hours. Serum lipids and lipoproteins (total, HDL, LDL, and VLDL cholesterol and triglycerides respectively) were determined from fresh serum samples were drawn after 12 hour overnight fast. The Euglycemic Clamp procedure was followed on day 2 after a 2 hour fast, with insulin infusion of 40mU/m ² /minute and blood glucose clamped at 5.5 mmol/litre for two hours. Whole body glucose uptake (averaged over 60-120 minute period) was determined (mg/kg/min).	As there were no differences between men and women, combined data were reported. Correlations were determined to measure the association between insulin resistance (whole body glucose uptake) as measured by the euglycemic clamp and the following tests on persons without diabetes and with normal glucose tolerance: HDL cholesterol: r=0.26, p>0.05, ns Total triglycerides: r=-0.29, p<0.05 VLDL triglycerides: r=-0.35, p<0.05 Data on non-significant correlations with other tests were not presented. The authors concluded that low HDL cholesterol and high total and VLDL triglycerides were associated with insulin resistance measured by the Euglycemic Clamp. They discuss various possible mechanisms to explain the relationship between IR and lipid and lipoprotein changes but conclude that this is still unclear.	Quality gradings <ul style="list-style-type: none"> ▪ quality of design? Ø ▪ quality of results? Ø/- ▪ could applicability be determined? - ▪ are findings applicable in usual practice? - Specific limitations <ul style="list-style-type: none"> ▪ relatively small sample size and unreported (original) participation rate ▪ by design, sampled from three groups: normoglycemics, impaired glucose tolerance, and NIDDM, however, only the first group's results are reported here, resulting in a healthier sample than in the general population. The sample is also aged over 50 years. This makes the sample of limited generalisability to NZ general population settings ▪ not clear whether the euglycemic clamp was administered blind to the lipid and lipoprotein test results.

KEY: Quality gradings: + (Very well), Ø (Okay), - (Poorly).

Table 1. Evidence table of research studies relating to what clinical features best determine insulin resistance (continued)

Authors Country	Study design, setting, comparisons	Sample characteristics, inclusion and exclusion criteria	Methods	Results and authors conclusions	Quality gradings and limitations
Laakso (1990) Finland (continued)			Pearsons correlation coefficients (r) reported.	[Note that the study also considered results for glucose intolerant and diabetic sub-groups not discussed here].	<ul style="list-style-type: none"> ▪ test accuracy including Se, Sp, and Likelihood Ratio's not determined ▪ the correlation coefficients suggest that total triglycerides explain only 8% and VLDL triglycerides explain 12% respectively of the variance in insulin resistance (as measured by the euglycemic clamp) ▪ more than one test applied per individual and therefore tests are not independent from each other. Correlation coefficient (r) will be overestimated when lack of independence is present.

References

DeFronzo, R. A., & Ferrannini, E. (1991). Insulin resistance - a multifaceted syndrome responsible for niddm, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular-disease. *Diabetes Care*, 14, 173-194.

DeFronzo, R. A., Tobin, J. D., & Andres, R. (1979). Glucose clamp technique: a method for quantifying insulin secretion and resistance. *American Journal of Physiology*, 237, E214-223.

Ferrannini, E., & Mari, A. (1998). How to measure insulin sensitivity. *Journal of Hypertension*, 16, 895-906.

Lebovitz, H. E. (2001). Insulin resistance: Definition and consequences. *Experimental & Clinical Endocrinology & Diabetes*, 109, S135-S148.

McAuley, K. A., Williams, S. M., Mann, J. I., Walker, R. J., Lewis-Barned, N. J., Temple, L. A., & Duncan, A. W. (2001). Diagnosing insulin resistance in the general population. *Diabetes Care*, 24, 460-464.

Scheen, A. J., Paquot, N., Castillo, M. J., & Lefebvre, P. J. (1994). How to measure insulin action in-vivo. *Diabetes-Metabolism Reviews*, 10, 151-188.

Appendix 1: Search strategies

SEARCH STRATEGIES

Medline

- 1 exp Insulin Resistance/ (10718)
- 2 insulin resistance syndrome x.tw. (17)
- 3 metabolic cardiovascular syndrome\$.tw. (37)
- 4 metabolic syndrome\$.tw. (989)
- 5 syndrome x.tw. (1169)
- 6 or/1-5 (12161)
- 7 euglycaemic insulin clamp.mp. (57)
- 8 Glucose Clamp Technique/ (2309)
- 9 euglycemic insulin clamp.mp. (250)
- 10 or/7-9 (2538)
- 11 6 and 10 (910)
- 12 limit 11 to (human and english language and yr=1990-2002) (611)
- 13 from 12 keep [SELECTED REFERENCES] (35)

- 1 Metabolic Syndrome X/ (144)
- 2 insulin resistance syndrome x.tw. (16)
- 3 reaven syndrome x.tw. (1)
- 4 metabolic cardiovascular syndrome\$.tw. (37)
- 5 or/1-4 (198)
- 6 metabolic syndrome.tw. (953)
- 7 *insulin resistance/ (5993)
- 8 syndrome x.tw. (1166)
- 9 or/6-8 (7622)
- 10 co.fs. (921413)
- 11 risk factors/ (197474)
- 12 exp ethnic groups/ (58708)
- 13 or/10-12 (1131987)
- 14 9 and 13 (1956)
- 15 14 (1956)
- 16 limit 15 to (human and english language and yr=1990-2002) (1401)
- 17 limit 5 to (human and english language and yr=1990-2002) (151)
- 18 from 17 keep [SELECTED REFERENCES] (66)
- 19 16 not 17 (1350)
- 20 from 19 keep [SELECTED REFERENCES] (103)
- 21 Glucose Clamp Technique/ (2307)
- 22 9 and 21 (624)
- 23 22 not (19 or 5) (543)
- 24 limit 23 to (human and english language and yr=1990-2002) (341)
- 25 from 24 keep [SELECTED REFERENCES] (198)

Embase

- 1 insulin resistance/ (11048)
- 2 insulin resistance syndrome.mp. (708)
- 3 1 or 2 (11127)
- 4 euglycaemic insulin clamp.mp. (44)
- 5 euglycemic insulin clamp.mp. (183)
- 6 insulin resistance/di (215)
- 7 or/4-6 (438)

- 8 exp *glucose tolerance test/ (850)
- 9 8 and 3 (75)
- 10 limit 7 to (human and english language and yr=1990-2002) (339)
- 11 from 10 keep [SELECTED REFERENCES] (21)
- 12 9 not 10 (68)
- 13 limit 12 to (human and english language and yr=1990-2002) (40)
- 14 from 13 keep [SELECTED REFERENCES] (2)
- 15 14 or 12 (23)

Cinahl

- 1 euglycaemic insulin clamp.mp. (0)
- 2 euglycemic insulin clamp.mp. (11)
- 3 insulin resistance/ (357)
- 4 2 and 3 (4)
- 5 from 2 keep [SELECTED REFERENCES] (4)

Current Contents

- 1 euglycaemic insulin clamp.mp. (24)
- 2 euglycemic insulin clamp.mp. (99)
- 3 1 or 2 (123)
- 4 limit 3 to english language (122)
- 5 from 4 keep 6,13,18,34,45,52,85 (7)
- 6 from 5 keep 1-7 (7)

SEARCHES FROM OTHER SOURCES

In databases and all other sources without controlled vocabulary combinations of the index terms and additional keywords from the above strategies, were used in the search.

Appendix 2: Excluded papers

RETRIEVED STUDIES EXCLUDED FOR REVIEW

Ahren, B., & Larsson, H. (2002). Quantification of insulin secretion in relation to insulin sensitivity in nondiabetic postmenopausal women. *Diabetes*, 52, 202-211.

Excluded as sample are all 61 year old post menopausal women and not representative of general population.

Anderson, R. L., Hamman, R. F., Savage, P. J., Saad, M. F., Laws, A., Kades, W. W., Sands, R. E. et al. (1995). Exploration of simple insulin sensitivity measures derived from frequently sampled intravenous glucose tolerance (FSIGT) tests. The Insulin Resistance Atherosclerosis Study. *American Journal of Epidemiology*, 142, 724-732.

This study compares the euglycemic clamp with minimal model analysis of data from a frequently sampled intravenous glucose tolerance test (IVGTT) which is not an eligible comparison test.

Belfiore, F. (2000). Insulin sensitivity indexes calculated from oral glucose tolerance test data: letter. *Diabetes Care*, 23, 1595.

Excluded as journal correspondence.

Belfiore, F., Iannello, S., Camuto, M., Fagone, S., & Cavaleri, A. (2001). Insulin sensitivity of blood glucose versus insulin sensitivity of blood free fatty acids in normal, obese, and obese-diabetic subjects. *Metabolism-Clinical and Experimental*, 50, 573-582.

This study compares the euglycemic clamp with the Belfiore insulin sensitivity index, which is not an eligible comparison test.

Belfiore, F., Iannello, S., & Volpicelli, G. (1998). Insulin sensitivity indices calculated from basal and OGTT-induced insulin, glucose, and FFA. *Molecular Genetics and Metabolism*, 63, 134-141.

Excluded as a narrative review providing background information for the review rather than original data.

Castillo, M. J., Scheen, A. J., Letiexhe, M. R., & Lefebvre, P. J. (1994). How to measure insulin-clearance. *Diabetes-Metabolism Reviews*, 10, 119-150.

Excluded as a narrative review providing background information for the review rather than original data.

Ferrannini, E., & Balkau, B. (2002). Insulin: In search of a syndrome. *Diabetic Medicine*, 19, 724-729.

Excluded as a narrative review providing background information for the review rather than original data.

Ferrannini, E., & Mari, A. (1998). How to measure insulin sensitivity. *Journal of Hypertension*, 16, 895-906.

Excluded as a narrative review providing background information for the review rather than original data.

Ferrara, C. M., & Goldberg, A. P. (2001). Limited value of the homeostasis model assessment to predict insulin resistance in older men with impaired glucose tolerance. *Diabetes Care*, 24, 245-249.

Excluded as sample are all obese and not representative of general population.

Fukushima, M., Taniguchi, A., Sakai, M., Doi, K., Nagata, I., Nagasaka, S., Tokuyama, K. et al. (2000). Assessment of insulin sensitivity: Comparison between simplified evaluations and minimal model analysis. *Diabetes Care*, 23, 1038-1039.

Excluded as journal correspondence.

Godsland, I. F., & Walton, C. (2001). Maximizing the success rate of minimal model insulin sensitivity measurement in humans: the importance of basal glucose levels. *Clinical Science*, 101, 1-9.

This study compares the euglycemic clamp with minimal model analysis of data from an intravenous glucose tolerance test (IVGTT), which is not an eligible comparison test.

Grulet, H., Durlach, V., Hecart, A. C., Gross, A., & Leutenegger, M. (1993). Study of the rate of early glucose disappearance following insulin injection: insulin sensitivity index. *Diabetes Research & Clinical Practice - Supplement*, 20, 201-207.

Excluded due to a small sample size for relevant analyses (n=13).

Gutt, M., Davis, C. L., Spitzer, S. B., Llabre, M. M., Kumar, M., Czarnecki, E. M., Schneiderman, N. et al. (2000). Validation of the insulin sensitivity index (ISI(0,120)): comparison with other measures. *Diabetes Research & Clinical Practice - Supplement*, 47, 177-184.

This study compares the euglycemic clamp with the insulin sensitivity index (ISI_{1,120}), which is not an eligible comparison test.

Hrebicek, J., Janout, V., Malincikova, J., Horakova, D., & Cizek, L. (2002). Detection of insulin resistance by simple quantitative insulin sensitivity check index QUICKI for epidemiological assessment and prevention. *Journal of Clinical Endocrinology and Metabolism*, 87, 144-147.

This study did not include the euglycemic clamp as a comparison test or reference standard.

Ikeda, Y., Suehiro, T., Nakamura, T., Kumon, Y., & Hashimoto, K. (2001). Clinical significance of the insulin resistance index as assessed by homeostasis model assessment. *Endocrine Journal*, 48, 81-86.

This study compares the euglycemic clamp with homeostasis model assessment (HOMA), which is not an eligible comparison test.

Kanauchi, M., Tsujimoto, N., & Hashimoto, T. (2002). Validation of simple indices to assess insulin sensitivity based on the oral glucose tolerance test in the Japanese population. *Diabetes Research & Clinical Practice*, 55, 229-235.

This study compares the euglycemic clamp with homeostasis model assessment (HOMA), and various insulin sensitivity indexes (ISIs) derived from the OGTT, which are not an eligible comparison tests.

Katz, A., Nambi, S. S., Mather, K., Baron, A. D., Follmann, D. A., Sullivan, G., & Quon, M. J. (2000). Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. *Journal of Clinical Endocrinology & Metabolism*, 85, 2402-2410.

This study compares the euglycemic clamp with the quantitative insulin sensitivity check index (QUICKI), which is not an eligible comparison test.

Kuo, C. S., Hwu, C. M., Kwok, C. F., Hsiao, L. C., Weih, M. J., Lee, S. H., Lee, Y. S. et al. (2002). Surrogate estimates of insulin sensitivity in Chinese diabetic patients and their offspring. *Diabetic Medicine*, 19, 735-740.

This study considers diabetic Chinese families. As considering a specific, atypical sub-population this study was excluded on the basis that the results would not be generaliseable to the NZ general population.

Lansang, M. C., Williams, G. H., & Carroll, J. S. (2001). Correlation between the glucose clamp technique and the homeostasis model assessment in hypertension. *American Journal of Hypertension*, 14, 51-53.

This study compares the euglycemic clamp with homeostasis model assessment (HOMA), which is not an eligible comparison test.

Matsuda, M., & DeFronzo, R. A. (1999). Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care*, 22, 1462-1470.

This study compares the euglycemic clamp with a composite insulin sensitivity index (ISIs) derived from the OGTT, which is not an eligible comparison test.

Matsuda, M., & DeFronzo, R. A. (2000). Insulin sensitivity indexes calculated from oral glucose tolerance test data: response to letter. *Diabetes Care*, 23, 1595-1596.

This study compares the euglycemic clamp with various insulin sensitivity indexes (ISIs) derived from the OGTT, which are not eligible comparison tests.

Meneilly, G. S., & Elliott, T. (1998). Assessment of insulin sensitivity in older adults using the hyperglycemic clamp technique. *Journal of the American Geriatrics Society*, 46, 88-91.

This study compares the euglycemic clamp with the hyperglycemic clamp, which is not an eligible comparison test.

Mitrakou, A., Vuorinen-Markkola, H., Raptis, G., Toft, I., Mookan, M., Strumph, P., Pimenta, W. et al. (1992). Simultaneous assessment of insulin secretion and insulin sensitivity using a hyperglycemia clamp. *Journal of Clinical Endocrinology & Metabolism*, 75, 379-382.

This study compares the euglycemic clamp with the hyperglycemic clamp, which is not an eligible comparison test.

Morris, A. D., Ueda, S., Petrie, J. R., Connell, J. M., Elliott, H. L., & Donnelly, R. (1997). The euglycaemic hyperinsulinaemic clamp: an evaluation of current methodology. *Clinical & Experimental Pharmacology & Physiology*, 24, 513-518.

Study not relevant to study question. This study considered the reproducibility and inter-subject variation of measures of insulin sensitivity using the euglycemic clamp as well as investigating the effect of hand-warming on responses.

Phillips D. I. W., Clark, P. M., Hales, C. N., Osmond, C. (1994). Understanding oral glucose tolerance: Comparison of glucose or insulin measurements during the oral glucose tolerance test with specific measurements of insulin resistance and insulin secretion. *Diabetic Medicine*, 11, 286-292.

This study did not include the euglycemic clamp as a comparison test or reference standard.

Piatti, P. M., Monti, L. D., Caumo, A., Santambrogio, G., Magni, F., Galli-Kienle, M., Costa, S. et al. (1995). The continuous low dose insulin and glucose infusion test: a simplified and accurate method for the evaluation of insulin sensitivity and insulin secretion in population studies. *Journal of Clinical Endocrinology & Metabolism*, 80, 34-40.

Excluded due to a small sample size for relevant analyses.

Rabasa-Lhoret, R., & Laville, M. (2001). How to measure insulin sensitivity in clinical practice? *Diabetes & Metabolism*, 27, 201-208.

Article is in French with English abstract.

Raynaud, E., Perez-Martin, A., Khaled, S., Mercier, J., & Brun, J. F. (1998). Concerning the validity of the "FIRI" insulin resistance index. *Diabetes & Metabolism*, 24, 160-161.

Excluded as journal correspondence.

Scheen, A. J., Paquot, N., Castillo, M. J., & Lefebvre, P. J. (1994). How to measure insulin action in vivo. *Diabetes-Metabolism Reviews*, 10, 151-188.

Excluded as a narrative review providing background information for the review rather than original data.

Stumvoll, M., Mitrakou, A., Pimenta, W., Jenssen, T., Yki-Jarvinen, H., Van Haefen, T., Renn, W. et al. (2000). Use of the oral glucose tolerance test to assess insulin release and insulin sensitivity. *Diabetes Care*, 23, 295-301.

This study compares the euglycemic clamp with the Stumvoll insulin sensitivity index, which is not an eligible comparison test.

Yeni-Komshian, H., Carantoni, M., Abbasi, F., & Reaven, G. M. (2000). Relationship between several surrogate estimates of insulin resistance and quantification of insulin-mediated glucose disposal in 490 healthy nondiabetic volunteers. *Diabetes Care*, 23, 171-175.

This study did not include the euglycemic clamp as a comparison test or reference standard.

Appendix 3: Included papers

STUDIES INCLUDED FOR REVIEW AND APPRAISAL

Donahue, R. P. (1996). Insulin sensitivity and blood pressure in a biethnic sample: the Miami Community Health Study. *Journal of Clinical Epidemiology*, 49, 859-864.

Hanson, R. L., Pratley, R. E., Bogardus, C., Narayan, K. M. V., Roumain, J. M. L., Imperatore, G., Fagot-Campagna, A. et al. (2000). Evaluation of simple indices of insulin sensitivity and insulin secretion for use in epidemiologic studies. *American Journal of Epidemiology*, 151, 190-198.

Laakso, M. (1993). How good a marker is insulin level for insulin resistance? *American Journal of Epidemiology*, 137, 959-965.

Laakso, M., Sarlund, H., & Mykkanen, L. (1990). Insulin resistance is associated with lipid and lipoprotein abnormalities in subjects with varying degrees of glucose tolerance. *Arteriosclerosis*, 10, 223-231.

McAuley, K. A., Williams, S. M., Mann, J. I., Walker, R. J., Lewis-Barned, N. J., Temple, L. A., & Duncan, A. W. (2001). Diagnosing insulin resistance in the general population. *Diabetes Care*, 24, 460-464.