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Mathematical and Statistical Modelling in Medicine

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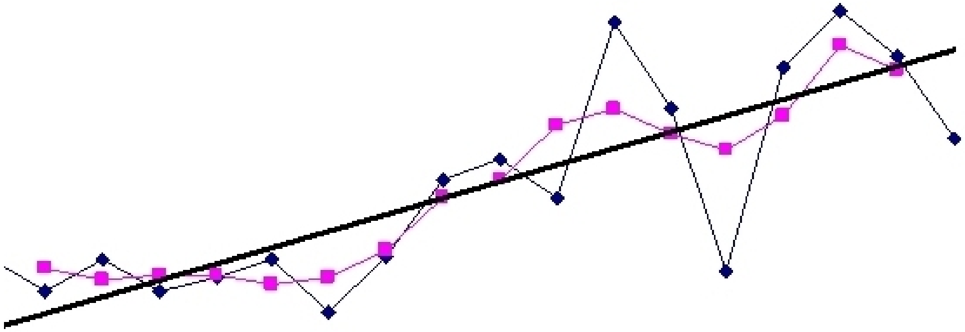
Diagnostic Study:
Conditional probability



The concept of probability

- Lets repeat an experiment n times under the same conditions. In a large number of n experiments the event A is observed to occur k times ($0 \leq k \leq n$).
- ***k*** : **frequency** of the occurrence of the event A.
- ***k/n*** : **relative frequency** of the occurrence of the event A.

$$0 \leq k/n \leq 1$$

If n is large, k/n will approximate a given number. This number is called the probability of the occurrence of the event A and it is denoted by P(A).

$$0 \leq \mathrm{P(A)} \leq 1$$

Probability facts

- Any probability is a number between 0 and 1.
- All possible outcomes together must have probability 1.
- The probability of the complementary event of A is 1-P(A).

Rules of probability calculus

- Assumption: all elementary events are equally probable

$$P(A) = \frac{F}{T} = \frac{\text{number of favorite outcomes}}{\text{total number of outcomes}}$$

Examples:

- Rolling a dice. What is the probability that the dice shows 5?
  - If we let X represent the value of the outcome, then P(X=5)=1/6.
- What is the probability that the dice shows an odd number?
  - P(odd)=1/2. Here F=3, T=6, so F/T=3/6=1/2.

Conditional probability: Definition

- Conditional probability is the probability of an event A, given the occurrence of an other event B. Conditional probability is written P(A|B), and P(B)>0.
- When in a random experiment the event B is known to have occurred, the possible outcomes of the experiment are reduced to B, and hence the probability of the occurrence of A is changed from the unconditional probability into the conditional probability given B.

$$P(A|B) = \frac{P(A \cap B)}{P(B)}$$

- *General Multiplication rule: $P(A \cap B)=P(A|B)P(B)$.*

Conditional probability and Independency

- Two random events A and B are statistically independent if and only if
  $P(A \cap B)=P(A)*P(B)$
- Thus, if A and B are independent, then their joint probability can be expressed as a simple product of their individual probabilities.
- Equivalently, for two independent events A and B with non-zero probabilities,
- $P(A|B)=P(A)$ and
- $P(B|A)=P(B)$
- *In other words, if A and B are independent, then the conditional probability of A, given B is simply the individual probability of A alone; likewise, the probability of B given A is simply the probability of B alone*

Diagnostic study

- Events:
  - K: Person has a disese
  - T^+: positiv test result
- *$T^+|K$: Positive test result under the condition that person has the disease*
- $P(T^+|K) = \mathrm{P}(\mathrm{T}^+ \cap K)/P(K)$ /= Sensitivity /
  - Probability P($T^+ \cap$ K) „Person hat a disease *and a* positive test result" regarding P*(K), probability* „Person has a disease".

Measures of diagnostic test

- sensitivity
- specificity
- positive predictive value (PPV)
- negative predictive value (NPV)

Sensitivity

- The *sensitivity* $P(T^+|K)$ of a diagnostic test is the probability of a positive test result once the person has the disease :
- $P(T^+|K) = \mathrm{P}(\mathrm{T}^+ \cap K)/P(K)$
  - The number of ill persons with positive test results / The number of all persons who have the disease.

Specificity

- The *specificity* $P(T^- | \overline{K})$ of a diagnostic test is the probability of a negative test result once the person is healthy .
- $P(T^- | \overline{K}) = \mathrm{P}(\mathrm{T}^- \cap \overline{K})/P(\overline{K})$
  - The number of healthy persons with negative test results / The number of all healthy persons

Positive (PPV) and negative (NPV) predictive values

- Positive predictive value P(K|T^{+}) is a probability that someone does have the disease once the test has given a positive result.
  - PPV
    - The number of persons diagnosed as have that disease with poititive test results / The number of all positive test results.
- Negative predictive value P($\overline{K}$|T^{-}) is a probability that someone really does not have the disease once the test has given a negative result.
  - NPV
    - The number of healthy persons with negative test results / The number of all negative test results.

Aim of diagnostic tests

- Investigations often require classification of each individual studied according to the outcome of a disease status. These classification procedures will be called diagnostic tests.
- **The „goodness” of a diagnostisc tests**

Calculations of diagnostic tests

GOLD STANDARD

	Disease status		
	disease	helath	Total
Positive Test	a	b	a+b
Negative Test	c	d	c+d
Total	a+c	b+d	N

- **The four observed frequency**
- Sensitivity=a/(a+c) viz. $P(T^{+}|K) = \mathrm{P}(\mathrm{T}^{+} \cap K)/P(K)$
  - *Where sensitivity* $= P(T^{+}|K)$, $\mathrm{P}(\mathrm{T}^{+} \cap K) = a/N$ *and* $P(K)=(a+c)/N$
- Specificity=d/(b+d) viz. $P(T^{-}|\overline{K}) = \mathrm{P}(\mathrm{T}^{+} \cap \overline{K})/P(\overline{K})$
  - *Where specificity* $= P(T^{-}|\overline{K})$, $\mathrm{P}(\mathrm{T}^{-} \cap \overline{K}) = d/N$ *and* $P(\overline{K})=(b+d)/N$
- Positive predictive value of a test = a/(a+b)

Summary of calculations

- Sensitivity=$a/(a+c)$
- Specificity=$d/(b+d)$
- Positive predictive value of a test = $a/(a+b)$
- Negative predictive value of a test = $d/(c+d)$
- Validity =$(a+d)/(a+b+c+d)$ viz. $(a+d) / n$
- For false negative rate : $c/(a+c)$;
- For false positives rate: $b(b+d)$;

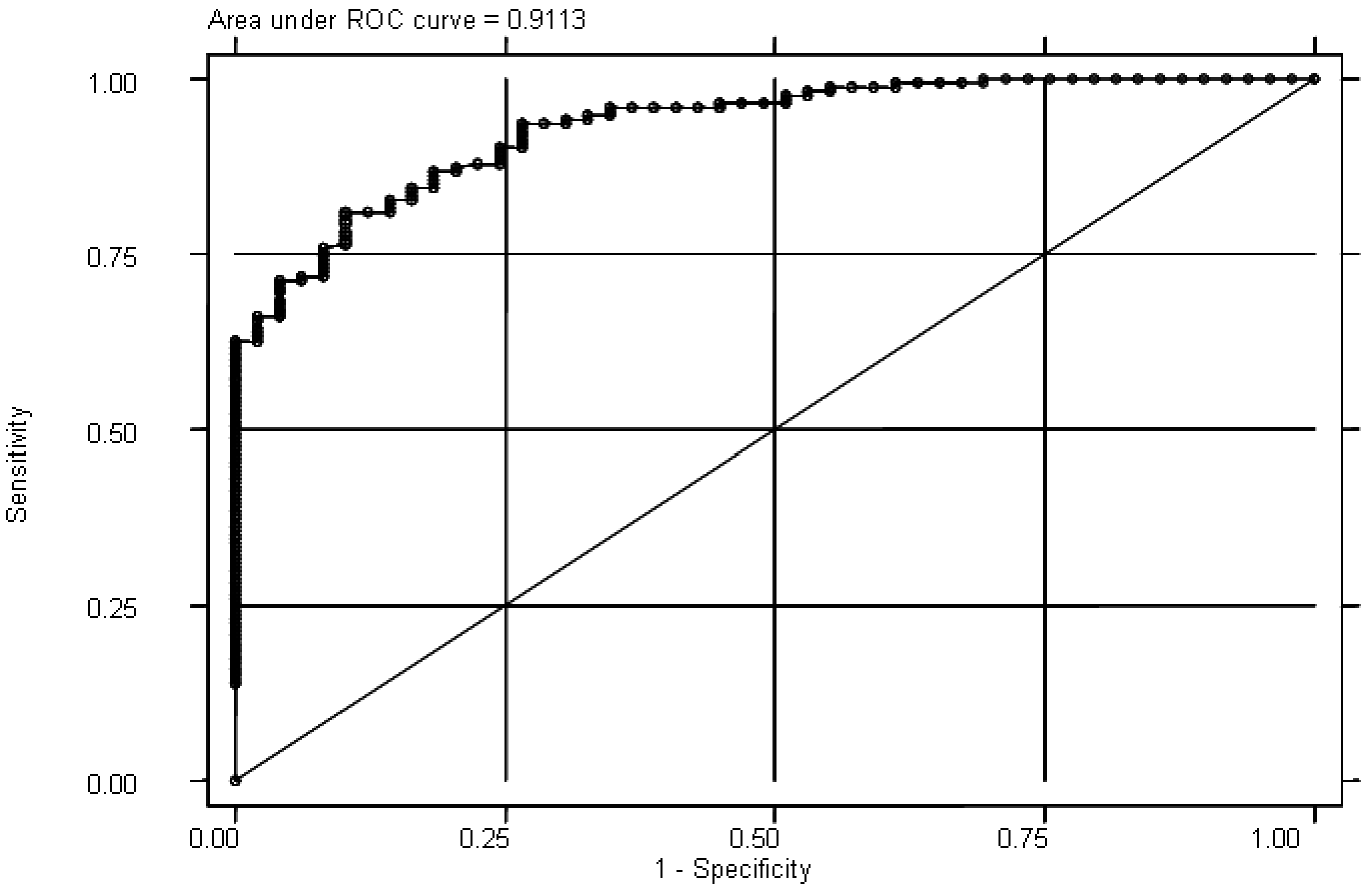
ROC curve

- ROC : Receiver Operating Characteristic
- Threshold (cut-points) value finding method
- A plot of Sensitivity vs 1−Specificity
- Area under the ROC curve

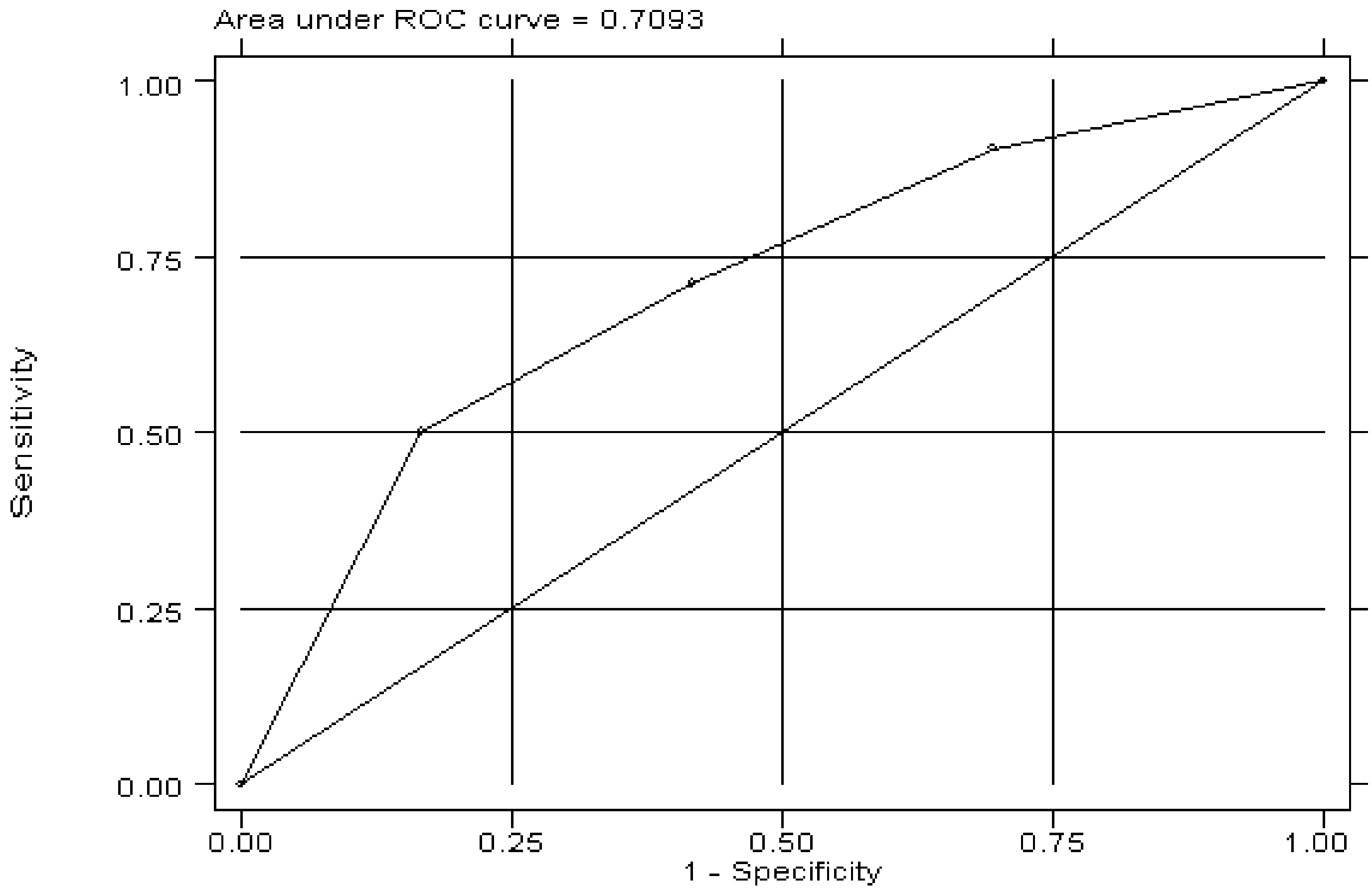
Classification based on the area under the ROC curve

$\text{ROC} = 0.5$	undiscrimination
$\text{ROC} < 0.7$	poor discrimination
$0.7 \leq \text{ROC} < 0.8$	average discrimination
$0.8 \leq \text{ROC} < 0.9$	good discrimination
$\text{ROC} \geq 0.9$	near perfect discrimination

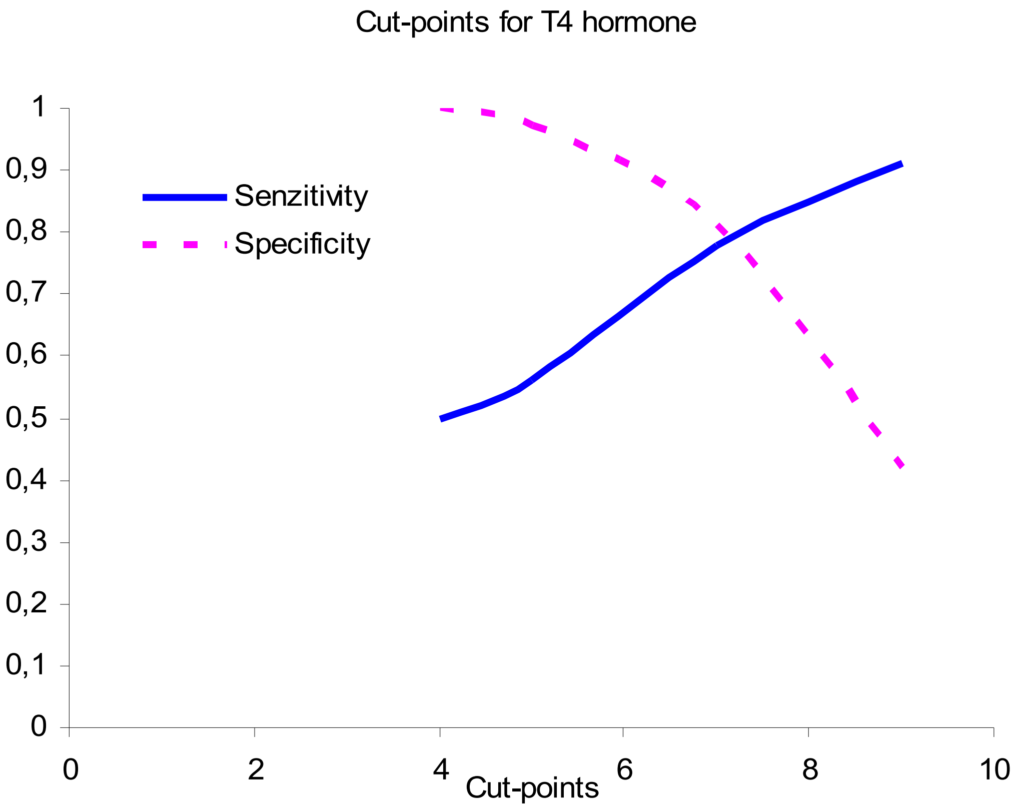
A near perfect discrimination



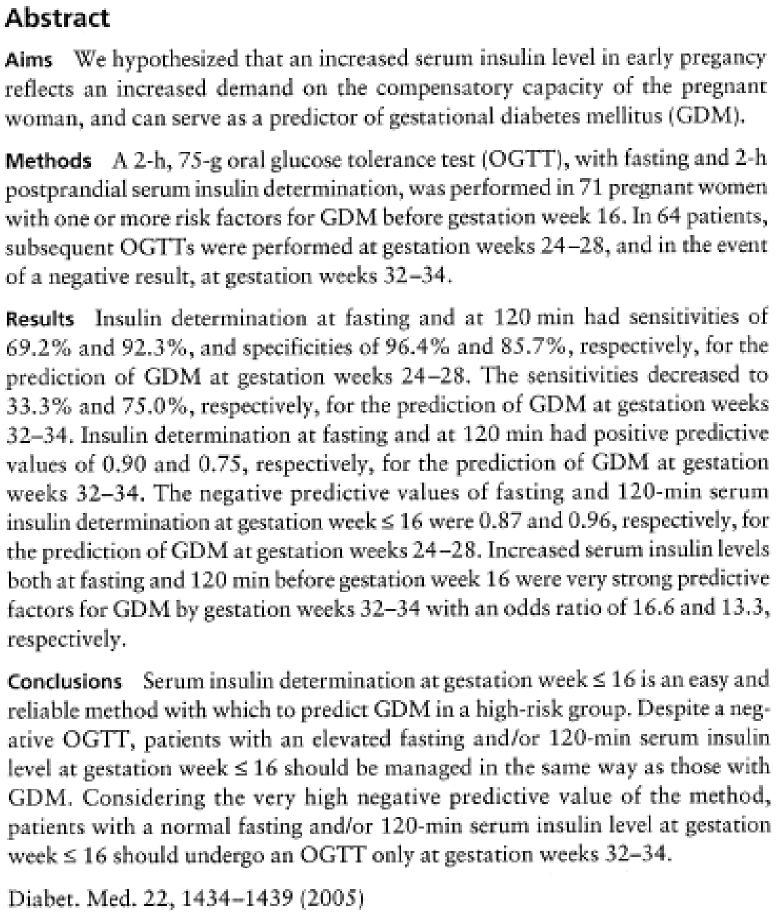
An average discrimination



Plot of sensitivity and specificity



Bito et al.



Abstract

Aims We hypothesized that an increased serum insulin level in early pregancy reflects an increased demand on the compensatory capacity of the pregnant woman, and can serve as a predictor of gestational diabetes mellitus (GDM).

Methods A 2-h, 75-g oral glucose tolerance test (OGTT), with fasting and 2-h postprandial serum insulin determination, was performed in 71 pregnant women with one or more risk factors for GDM before gestation week 16. In 64 patients, subsequent OGTTs were performed at gestation weeks 24–28, and in the event of a negative result, at gestation weeks 32–34.

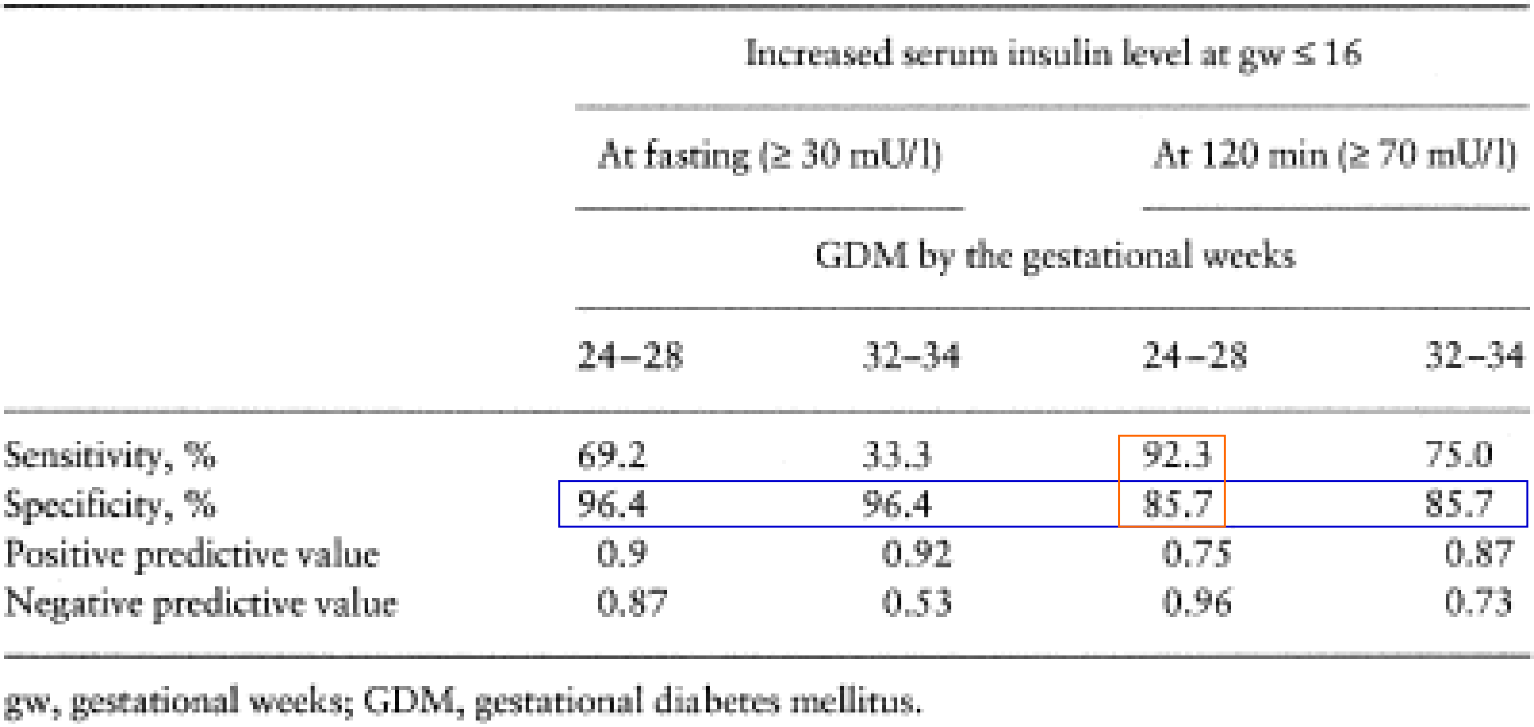
Results Insulin determination at fasting and at 120 min had sensitivities of 69.2% and 92.3%, and specificities of 96.4% and 85.7%, respectively, for the prediction of GDM at gestation weeks 24–28. The sensitivities decreased to 33.3% and 75.0%, respectively, for the prediction of GDM at gestation weeks 32–34. Insulin determination at fasting and at 120 min had positive predictive values of 0.90 and 0.75, respectively, for the prediction of GDM at gestation weeks 32–34. The negative predictive values of fasting and 120-min serum insulin determination at gestation week ≤ 16 were 0.87 and 0.96, respectively, for the prediction of GDM at gestation weeks 24–28. Increased serum insulin levels both at fasting and 120 min before gestation week 16 were very strong predictive factors for GDM by gestation weeks 32–34 with an odds ratio of 16.6 and 13.3, respectively.

Conclusions Serum insulin determination at gestation week ≤ 16 is an easy and reliable method with which to predict GDM in a high-risk group. Despite a negative OGTT, patients with an elevated fasting and/or 120-min serum insulin level at gestation week ≤ 16 should be managed in the same way as those with GDM. Considering the very high negative predictive value of the method, patients with a normal fasting and/or 120-min serum insulin level at gestation week ≤ 16 should undergo an OGTT only at gestation weeks 32–34.

Diabet. Med. 22, 1434–1439 (2005)

- Diab. Med.22:1434-1439 (2005)

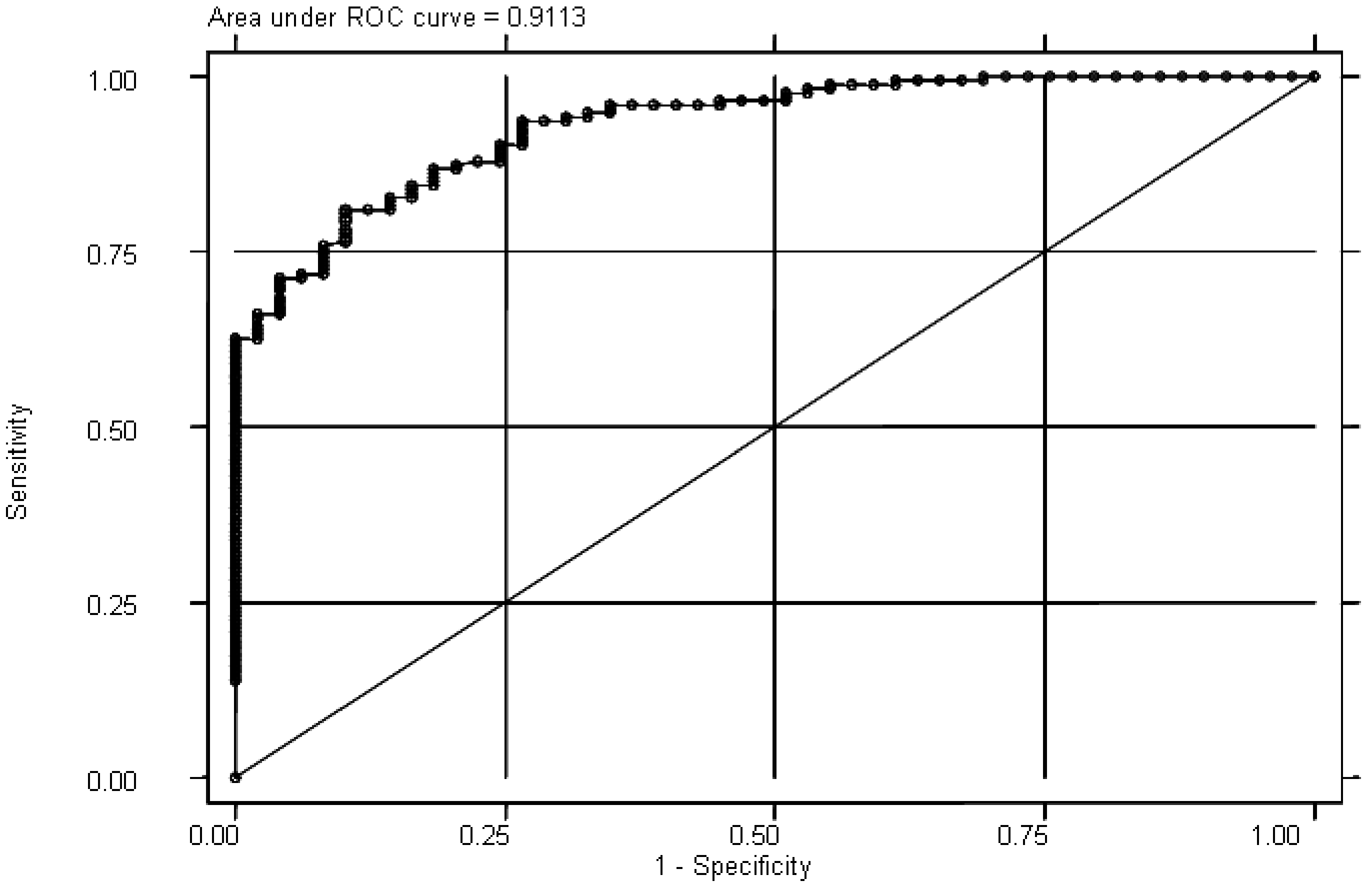
Results



	Increased serum insulin level at gw ≤ 16			
	At fasting (≥ 30 mU/l)		At 120 min (≥ 70 mU/l)	
	GDM by the gestational weeks			
	24–28	32–34	24–28	32–34
Sensitivity, %	69.2	33.3	92.3	75.0
Specificity, %	96.4	96.4	85.7	85.7
Positive predictive value	0.9	0.92	0.75	0.87
Negative predictive value	0.87	0.53	0.96	0.73

gw, gestational weeks; GDM, gestational diabetes mellitus.

A near perfect discrimination



Example

- Ditchburn and Ditchburn(1990) describe a number of tests for rapid diagnosis of urinary tract infections (UTIs). They took urine samples over 200 patients with symptoms of UTI which were sent to a hospital microbiology laboratory for a culture test. This test taken to be the standard against which all other tests are to be compared. All the other tests were more immediate, and thus suitable for general practice. We consider a dipstick test to detect pyuria. The results are given in the following table :

Data

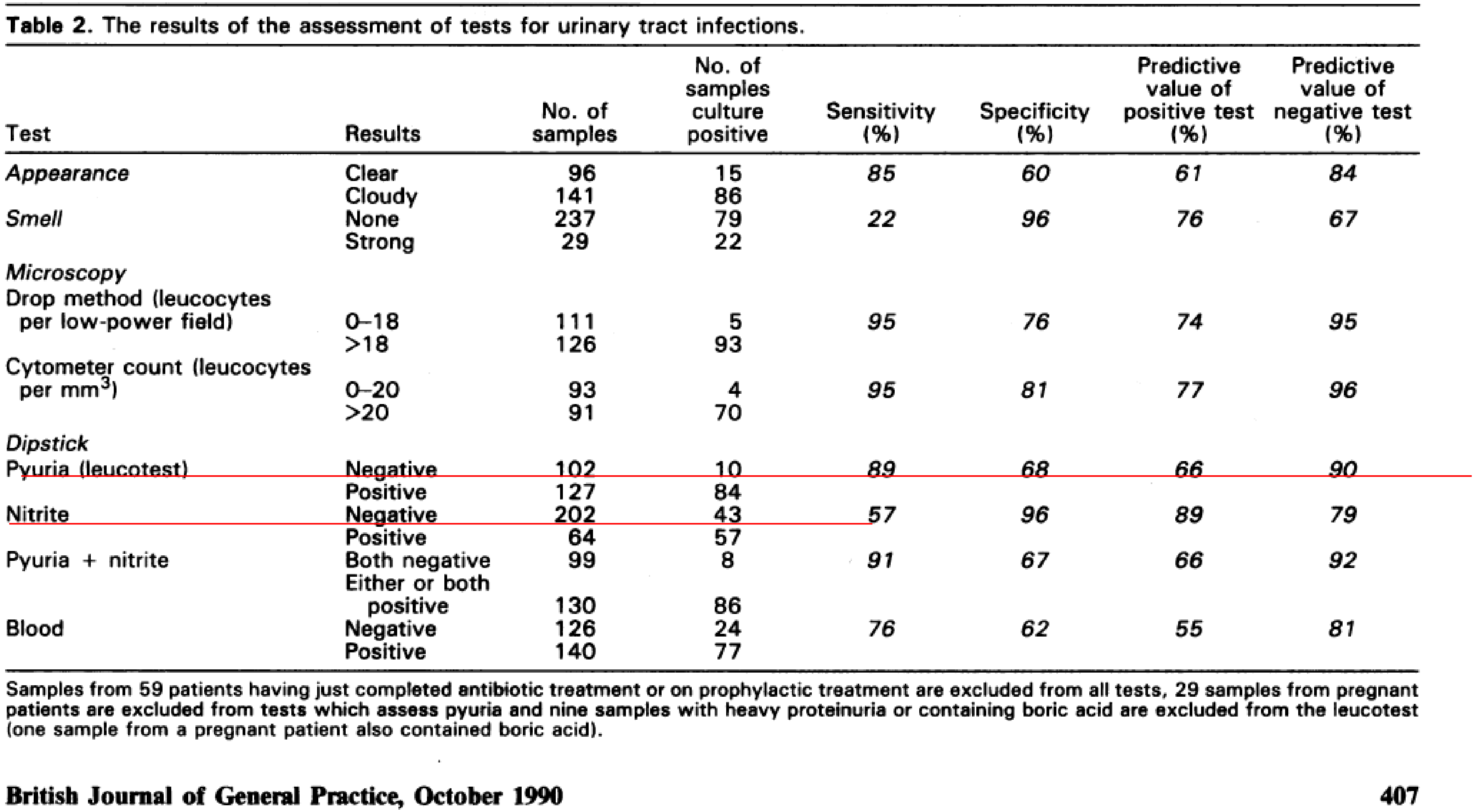


Table 2. The results of the assessment of tests for urinary tract infections.

Test	Results	No. of samples	No. of samples culture positive	Sensitivity (%)	Specificity (%)	Predictive value of positive test (%)	Predictive value of negative test (%)
Appearance	Clear	96	15	*85*	*60*	*61*	*84*
	Cloudy	141	86				
Smell	None	237	79	*22*	*96*	*76*	*67*
	Strong	29	22				
Microscopy							
Drop method (leucocytes per low-power field)	0–18	111	5	*95*	*76*	*74*	*95*
	>18	126	93				
Cytometer count (leucocytes per mm^3)	0–20	93	4	*95*	*81*	*77*	*96*
	>20	91	70				
Dipstick							
Pyuria (leucotest)	Negative	102	10	*89*	*68*	*66*	*90*
	Positive	127	84				
Nitrite	Negative	202	43	*57*	*96*	*89*	*79*
	Positive	64	57				
Pyuria + nitrite	Both negative	99	8	*91*	*67*	*66*	*92*
	Either or both positive	130	86				
Blood	Negative	126	24	*76*	*62*	*55*	*81*
	Positive	140	77				

Samples from 59 patients having just completed antibiotic treatment or on prophylactic treatment are excluded from all tests, 29 samples from pregnant patients are excluded from tests which assess pyuria and nine samples with heavy proteinuria or containing boric acid are excluded from the leucotest (one sample from a pregnant patient also contained boric acid).

British Journal of General Practice, October 1990 **407**

Observed frequencies

	Culture test		
Dipstick	Positive	Negative	Total
Positive	**84**	43	127
Negative	10	**92**	102
Total	94	135	229

- Sensitivity = a/(a+c)=84/94 = 0.894
- Specificity = d/(b+d)=92/135 = 0.681
- Positive predictive value = a/(a+b)=84/127 = 0.661
- Negative predictive value =d/(c+d) 92/102 = 0.902
- Validity = (84+92)/ 229 =0.77

Screening of rare disease

- A diagnostic test of screening has:
  - Sensitivity approximately 90%,
  - Specificity 99% (almost perfect).

Olympic Games

- Why two dopping tests are carried out?
    - 1st test has high specificity (99.9%) and NPV.
    - 2nd test has high sensitivity (99.9%) and PPV.

Example

- (HP Beck-Bonhold and HH Dubben:
- A visitor has just returned from an exotic country. At home, however, he has got information about an epidemic of a rare disease in that exotic country. He was examined by his GP and the result of the test to screen for that disease was positive.
- We know about the test and the disease :
- Sensitivity and specificity of the test are 0.99 and 0.98, respectively. And the probability of exposure to infection is 0.001 (1/1000).
- What is the probability of the person does have the disease once the test has given a positive result?

What is the probability of the person does have the disease once the test has given a positive result?

- 99%
- 98%
- 95%
- 50%
- 5%
- 2%
- 1%

From sensitivity

	Disease status		
Diagnostic test	Yes	No	Total
Positive	99		
Negative	1		
Total	100		

From probabilty of exposure to infection

	Disease status		
Diagnostic test	Yes	No	Total
Positive	99		
Negative	1		
Total	100	100 000	

According to specificity

	Disease status		
Diagnostic test	Yes	No	Total
Positive	99	2 000	
Negative	1	98 000	
Total	100	100 000	

	Disease status		
Diagnostic test	Yes	No	Total
Positive	99	2 000	2 099
Negative	1	98 000	98 001
Total	100	100 000	100 100

Predictive value of a positive test=99/2099=0.047

Cohen's Kappa

- Kappa measures the **agreement** between two test results.
  - Jacob Cohen (1923 – 1998) was a US statistician and psychologist.
  - He described kappa statistic in 1960.
- H_0: $\kappa=0$
- H_A: $\kappa\neq0$

Measuring agreements (observed frequencies)

	Test 1			
Test 2	Positive	Negative	Total	
Positive	**a**	b	Z_1=a+b	Z_1/N
Negative	c	**d**	Z_2=c+d	Z_2/N
Total	S_1=a+c	S_2=b+d	N	N
	S_1/N	S_2/N		

- Agreement in the diagonal.
- Probability of a positive and negative results of the Test I are S_1/N and S_2/N, respectively
- Probability of a positive and negative results of the Test II are : Z_1/N and Z_2/N, respectively
- Observed probability of agreement: p_{obs}=(a+d)/N

$$p_O = \frac{a+d}{N}$$

Expected frequencies

$$P(AB) = P(A)P(B) \Rightarrow \frac{E_{11}}{N} = \frac{S_1}{N}\frac{Z_1}{N}$$

	Test I	
	Positiv	Negativ
Positiv	**E11** $= \frac{S_1}{N}\frac{Z_1}{N}N$	E12
Negativ	E21	**E22** $= \frac{S_2}{N}\frac{Z_2}{N}N$

- Expected probability of agreement : $p_{\text{Expected}}=(E_{11}+E_{22})/N$

$$p_E = \frac{E_{11} + E_{22}}{N}$$

Cohen’s kappa

$$p_{observed} = \frac{a+d}{N} \qquad p_E = \frac{E_{11}+E_{22}}{N}$$

$$\kappa = \frac{p_{Observed} - p_{Expected}}{1 - p_{Expected}}$$

Standard error (SE) for kappa:

$$\overset{\wedge}{se}(\kappa) = \sqrt{\frac{1}{(1-p_E)^2 N}\left(p_E^2 + p_E - \sum_{i=1}^{l} \frac{S_i Z_i}{N}\{S_i + Z_i\} \right)}$$

The test statistic for kappa:

$$\left(\frac{\kappa}{\overset{\wedge}{se}(\kappa)} \right)^2$$

This follows a χ^2 with 1 df.

$\chi^2_{\text{table}(\alpha=0{,}05;\ FG=1)}$–value = 3.841 (=$1.96^2$)

Characteristics of kappa

- It takes the value 1 if the agreement is perfect and 0 if the amount of agreement is entirely attributable to chance.
- If $\kappa<0$ then the amount of agreement is less then would be expected by chance.
- If $\kappa>1$ then there is more than chance agreement.
- According to Fleiss:
  - Excellent agreement if $\kappa>0.75$
  - Good agreement if $0.4<\kappa<0.75$
  - Poor agreement if $\kappa<0.4$

Altman DG, Bland JM. Statistics Notes: Diagnostic tests : sensitivity and specificity *BMJ* 1994; 308 : 1552

- Relation between results of liver scan and correct diagnosis

Liver scan	Pathology		
	abnormal (+)	normal (-)	Total
abnormal (+)	231	32	263
normal(-)	27	54	81
Total	258	86	344

The expected freqencies

$$P(AB) = P(A)P(B) \Rightarrow \frac{E_{11}}{N} = \frac{S_1}{N}\frac{Z_1}{N}$$

- E_{11}=(263/344)*(258/344)*344=197.25
- E_{22}=(81/344)*(86/344)*344=20.25

Liver scan	Pathology		
	abnormal (+)	normal (-)	Total
abnormal (+)	**197.25**		263
normal(-)		**20.25**	81
Total	258	86	344

Cohen’s kappa

- The observed p_{Obs} and p_{Exp} values are 0.828 and 0.63, respectively . Cohen’s kappa (κ)=0.53.

$$p_{obs} = \frac{a + d}{N} = \frac{231 + 54}{344} = 0.828$$

$$p_E = \frac{E_{11} + E_{22}}{N} = \frac{197.25 + 20.25}{344} = 0.63$$

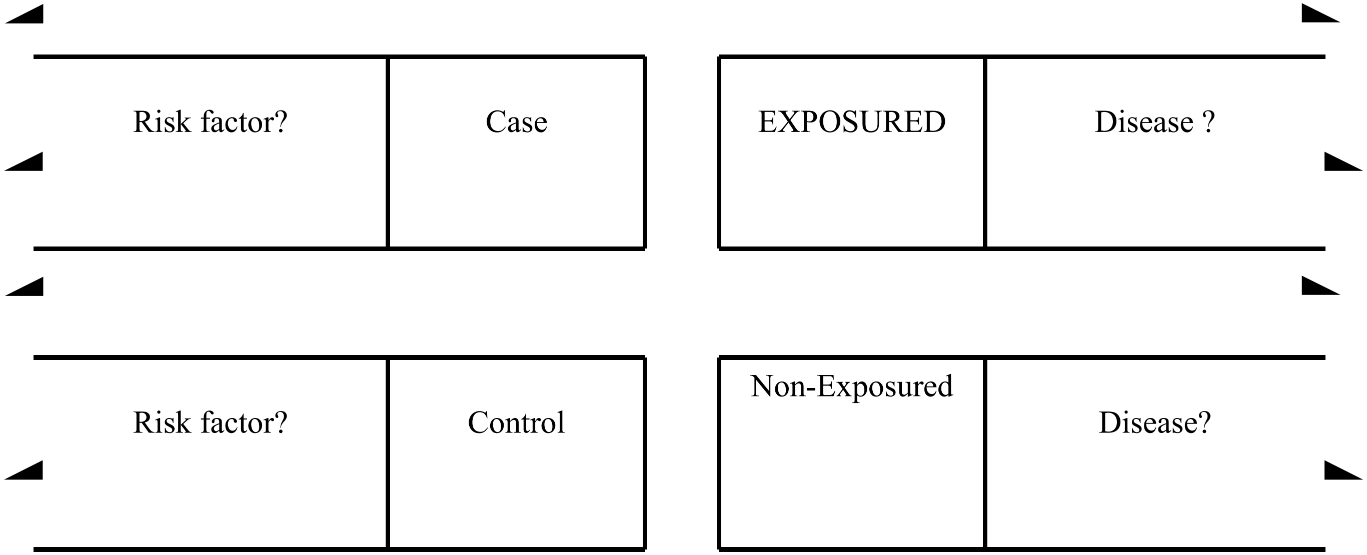
$$\kappa = \frac{p_{obs} - p_E}{1 - p_E} = \frac{0.828 - 0.632}{1 - 0.632} = 0.53$$

Decision

- Here $\kappa=0.53$
- As $0.4<\kappa\leq0.75$: good agreement

Other applications

Study types



Case-control

Cohort

Risk factor?

Case

EXPOSURED

Disease ?

Risk factor?

Control

Non-Exposured

Disease?

Retrospectively

PRESENT TIME

Prospectively

Prevalence and incidence

- **Prevalence** quantifies the proportion of individuals in a population who have a specific disease at a specific point of time.

$$\text{Pr evalence} = \frac{\text{number of existing cases of disease}}{\text{total population}} \qquad \text{at a given time point}$$

- In contrast with the prevalence, the incidence quantifies the number of new events or cases of disease that develop in a population of individuals at risk during a specified period of time.

$$\text{Incidence risk} = \frac{\text{number of new cases of disease during a given period of time}}{\text{number at risk of contracting the disease at the beginning of the period}}$$

- There are two specific types of incidence measures: **incidence risk** and **incidence rate**.
  - The incidence risk is the proportion of people who become diseased during a specified period of time, and is calculated as

Odds ratio

- It measures of association in case-control studies.
- H_0: OR=1
- H_A: OR≠1

$$OR = \frac{a/b}{c/d} = \frac{ad}{cb} \text{ and SE(OR)} = \sqrt{\left(\frac{1}{a}\right)+\left(\frac{1}{b}\right)+\left(\frac{1}{c}\right)+\left(\frac{1}{d}\right)}$$

- An alternative measure of incidence is the odds of disease to non-disease. This equals the total number of cases divided by those still at risk at the end of the study. Using the notation of previous Table , reproduced on next slide:

Odds ratio

	Disease		
	Yes	No	Total
Exposed	a	b	e=a+b
Non-exposed	c	d	f=c+d
Total	g=a+c	h=b+d	n=g+h

the odds of disease among the exposed is a/b and that among the unexposed is c/d.

Their ratio, called the odds ratio, is

$$OR = \frac{a/b}{c/d} = \frac{ad}{cb} \text{ and SE(OR)} = \sqrt{\left(\frac{1}{a}\right) + \left(\frac{1}{b}\right) + \left(\frac{1}{c}\right) + \left(\frac{1}{d}\right)}$$

Case-control studies

- In a case-control study, the sampling is carried out according to the disease rather than the exposure status.
- A group of individuals identified as having the disease, the cases, is compared with a group of individuals not having the disease, the controls, with respect to their prior exposure to the factor of interest.
- No information is obtained directly about the incidence in the exposed and non-exposed populations, and so the relative risk cannot be estimated; instead, the odds ratio is used as the measure of association.
- It can be shown, however, that for a rare disease the odds ratio is numerically equivalent to the relative risk.
- The 95% confidence interval for the odds ratio is calculated in the same way as that for relative risk:

$$95\%\ \mathrm{CI} = e^{\left(\ln(\mathrm{OR}) \pm 1.96\sqrt{\left(\frac{1}{a}\right)+\left(\frac{1}{b}\right)+\left(\frac{1}{c}\right)+\left(\frac{1}{d}\right)}\right)}, \text{ where } e = 2.718$$

Example

- The risk of HPV infection for smokers was measured in a study.
- H_0: OR=1
- H_A: OR≠1
- Calculate the odds ratio and 95% confidence interval using the data table

		HPV		
		Yes	No	Total
Smoking	Yes	**33**	**81**	114
	No	**58**	**225**	283
Total		91	306	397

$$OR = \frac{ad}{cb} = \frac{33*225}{81*58} = 1.58046$$

$$SE(OR) = \sqrt{\left(\frac{1}{33}\right)+\left(\frac{1}{225}\right)+\left(\frac{1}{81}\right)+\left(\frac{1}{58}\right)} = 0.25364$$

Results of Risk Estimate

$$OR = \frac{ad}{cb} = \frac{33*225}{81*58} = 1.58046$$

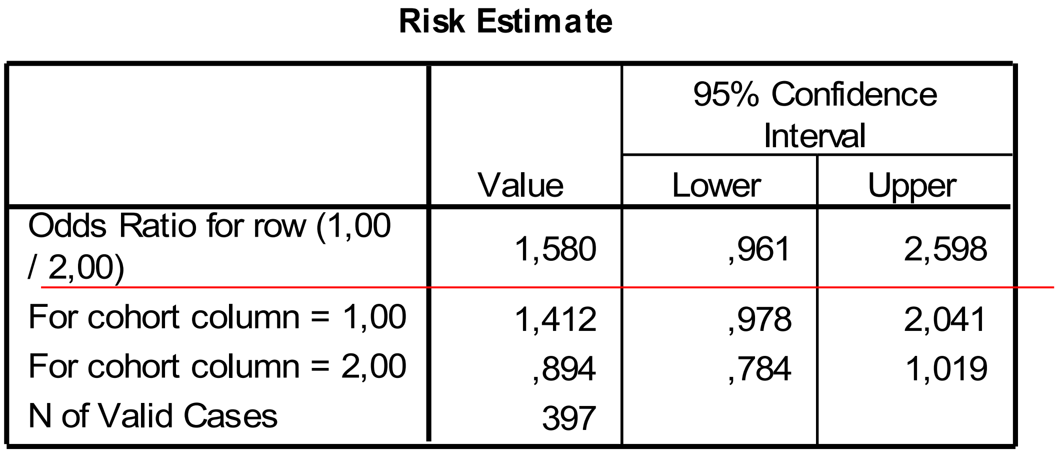
$$SE(OR) = \sqrt{\left(\frac{1}{33}\right)+\left(\frac{1}{225}\right)+\left(\frac{1}{81}\right)+\left(\frac{1}{58}\right)} = 0.25364$$

$$95\%\,\text{CI} = 2.718^{\left(\ln(1.5804)\pm 1.96\sqrt{\left(\frac{1}{33}\right)+\left(\frac{1}{225}\right)+\left(\frac{1}{81}\right)+\left(\frac{1}{58}\right)}\right)} = 0.961\ ;2.598$$

As OR=1.58 and its 95% confidence interval (95%CI) [0.96 – 2.59] contains 1, the H_0 is accepted.

SPSS results fo Risk Estimate

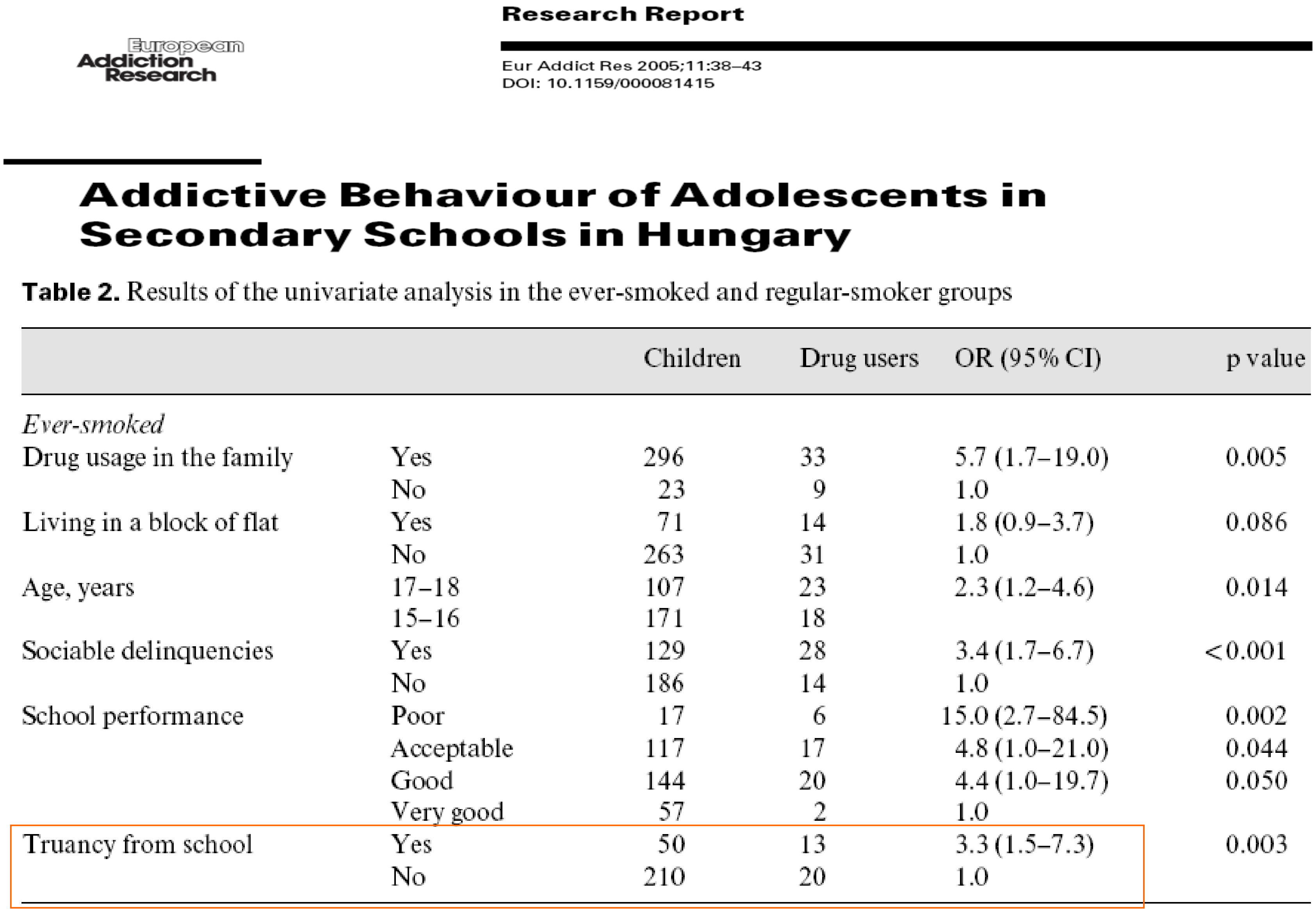
- As OR=1.58 and its 95% confidence interval (95%CI) [0.96 – 2.59] contains 1, the H_0 is accepted.



Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for row (1,00 / 2,00)	1,580	,961	2,598
For cohort column = 1,00	1,412	,978	2,041
For cohort column = 2,00	,894	,784	1,019
N of Valid Cases	397		

Example



European Addiction Research

Research Report

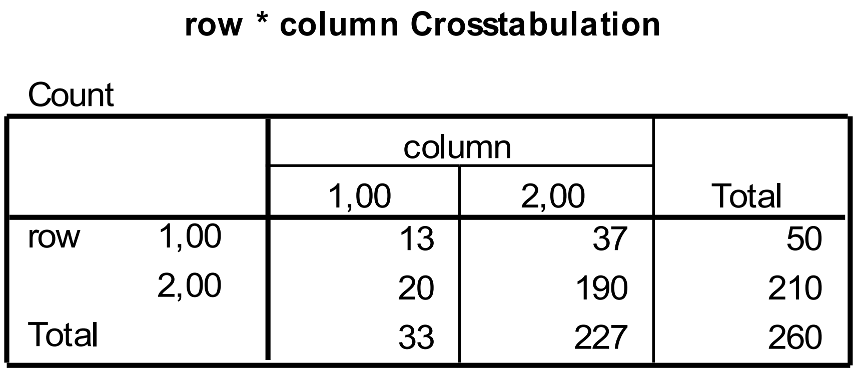
Eur Addict Res 2005;11:38–43
DOI: 10.1159/000081415

Addictive Behaviour of Adolescents in Secondary Schools in Hungary

Table 2. Results of the univariate analysis in the ever-smoked and regular-smoker groups

		Children	Drug users	OR (95% CI)	p value
Ever-smoked					
Drug usage in the family	Yes	296	33	5.7 (1.7–19.0)	0.005
	No	23	9	1.0	
Living in a block of flat	Yes	71	14	1.8 (0.9–3.7)	0.086
	No	263	31	1.0	
Age, years	17–18	107	23	2.3 (1.2–4.6)	0.014
	15–16	171	18		
Sociable delinquencies	Yes	129	28	3.4 (1.7–6.7)	<0.001
	No	186	14	1.0	
School performance	Poor	17	6	15.0 (2.7–84.5)	0.002
	Acceptable	117	17	4.8 (1.0–21.0)	0.044
	Good	144	20	4.4 (1.0–19.7)	0.050
	Very good	57	2	1.0	
Truancy from school	Yes	50	13	3.3 (1.5–7.3)	0.003
	No	210	20	1.0	

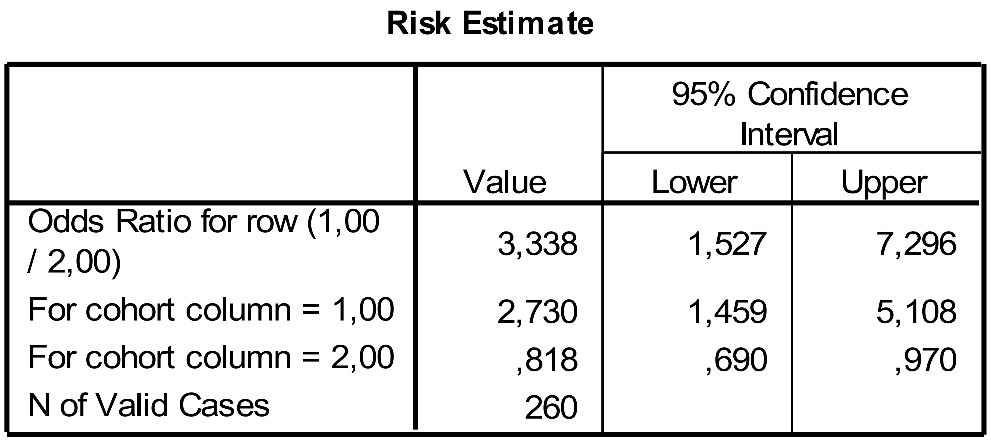
SPSS Results



row * column Crosstabulation

Count

		column		Total
		1,00	2,00	
row	1,00	13	37	50
	2,00	20	190	210
Total		33	227	260

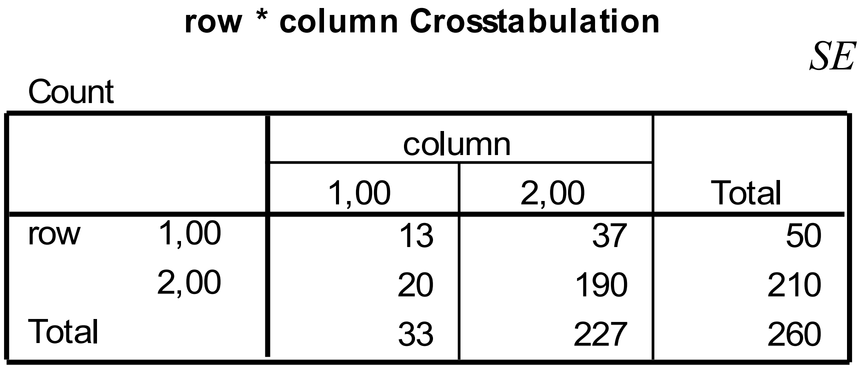


Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for row (1,00 / 2,00)	3,338	1,527	7,296
For cohort column = 1,00	2,730	1,459	5,108
For cohort column = 2,00	,818	,690	,970
N of Valid Cases	260		

Results

- H_0: OR=1
- H_A: OR≠1



row * column Crosstabulation

Count

		column		
		1,00	2,00	Total
row	1,00	13	37	50
	2,00	20	190	210
Total		33	227	260

$$SE(OR) = \sqrt{\left(\frac{1}{13}\right)+\left(\frac{1}{37}\right)+\left(\frac{1}{20}\right)+\left(\frac{1}{190}\right)} = 0.399$$

- OR=(13*190)/ (37*20)=3.337 ⇒ ln(OR)=1.205
- SE=0.399
- Lower bound =exp(1.205–1.96*0.399)=1.5269
- Upper bound =exp(1.205+1.96*0.399)=7.296
- As the 95% confidence interval (95%CI) [1.53 – 7.29] does not contain 1, thus H_A is accepted .

Mantel – Haenszel Odds ratio

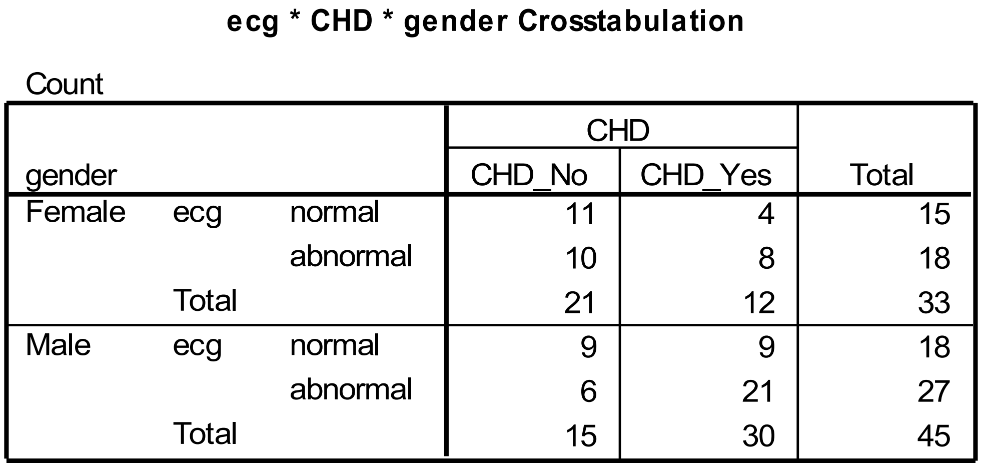
	Risk yes	Risk no	Total	
1st group	$\boldsymbol{n_{111}}$	$\boldsymbol{n_{112}}$	n_{11+}	$p_{11}= n_{111} / n_{11+}$
2nd group	$\boldsymbol{n_{121}}$	$\boldsymbol{n_{122}}$	n_{12+}	$p_{12}= n_{121} / n_{12+}$
Total	n_{1+1}	n_{1+2}	n_1	

	Risk yes	Risk no	Total	
1st group	$\boldsymbol{n_{211}}$	$\boldsymbol{n_{212}}$	n_{21+}	$p_{21}= n_{211} / n_{21+}$
2nd group	$\boldsymbol{n_{221}}$	$\boldsymbol{n_{222}}$	n_{22+}	$p_{22}= n_{221} / n_{22+}$
Total	n_{2+1}	n_{2+2}	n_2	

$$EH = \frac{\sum_{i=1}^{2} \frac{n_{i11} * n_{i22}}{n_i}}{\sum_{i=1}^{2} \frac{n_{i12} * n_{i21}}{n_i}}$$

Example

- In a study the risk of coronary heart disease was investigated using ECG diagnosis by gender.

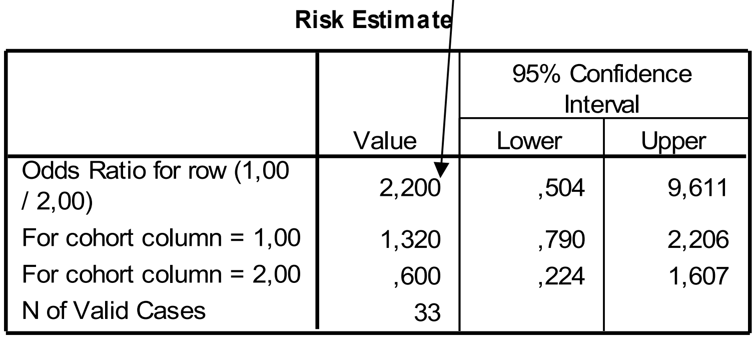


ecg * CHD * gender Crosstabulation

Count

gender			CHD		Total
			CHD_No	CHD_Yes	
Female	ecg	normal	11	4	15
		abnormal	10	8	18
	Total		21	12	33
Male	ecg	normal	9	9	18
		abnormal	6	21	27
	Total		15	30	45

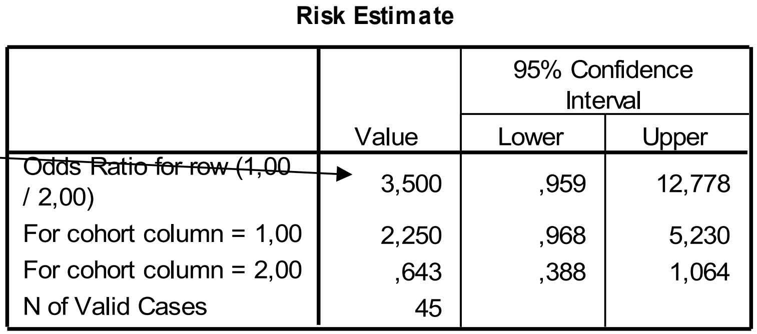
- Female OR=2.2



Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for row (1,00 / 2,00)	2,200	,504	9,611
For cohort column = 1,00	1,320	,790	2,206
For cohort column = 2,00	,600	,224	1,607
N of Valid Cases	33		

- Male OR=3.5



Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for row (1,00 / 2,00)	3,500	,959	12,778
For cohort column = 1,00	2,250	,968	5,230
For cohort column = 2,00	,643	,388	1,064
N of Valid Cases	45		

Results

ecg * CHD * gender Crosstabulation

Count

gender			CHD CHD_No	 CHD_Yes	Total
Female	ecg	normal	11	4	15
		abnormal	10	8	18
	Total		21	12	33
Male	ecg	normal	9	9	18
		abnormal	6	21	27
	Total		15	30	45

$$EH = \frac{\sum_{i=1}^{2} \frac{n_{i11} * n_{i22}}{n_i}}{\sum_{i=1}^{2} \frac{n_{i12} * n_{i21}}{n_i}} =$$

$$EH = \frac{\frac{11 \cdot 8}{33} + \frac{9 \cdot 21}{45}}{\frac{10 \cdot 4}{33} + \frac{9 \cdot 6}{45}} = \frac{\frac{88}{33} + \frac{189}{45}}{\frac{40}{33} + \frac{54}{45}} = 2.84673$$

Mantel-Haenszel Common Odds Ratio Estimate

Estimate			2,847
ln(Estimate)			1,046
Std. Error of ln(Estimate)			,496
Asymp. Sig. (2-sided)			,035
Asymp. 95% Confidence Interval	Common Odds Ratio	Lower Bound	1,077
		Upper Bound	7,528
	ln(Common Odds Ratio)	Lower Bound	,074
		Upper Bound	2,019

The Mantel-Haenszel common odds ratio estimate is asymptotically normally distributed under the common odds ratio of 1,000 assumption. So is the natural log of the estimate.

Incidence risk

- The incidence risk, then, provides an estimate of the probability, or risk, that an individual will develop a disease during a specified period of time. This assumes that the entire population has been followed for the specified time interval for the development of the outcome under investigation. However, there are often varying times of entering or leaving a study and the length of the follow-up is not the same for each individual. The incidence rate utilizes information on the follow-up time for each subjects, and is calculated as

$$\text{Incidence rate} = \frac{\text{number of new cases of disease during a given period of time}}{\text{total "person - time" of observation}}$$

  - (The denominator is the sum of each individual's time at risk)

Example

- In a study of oral contraceptive (OC) use and bacteriuria, a total of 2 390 women aged between 16 to 49 years were identified who were free from bacteriuria. Of these, 482 were OC users at the initial survey in 1993. At a second survey in 1996, 27 of the OC users had developed bacteriuria. Thus,
- Incidence risk=27 per 482, or 5.6 percent during this 3-year period

Example

- In a study on postmenopausal hormone use and the risk of coronary heart disease, 90 cases were diagnosed among 32 317 postmenopausal women during a total of
105 782.2 person-years of follow-up. Thus,
- Incidence rate=90 per 105 782.2 person-years, or 85.1 per 1 000 000 person-years

Issues in the calculation of measures of incidence

- Precise definition of the denominator is essential.
- The denominator should, in theory, include only those who are considered at risk of developing the disease, i.e. the total population from which new cases could arise.
- Consequently, those who currently have or have already had the disease under study, or those who cannot develop the disease for reasons such as age, immunizations or prior removal of an organ, should, in principal, be excluded from the denominator.

Measures of association in cohort studies

	Lung cancer			
	Yes	No	Total	Incidence rate
Smokers	39	29 961	30 000	1.30/1000/year
Non-smokers	6	59 994	60 000	0.10/1000/year
Total	45	89 555	90 000	

Relative risk

	Disease		
	Yes	No	Total
Exposed	a	b	e=a+b
Non-exposed	c	d	f=c+d
Total	g=a+c	h=b+d	n=g+h

$$RR = \frac{I_{\exp}}{I_{non\ \exp}} = \frac{a/e}{c/f}$$

Relative risk

- The further the relative risk is from 1, the stronger the association.
- Its statistical association can be tested by using a 2 x 2 χ2 – test
- Confidence interval for RR:

$$95\%\ \mathrm{CI} = \mathrm{RR}^{\left(1 \pm 1.96\sqrt{\chi^2}\right)}$$

- In the above example, $95\%\ \mathrm{CI} = 13.0^{\left(1 \pm 1.96\sqrt{55.5}\right)} = 6.7, 25.3$. The 95% confidence interval for the relative risk is therefore 6.7 to 25.3

Incidence rates (IR)

- Neuroblastoma is one of the most common solid tumour in children and the most common tumour in infants, accounting for about 9% of all cases of paediatric cancer and is a major contributor to childhood cancer mortality worldwide
- The incidence and distribution of the age and stage of neuroblastoma at diagnosis, and outcome in Hungary over a period of 11 years were investigated and compared with that reported for some Western European countries.

Age-specific and directly age-standardized (world population) incidence rates (per million) for neuroblastoma in Hungary (1988-1998) and in Austria (1987-1991)

		Hungary			**Austria**
Age-specific	IR	95%CI		IR	95%CI
< 1 year	60.9	(40.6-81.1)		65.8	(44.1-94.5)
1-4 years	25.5	(19.8-31.2)		17.0	(11.4-24.2)
5-9 years	4.2	(2.6-5.8)		3.1	(1.2-6.4)
10-14 years	1.7	(0.8-2.4)		1.3	(0.3-3.9)
Age-standardized	14.4	(12.6-16.2)		11.7	(9.0-14.5)