NICE National Institute for Health and Care Excellence

University of BRISTOL

MSR186

Methods to Incorporate Conditional Dependencies in Diagnostic Simulation Models

Alfredo Mariani[1], Hayley E Jones[2]

[1] National Institute for Health and Care Excellence, UK

[2] Population Health Sciences, Bristol Medical School, University of Bristol, UK

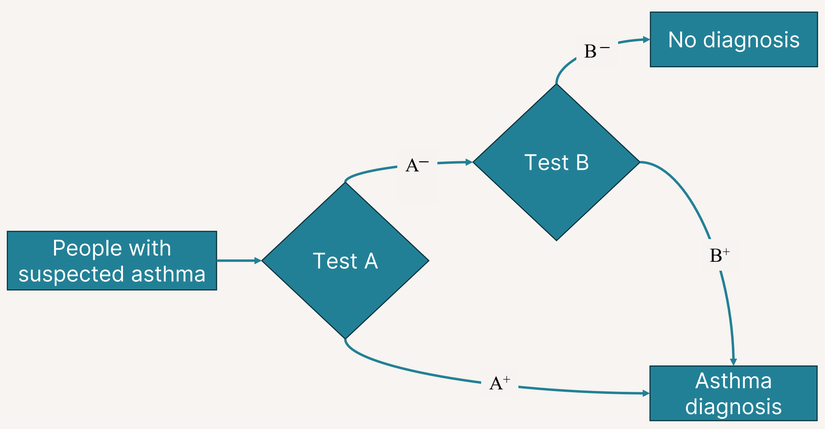
Background

Asthma is one of the most diagnosed diseases in adults and children. As there is no established "gold standard" test, a diagnosis is often reached through the use of multiple tests, administered in sequence. Some degree of conditional dependency in these tests (i.e. correlation between their results within disease state) is expected. This can arise due to tests measuring the same phenomenon or being affected by patients' characteristics. In this poster, we presented two methodologies to account for test correlation when estimating the sensitivity of four diagnostic strategies. These were employed to estimate the cost-effectiveness of several diagnostic strategies for the new BTS/SIGN/NICE joint guideline on the management of asthma.

Tests for asthma

As most diagnostic tests for asthma are highly specific but may miss some cases, the standard approach consists of administering a first test to all individuals, then re-testing those who were negative using a different test, to catch any missed cases (Figure 1).

Figure 1: two-step diagnostic sequence



There are two types of tests used for asthma:

1. Tests that measure inflammation or atopy such as FeNO, or skin prick tests (SPT)
2. Tests that measure lung function such as spirometry or bronchodilator reversibility (BDR) test

While the guideline model included 7 tests, in this poster we focus on the sensitivity of 4 for brevity in both adults and children. There is evidence of sensitivity differing across these two populations.

Table 1: Estimated sensitivity of four tests for asthma

Test	Measures	Sensitivity (adults)*	Sensitivity (children)**
FeNO	Inflammation or atopy	0.53 (0.41 – 0.64)	0.52 (0.39 – 0.64)
SPT	Inflammation or atopy	0.74 (0.63 – 0.83)	0.83 (0.72 – 0.83)
Spirometry	Lung function	0.37 (0.27 – 0.49)	0.15 (0.09 – 0.25)
BDR	Lung function	0.41 (0.31 – 0.53)	0.16 (0.1 – 0.26)

* RADicA[1]
** Manchester Asthma and Allergy Study[2] except for SPT from Drkulec et al. (2013)

Method 1: Using IPD

The sensitivity of a two-step strategy (Figure 1) is:

$$= Sens(A) + [1 - Sens(A)] \times Sens(B|A^{-})$$

where Sens(B|A⁻) is the sensitivity of Test B among people who were negative on Test A.

If Tests A and B are considered conditionally independent then we estimate:

$$Sens(B|A^{-}) = Sens(B)$$

This approach is "naïve" as it does not account for correlations between test results.

If Tests A and B are (positively) conditionally dependent, B is also more likely to produce an erroneous negative result, decreasing its sensitivity:

$$Sens(B|A^{-}) < Sens(B)$$

For adults, as we had IPD[1], we could estimate the sensitivity of test sequences directly.

We see (Table 2) that appropriately accounting for conditional dependence can significantly impact estimated sensitivity and even change the ranking of test strategies.

However, in many cases, IPD may not be available or may only be available for one population – such as adults – but not for others, like children.

Table 2: Sensitivity of diagnostic strategies in adults

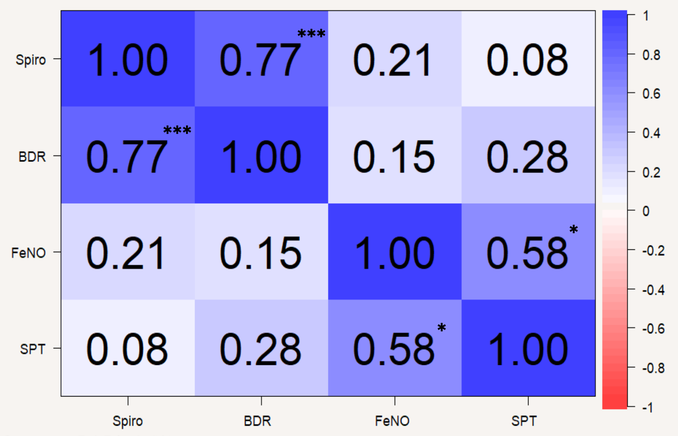
Test	Naïve estimates	Adjusted estimates
FeNO + BDR	0.72	0.70
FeNO + SPT	**0.88**	0.80
Spiro + BDR	0.63	0.50
Spiro + SPT	0.84	**0.83**

Method 2: multivariate probit

As IPD were not available for children, but sensitivity varied across populations (Table 1), we "borrowed" the correlation structure from the adult population.

Figure 2 illustrates estimated polychoric correlations from the adult population, showing a particularly high correlation between tests measuring the same phenomena.

Figure 2: Bootstrapped polychoric correlation plot



Source: RADicA [1]
*** ρ < .001, ** ρ < 0.01, * ρ < 0.05

We simulated from a multivariate probit model, with means based on Table 1 (children) and correlations based on Figure 2, to estimate the sensitivity of test sequences in children.

"Naïve" and adjusted sensitivities are presented in Table 3.

Table 3: Sensitivity of diagnostic strategies in children

Test	Naïve estimates	Adjusted estimates
FeNO + BDR	0.60	0.58
FeNO + SPT	**0.92**	**0.86**
Spiro + BDR	0.29	0.21
Spiro + SPT	0.86	**0.85**

Conclusions

When modelling cost-effectiveness of diagnostic strategies with multiple tests, failing to account for conditional dependencies can result in biased conclusions. Accounting for such dependence is straightforward if IPD are available. Where IPD are not available for the population of interest, we demonstrated a multivariate probit approach to "borrow" correlation structure from another population.

1. Simpson AJ, Drake S, Healy L, et al. (2024) Asthma diagnosis: a comparison of established diagnostic guidelines in adults with respiratory symptoms EClinicalMedicine 76.

2. Murray C, Foden P, Lowe L, et al. (2017) Diagnosis of asthma in symptomatic children based on measures of lung function: an analysis of data from a population-based birth cohort study The Lancet Child & adolescent health 1 (2): 114-123.

Alfredo Mariani
Health Economics Advisor
National Institute for Health and Care Excellence
Email: alfredo.mariani@nice.org.uk
Telephone: 020 8171 7002

nice.org.uk