Case-control studies: sources of bias

Researchers explored the association between maternal intake of folic acid supplements, multivitamins, and dietary folates in the prevention of cleft lip (with or without cleft palate) in the mothers' babies. A population based case-control study was performed. All babies with cleft lip referred for corrective surgery in Norway between 1996 and 2001 were identified. For each case—a baby with a cleft lip—a maximum of two live births without facial clefts were randomly selected from the Norwegian medical birth registry for 1996 to 2001 to serve as controls. Controls were matched to each case by date of birth to within six weeks of delivery.

The mothers of all cases and controls were invited to take part in the study. If women agreed, they completed questionnaires several months after delivery, providing demographic characteristics, reproductive history, and details about smoking, alcohol and drug consumption, and other exposures during early pregnancy. Women were also asked to report whether they took folic acid supplements and, if so, the dosage consumed for each of the six months preceding pregnancy and each of the first three months of pregnancy. Similar information was also provided about multivitamins. Women were asked to recall their diet during the first three months of pregnancy by using a food frequency questionnaire so that dietary folates could be estimated.

The researchers reported that folic acid supplements in early pregnancy reduced the risk of isolated cleft lip (with or without cleft palate) by about a third. Other vitamins and dietary factors may also have provided additional benefit.

Which of the following types of bias, if any, may the above study have been prone to?

- a) Allocation bias
- b) Selection bias
- c) Recall bias
- d) Confounding

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Persistent fever and rash in a young child

A 22 month old white Australian boy presented to his general practitioner with irritability, red eyes, and a two day history of high fever (highest at 41°C) that did not respond to paracetamol and ibuprofen. He had no history of cough, coryza, or rash. His medical history was unremarkable, and immunisations were up to date. On examination, he had bilateral non-exudative conjunctival injection and was diagnosed with a non-specific febrile illness with associated conjunctivitis.

His family then took him on a planned family holiday to Thailand where his conjunctivitis improved, but the fevers continued unabated. In addition to the fevers, his parents noted a mild nappy rash. On day 8 of the illness, his parents took him to a local clinic after a couple of episodes of diarrhoea. He was diagnosed with gastroenteritis. Later that day he became more unwell with increasing irritability and a progressive rash, so his parents took him to hospital. He was dehydrated and lethargic, and physical examination showed cervical lymphadenopathy, fissured lips, and an injected pharynx. His hands and feet were oedematus, and his legs were covered in a pink maculopapular rash. Blood tests showed leucocytosis and increased acute phase reactants, but other haematological markers were normal. A chest radiograph was normal. He was admitted with presumed bacterial sepsis and started on broad spectrum intravenous antibiotics. However, after two days of antibiotics, his symptoms did not improve.

1. What is the most likely diagnosis in this case?
2. How is this condition diagnosed, and what further investigations are needed for a definitive diagnosis?
3. What is the treatment for this condition?
4. What are the cardiovascular complications of this condition?

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