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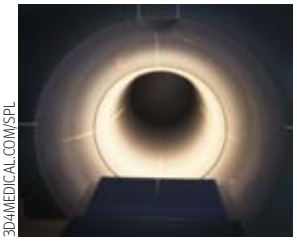
RESEARCH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THIS WEEK'S RESEARCH QUESTIONS

10 000 step guide to health

Only about a third of men and women in England aged 45-54 meet physical activity recommendations; no wonder that a quarter of people in this group are obese (http://bit.ly/dL90Kl). However, researchers in Australia have suggested that walking 10 000 steps a day—about five miles—might help middle aged people keep their weight down and reduce the risk of type 2 diabetes, a common complication of obesity (p 216).

The researchers fitted 592 Tasmanians with pedometers and measured how many steps they took over two days, then did the same thing again five years later. Alas daily step count decreased between these two time points for 65% of participants. However, those who did manage to increase their step count had a lower body mass index, lower waist to hip ratio, and greater insulin sensitivity. The authors estimate that a sedentary person who increases their physical activity so they hit the 10 000 steps a day target would increase their insulin sensitivity threefold.

The 10 000 step concept isn't entirely new—*BBC News* tested out its feasibility in 2004 (http://bbc.in/eze8Cb) and NHS Choices already recommends this approach (http://bit.ly/gHWbTG). What is new in this study is the effect regular walking can have on the risk of diabetes.

Does white matter matter in headache?

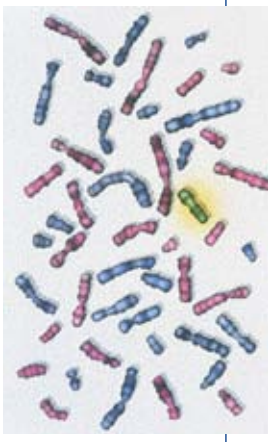
Migraine has been associated with an increased prevalence of white matter hyperintensities on brain magnetic resonance imaging. But what about other types of headache?

Tobias Kurth and colleagues have found an association between any history of severe headache, not just migraine, and increasing volume of white matter hyperintensities (p 215). Tension-type headaches in particular were implicated. However, migraine with aura was the only type of headache strongly associated with brain infarcts.

This study looked at a cross section of 780 elderly men and women from Nantes, France, 163 of whom reported a history of severe headache and 116 had migraine. There was no evidence that migraine or other severe headaches were associated with cognitive impairment, irrespective of the presence of structural brain lesions.

A meta-analysis published by the *BMJ* last year found that white matter hyperintensities predict an increased risk of stroke, dementia, and death (*BMJ* 2010;341:c3666). Kurth and colleagues suggest that further research is needed to determine whether preventive strategies should be tested to avoid these outcomes in people with headache.

Down's syndrome


CHRIS BJORNBERG/SPL

Current techniques for prenatal diagnosis of trisomy 21, which causes most cases of Down's syndrome, are invasive and associated with a small risk of miscarriage. Rossa Chiu and colleagues have looked into whether measuring the amount of fetal chromosome 21 in the blood of pregnant women is a suitable alternative (p 217).

The authors tested 2-plex and 8-plex massively parallel sequencing of DNA molecules in plasma from 753 women to determine the proportion of fetal DNA molecules that originated from chromosome 21. Cases where this proportion was above a certain threshold were classed as having a trisomy 21 fetus. When the findings were validated against full karyotyping of prospectively collected or archived samples, the researchers found that the 2-plex protocol detected trisomy 21 fetuses with 100% sensitivity and 97.9% specificity. This approach might be used to rule out trisomy 21 among high risk pregnancies, reducing the number of cases that require amniocentesis or chorionic villus sampling.

The *BMJ* prioritises research that will help doctors to make better decisions, and by "doctors" we mean those working in research and policy as well as in clinical practice and public health. So, although this rather specialised study's results may take years to alter practice (http://bbc.in/hPNNQ5), we published it for its importance to researchers and to policy makers.

LATEST RESEARCH: For this and other new research articles see www.bmj.com/research

Strengths and weaknesses of hospital standardised mortality ratios
Alex Bottle and colleagues from the Dr Foster Unit at Imperial College, London, give a clear and detailed account of how their unit derives the hospital standardised mortality ratios (HSMRs) that the NHS in England uses to judge the performance of hospital trusts (doi:10.1136/bmj.c7116). They explain the complexities and potential problems of the data, coding, case mix, and other issues that make critics worry about the use of HSMRs, and include a case study from Mid Staffordshire NHS Trust to illustrate how changes in HSMRs over time may be interpreted.

CHRISTOPHER FURLONG/SPL

CME

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Use of weaning protocols for reducing duration of mechanical ventilation in critically ill adult patients: Cochrane systematic review and meta-analysis

Bronagh Blackwood,[1] Fiona Alderdice,[1] Karen Burns,[2] Chris Cardwell,[3] Gavin Lavery,[4] Peter O'Halloran[1]

[1]Nursing and Midwifery Research Unit, Queen's University Belfast, Belfast, BT9 5BN, Northern Ireland
[2]St Michael's Hospital, Interdepartmental Division of Critical Care Medicine, Toronto, Ontario, Canada
[3]Centre for Public Health, Queen's University Belfast, Belfast
[4]Belfast Health and Social Care Trust, Royal Victoria Hospital, Belfast, Belfast

Correspondence to: B Blackwood
b.blackwood@qub.ac.uk

Cite this as: *BMJ* 2011;342:c7237
doi: 10.1136/bmj.c7237

This is a summary of a paper that was published on bmj.com as *BMJ* 2011;342:c7237

STUDY QUESTION

What are the effects of weaning protocols on the total duration of mechanical ventilation?

SUMMARY ANSWER

Compared with usual care, weaning protocols are associated with a 25% reduction in the (geometric) mean duration of mechanical ventilation, but results vary markedly between studies (I^2=76%).

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

As prolonged mechanical ventilation is associated with adverse outcomes for patients, strategies that reduce the duration of mechanical ventilation are worthy of consideration. The review showed that weaning protocols are associated with a reduced duration of mechanical ventilation, though the heterogeneity of included trials and the fact that most were conducted in the United States urges caution in generalising from the findings.

Selection criteria for studies

We searched the Cochrane Central Register of Controlled Trials, Medline, Embase, CINAHL, LILACS, ISI Web of Science, ISI Conference Proceedings, Cambridge Scientific Abstracts, and reference lists of articles. There were no language restrictions. We included randomised and quasi-randomised controlled trials of use of weaning protocols versus weaning without protocols in critically ill adults on mechanical ventilation.

Primary outcome

The total duration of mechanical ventilation.

Main results and role of chance

The review included 11 trials (1971 patients). The total duration of mechanical ventilation geometric mean in the weaning protocol group was on average reduced by 25% compared with the usual care group (P=0.006); weaning duration was reduced by 78% (P=0.009); and length of stay in intensive care by 10% (P=0.02).

Bias, confounding, and other reasons for caution

There was significant heterogeneity among studies for total duration of mechanical ventilation (I^2=76%, P<0.01) and weaning duration (I^2=97%, P<0.01). Ventilator weaning is a complex process, and it is not easy to isolate the reasons for heterogeneity. Discordance in results among studies might be caused by contextual factors (populations of patients and usual practice) or intervention factors. Thus, in settings where objective criteria and guided approaches are already incorporated into standard weaning practice, further beneficial effects of weaning protocols on these outcomes might not be realised.

EFFECT OF WEANING PROTOCOLS ON OUTCOMES IN CRITICALLY ILL ADULTS ON MECHANICAL VENTILATION

Outcome	No of trials	No of patients	% reduction in geometric mean in protocol group *v* usual care (95% CI)*	Heterogeneity I^2 (P value)
Total duration of mechanical ventilation (hours)	10	1873	25% (9% to 39%)	76% (0.006)
Duration of weaning (hours)	6	834	78% (31% to 93%)	97% (<0.001)
Length of stay in intensive care (days)	8	1256	10% (2% to 19%)	0% (0.45)

*From random effects meta-analysis model.

Study funding/potential competing interests

The review was funded through a Cochrane Fellowship Award for BB from the Research and Development Office, Northern Ireland, and the Health Research Board, Ireland.

What types of article does the *BMJ* consider?

We are delighted to receive articles for publication—from doctors and others—on the clinical, scientific, social, political, and economic factors affecting health. We give priority to articles that will help doctors to make better decisions. Please see our advice to authors at http://resources.bmj.com/bmj/authors, and if you would like to submit an article do so via our online editorial office at http://submit.bmj.com.

All original research articles are submitted, although we may invite submission (without promising acceptance) if we come across research being presented at conferences, if we see it in abstract form, or if the authors make an inquiry about the suitability of their work before submission.

We are also pleased to consider submitted articles for sections which carry a mix of commissioned and submitted articles—editorials, analysis, clinical review, practice, fillers, and Career Focus. Please follow the specific advice on each of these article types (see http://resources.bmj.com/bmj/authors/types-of-article) before submitting your article. Some types of article—news, features, observations, head to head, views and reviews—are commissioned by the editors.

Headache, migraine, and structural brain lesions and function: population based Epidemiology of Vascular Ageing-MRI study

Tobias Kurth,[1 2 3] Shajahal Mohamed,[1] Pauline Maillard,[4] Yi-Cheng Zhu,[1 2 5 6] Hugues Chabriat,[5 7] Bernard Mazoyer,[4 8 9 10] Marie-Germaine Bousser,[5 7] Carole Dufouil,[1 2] Christophe Tzourio[1 2 5]

[1]INSERM Unit 708—Neuroepidemiology, Paris, France
[2]UPMC Université Paris 06, UMR_S708, Paris, France
[3]Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA
[4]CNRS-CEA UMR 6194 Groupe d'Imagerie Neurofonctionnelle, Caen, France
[5]Service de Neurologie, Groupe Hospitalier Lariboisière-Fernand-Widal, Assistance Publique Hôpitaux de Paris, Paris, France
[6]Department of Neurology, Peking Union Medical College Hospital, Beijing, China
[7]Université Paris Denis Diderot, Paris, France
[8]Université de Caen Basse-Normande, Caen, France
[9]Centre Hospitalier et Universitaire de Caen, Caen, France
[10]Institut Universitaire de France, Paris, France

Correspondence to: T Kurth, INSERM Unit 708—Neuroepidemiology, Hôpital de la Pitié-Salpêtrière, 47 boulevard de l'Hôpital, 75651, Paris, Cedex 13, France tobias.kurth@upmc.fr

Cite this as: *BMJ* 2011;342:c7357
doi: 10.1136/bmj.c7357

This is a summary of a paper that was published on bmj.com as *BMJ* 2011;342:c7357

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Watch a video about the latest research on migraine at bmj.com/video

STUDY QUESTION What is the association between overall and specific headaches and volume of white matter hyperintensities on magnetic resonance imaging of the brain, brain infarcts, and cognition?

SUMMARY ANSWER In this population based study, any history of severe headache was associated with an increased volume of white matter hyperintensities. Migraine with aura was the only headache type associated with brain infarcts. Evidence that headache of any type by itself or in combination with brain lesions was associated with cognitive impairment was lacking.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Migraine has been associated with an increased prevalence of white matter hyperintensities as well as with clinical and subclinical brain infarction. Any history of severe headache, not just migraine, is associated with white matter hyperintensities, brain infarcts are limited to the subgroup of patients who have migraine with aura, and we found no evidence that migraine or other severe headaches were associated with cognitive impairment, irrespective of the presence of structural brain lesions.

Participants and setting
Our study population comprised 780 participants of the Epidemiology of Vascular Ageing study (mean age 69, 58.5% women), Nantes, France with detailed headache assessment and available brain scans.

Design
Population based, cross sectional study.

Primary outcome(s)
We evaluated the volume of white matter hyperintensities using fully automated brain magnetic resonance imaging processing, and classified infarcts by visual reading. Cognitive function was assessed by a battery of tests, including the mini-mental state examination.

Main results and the role of chance
In total, 163 (20.9%) participants reported a history of severe headache and 116 had migraine, of whom 17 (14.7%) reported aura symptoms. We found an association between any history of severe headache and increasing volume of white matter hyperintensities. The adjusted odds ratio of being in the highest third for total volume of white matter hyperintensities was 2.0 (95% confidence interval 1.3 to 3.1, P for trend 0.002) for participants with any severe headache when compared with participants without severe headache being in the lowest third. The association pattern was similar for all headache types. Migraine with aura was the only headache type strongly associated with volume of deep white matter hyperintensities (highest third odds ratio 12.4, 1.6 to 99.4, P for trend 0.005) and with brain infarcts (3.4, 1.2 to 9.3). The location of infarcts was predominantly outside the cerebellum and brain stem. Evidence was lacking for cognitive impairment with any headache type with or without brain lesions.

Bias, confounding, and other reasons for caution
Subgroups comprised a relatively small number of participants, which should particularly caution the interpretation of the results for migraine with aura. Information on headaches may not have been recalled adequately in this older population. Residual and unmeasurable confounding is possible because our study was observational.

Generalisability to other populations
Participants were of higher socioeconomic status and somewhat healthier than their peer group, which may limit generalisability to other populations.

Study funding/potential competing interests
The Epidemiology of Vascular Ageing study was carried out under an agreement between INSERM (Institut National de la Santé et de la Recherche Médicale); Merck, Sharp, and Dohme—Chibret Laboratories (West Point, PA); and EISAI (Paris, France). This study was supported by a chair of excellence grant of the French National Research Agency (ANR, Agence Nationale de la Recherche) to TK. The sponsors were not involved in the design, data collection, analysis, or interpretation of the study nor were they involved in writing the manuscript.

ASSOCIATION BETWEEN HEADACHE HISTORY AND TOTAL VOLUME OF WHITE MATTER HYPERINTENSITIES (WMH) IN EPIDEMIOLOGY OF VASCULAR AGEING STUDY (N=780)

	No history of severe headache (n=617)	Migraine headache (n=116)		Non-migraine headache (n=47)	
Total WMH volume by thirds	No (%)	No (%)	Multiple adjusted* odds ratio (95% CI)	No (%)	Multiple adjusted* odds ratio (95% CI)
Lowest third	215 (34.8)	35 (30.2)	1.0	10 (21.3)	1.0
Middle third	211 (34.2)	34 (29.3)	1.0 (0.6 to 1.6)	15 (31.9)	1.6 (0.7 to 3.6)
Highest third	191 (31.0)	47 (40.5)	1.8 (1.0 to 2.9)	22 (46.8)	2.7 (1.2 to 5.9)
P for trend†	—	—	0.03	—	0.01

Odds ratios calculated by using multinomial logistic regression model with participants who had no history of severe headache and who were in lowest third for WMH volume as reference group. WMH volume was standardised to total white matter volume. Percentages may not add up to 100% owing to rounding.
*Adjusted for age, sex, history of hypertension, smoking, body mass index, total cholesterol level, alcohol consumption, and family history of severe headache.
†P for trend across mean values of the WMH thirds calculated by using logistic regression model contrasting specific headache group to participants without history of severe headache.

Association of change in daily step count over five years with insulin sensitivity and adiposity: population based cohort study

T Dwyer,[12] A-L Ponsonby,[12] O C Ukoumunne,[1] A Pezic,[1] A Venn,[2] D Dunstan,[3] E Barr,[3] S Blair,[4] J Cochrane,[2] P Zimmet,[3] J Shaw[3]

[1]Murdoch Children's Research Institute, Royal Children's Hospital, Parkville, Melbourne 3052, Australia
[2]Menzies Research Institute, University of Tasmania, Hobart 7000, Australia
[3]Baker IDI Heart and Diabetes Institute, Melbourne 3004, Australia
[4]Arnold School of Public Health, University of South Carolina, Columbia, SC 29208, USA

Correspondence to: T Dwyer
terry.dwyer@mcri.edu.au

Cite this as: *BMJ* 2010;341:c7249
doi: 10.1136/bmj.c7249

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;341:c7249

STUDY QUESTION What is the longitudinal association between higher daily step count and adiposity and insulin sensitivity, and to what extent may the association between daily step count and insulin sensitivity be mediated by adiposity?

SUMMARY ANSWER A higher daily step count in 2005 than in 2000 was associated with both a lower body mass index and greater insulin sensitivity in 2005, and the association with greater insulin sensitivity was reduced after adjustment for body mass index.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Randomised controlled trials have shown that physical activity reduces body mass index and progression to insulin resistance, but most have been in selected groups or used composite interventions (including dietary change, for example). Differences in the level of physical activity (measured objectively by a pedometer) over a five year period are associated with obesity and insulin sensitivity independently of other lifestyle factors in community dwelling adults.

Participants and setting

We included 592 adults (mean age 50.8 (SD 12.3) years) who participated in the Tasmanian component of the national AusDiab Study in 2000. We sampled adults aged 25 years and over in randomly selected census districts.

Design, size, and duration

This was a population based cohort study. Measures in 2000 and 2005 included physical activity assessed by pedometer and questionnaire, nutrient intake by food frequency questionnaire, and other lifestyle factors. The main outcome measures were body mass index, waist to hip ratio, and HOMA insulin sensitivity in 2005.

Main results and the role of chance

Over the five year period, the daily step count decreased for 65% (n=382) of participants. Having a higher average daily step count in 2005 than in 2000 was independently associated with lower body mass index (0.08 (95% confidence interval 0.04 to 0.12) lower per 1000 steps higher after adjustment), lower waist to hip ratio (0.15 (0.07 to 0.23) lower), and greater insulin sensitivity (1.38 (0.14 to 2.63) HOMA units higher) in 2005. The mean increase in HOMA units fell to 0.34 (−0.79 to 1.47) after adjustment for body mass index in 2005. We did not find high agreement between reported and objectively measured physical activity measures (Pearson's $r<0.25$), indicating the importance of obtaining objective measures.

Bias, confounding, and other reasons for caution

In an observational study such as this, confounding is always a possible explanation for observed associations. We were able to control for baseline age, sex, body mass index, waist to hip ratio, HOMA insulin sensitivity, socioeconomic status, total energy intake from all sources (kJ), current smoking status, alcohol consumption (g/day), education, and length of cohort follow-up. Adjustment for these factors did not materially alter the estimate of association. We weighted the results for the loss to follow-up that occurred and found that this did not affect the estimate of association between change in steps and insulin sensitivity.

Generalisability to other populations

Our estimate of the independent association of steps with body mass index (a 0.16 lower body mass index for an increase of 2000 steps) was lower than the 0.38 previously reported as the summary effect of pedometer use. This may reflect the fact that many previous studies involved interventions to increase pedometer use, and other associated effects such as a greater awareness of energy balance and thus caloric restriction may have been present.

Study funding/potential competing interests

This study was funded by various government departments and drug companies (see full version for details). DD is supported by a Victorian Health Promotion Foundation public health research fellowship. OCU is supported by NHMRC Population Health Capacity Building Grant 436914. JS is supported by an NHMRC senior research fellowship.

ASSOCIATION BETWEEN PHYSICAL ACTIVITY LEVEL AT BASELINE, CHANGE IN LEVELS BETWEEN 2000 AND 2005, AND HOMA INSULIN SENSITIVITY IN 2005

Physical activity by pedometer	Mean change* (95% CI)	P value
Average daily steps in 2000 (per 1000 higher per day)	1.72 (0.45 to 2.99)	0.01
Change in average daily steps 2000-5 (per 1000 higher per day)	1.38 (0.14 to 2.63)	0.03

*Adjusted for age, sex, HOMA insulin sensitivity in 2000, socioeconomic status in 2000, total energy intake from all sources (kJ) in 2000, smoking status in 2000, alcohol consumption (g/day) in 2000, education in 2000, and length of cohort follow-up.

Non-invasive prenatal assessment of trisomy 21 by multiplexed maternal plasma DNA sequencing: large scale validity study

Rossa W K Chiu,[1] Ranjit Akolekar,[3] Yama W L Zheng,[1] Tak Y Leung,[2] Hao Sun,[1] K C Allen Chan,[1] Fiona M F Lun,[1] Attie T J I Go,[4] Elizabeth T Lau,[5] William W K To,[6] Wing C Leung,[7] Rebecca Y K Tang,[8] Sidney K C Au-Yeung,[9] Helena Lam,[10] Yu Y Kung,[11] Xiuqing Zhang,[12 13] John M G van Vugt,[4] Ryoko Minekawa,[3] Mary H Y Tang,[5] Jun Wang,[12 13] Cees B M Oudejans,[4] Tze K Lau,[2] Kypros H Nicolaides,[3] Y M Dennis Lo[1 12]

[1]Centre for Research into Circulating Fetal Nucleic Acids, Li Ka Shing Institute of Health Sciences, Department of Chemical Pathology, The Chinese University of Hong Kong, Hong Kong SAR, China
[2]Department of Obstetrics and Gynaecology, The Chinese University of Hong Kong
[3]Harris Birthright Research Centre for Foetal Medicine, King's College Hospital, London SE5 9RS, UK
[4]VU University Medical Center, 10081 HV Amsterdam, Netherlands
[5]Tsan Yuk Hospital, Department of Obstetrics and Gynaecology, University of Hong Kong, Hong Kong
[6]United Christian Hospital, Hospital Authority, Hong Kong
[7]Kwong Wah Hospital, Hospital Authority, Hong Kong
[8]Pamela Youde Nethersole Eastern Hospital, Hospital Authority, Hong Kong
[9]Tuen Mun Hospital, Hospital Authority, Hong Kong
[10]Princess Margaret Hospital, Hospital Authority, Hong Kong
[11]YY Kung Medical Centre, Hong Kong
[12]Joint Chinese University of Hong Kong-Beijing Genomics Institute Genome Research Centre, Hong Kong
[13]Beijing Genomics Institute at Shenzhen, Shenzhen, China

Correspondence to: Y M D Lo
loym@cuhk.edu.hk

Cite this as: *BMJ* 2011;342:c7401
doi: 10.1136/bmj.c7401

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;341:c7401

STUDY QUESTION Can maternal plasma DNA sequencing accurately confirm or exclude fetal trisomy 21 among pregnancies clinically indicated for amniocentesis or chorionic villus sampling?

SUMMARY ANSWER Maternal plasma DNA sequencing is an effective, non-invasive means for ruling out fetal trisomy 21 and is practically achievable on a large scale.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Non-invasive prenatal detection of trisomy 21 by massively parallel sequencing of maternal plasma DNA has not been tested on a large scale. This study shows that it is practically feasible on a large scale. Its diagnostic performance suggests it could be used to rule out trisomy 21 among high risk pregnancies before resorting to invasive diagnostic testing.

Participants and setting

We prospectively collected or retrieved archived maternal plasma samples from pregnancies deemed to be at risk for fetal trisomy 21 according to conventional prenatal screening criteria, from prenatal diagnostic units in Hong Kong, the United Kingdom, and the Netherlands. The median maternal age was 35.4 years. The median gestational age at the time of blood sampling was 13.1 weeks.

Design, size, and duration

As cell-free DNA from the fetus is present in the blood of pregnant women (10–20% of total DNA circulating in the maternal plasma), a potential prenatal test for fetal trisomy 21 is to detect an elevated amount of chromosome 21 sequences in maternal blood, because of the extra copy of fetal chromosome 21. We evaluated two protocols, termed the 8-plex and 2-plex protocols, for sequencing maternal plasma DNA. Analytically valid results were available from 753 pregnancies with the 8-plex protocol and from 314 pregnancies with the 2-plex protocol. The sequencing results were compared against those obtained from full karyotyping of amniotic fluid or chorionic villus biopsy. All analyses were performed blindly.

Main results and the role of chance

With the 2-plex protocol, 100% of trisomy 21 fetuses were detected at 97.9% specificity (see table). This gave a positive predictive value of 96.6% and a negative predictive value of 100%. For the 8-plex protocol, 79.1% of the trisomy 21 fetuses were detected at 98.9% specificity, giving a positive predictive value of 91.9% and negative predictive value of 96.9%.

Bias, confounding, and other reasons for caution

An archived sample set was included, but all samples were processed using the same protocols and analysed prospectively. Our data show that there were no significant differences in the fetal DNA concentrations and test performances between the prospectively collected and archived sample groups.

Generalisability to other populations

To investigate if the sequencing test may have utility for beyond pregnancies at increased risk for trisomy 21, we determined the post-test probabilities for women with low prevalences of trisomy 21. A 20 year old woman at 12 weeks' gestation would have a probability for trisomy 21 by maternal age alone of 1 in 1068. With the 2-plex sequencing of maternal plasma DNA, however, the probability for a positive test result was 1 in 23, while the probability for a negative test result was 1 in infinity. These data suggest that the sequencing test could substantially alter the probabilities for having a trisomy 21 fetus even in women with a low a priori risk.

Study funding/potential competing interests

The authors declare support from a grant by the Government of the Hong Kong Special Administrative Region, China; from Sequenom; from the Li Ka Shing Foundation; and travel grants from Illumina and Life Technologies (see bmj.com for full details). The authors also declare patent applications on the detection of fetal nucleic acids in maternal plasma for prenatal diagnosis, and associated financial links with Sequenom and the Institut Jacques Boyd.

DIAGNOSTIC PERFORMANCE OF MATERNAL PLASMA DNA SEQUENCING FOR DETECTING FETAL TRISOMY 21*

8-plex sequencing protocol		2-plex sequencing protocol	
True detection rate	False positive rate	True detection rate	False positive rate
Among 86 trisomy 21 cases	Among 571 non-trisomy 21 cases	Among 86 trisomy 21 cases	Among 146 non-trisomy 21 cases
79.1% (68/86)	1.1% (6/571)	100% (86/86)	2.1% (3/146)

*Classification based on proportion of DNA molecules in maternal plasma that originated from chromosome 21. A trisomy 21 fetus was diagnosed when the z score for the proportion was >3