

# RESEARCH

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HENNI PHOTOGRAPHY/SPL

### Identifying the lowest effective dose of acetazolamide for the prophylaxis of acute mountain sickness

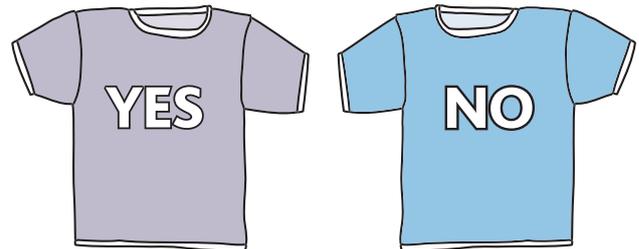
According to this meta-analysis, acetazolamide in doses of 250-750 mg daily are all more effective than placebo in preventing acute mountain sickness. Acetazolamide 250 mg daily is the lowest effective dose for which evidence is available, say the authors.

### Classroom based cognitive behavioural therapy in reducing symptoms of depression in high risk adolescents

In this three arm parallel cluster randomised controlled trial in eight UK secondary schools, outcomes in adolescents with depressive symptoms were similar for attention control, usual school provision, and cognitive behavioural therapy. Classroom based cognitive behavioural therapy programmes may result in increased self awareness and reporting of depressive symptoms but should not be undertaken without further evaluation and research, say the authors

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## Benzodiazepine use and risk of dementia: population based study

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### bmj.com rapid response

"It seems a shame that, in such a well planned and presented study, the 735 potential participants who had a preceding or prevalent history of benzodiazepine use were excluded. Inclusion of this group as a third arm may have allowed for greater powering of the association found."

Judah B Eastwell, GP specialty training year 2, University Hospital of South Manchester, Wythenshawe, Manchester.

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**STUDY QUESTION** Does the use of benzodiazepines increase the risk of dementia in elderly people?

**SUMMARY ANSWER** Over a 15 year follow-up period, starting treatment with benzodiazepines increased the risk of dementia by about 50% compared with non-users.

### WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Benzodiazepines can have delayed adverse effects on cognition, as reported in several case-control studies and a few cohort studies. Benzodiazepine exposure was associated with dementia, even after a long follow-up period, and adjustment for factors strongly associated with starting benzodiazepines or considered to be markers for a prodrome of early dementia did not alter the association.

### Participants and setting

We did analyses within the PAQUID study, which provides a 20 year follow-up of 3777 participants aged 65 and over, representative of the general population of southwest France.

### Design, size, and duration

In the main analysis, a cohort study over a 15 year follow-up compared 95 new users of benzodiazepines with 968 non-users (mean age 78.2 years) after a five year run-in period to ensure that participants were free of dementia and previous benzodiazepine use. A total of 253 incident cases of dementia occurred during follow-up, 30 among users and 223 among non-users. In a secondary analysis, we created four subsequent cohorts during follow-up to compare an additional 116 new benzodiazepine users with non-users. A nested case-control analysis compared 467 patients with dementia and 1810 controls with regard to past benzodiazepine use. We adjusted for age, sex, educational level, marital status, wine consumption, existence of diabetes mellitus or high blood pressure, use of statins, use of platelet inhibitors or oral anticoagulants, cognitive decline (mini-mental state examination), and depressive symptoms.

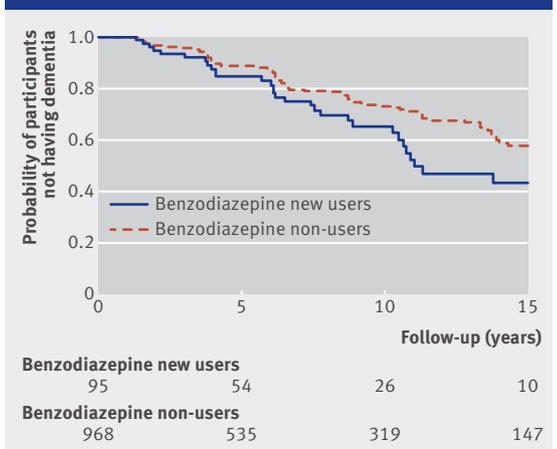
### Primary outcome, risks, and exposures

The outcome was incident dementia confirmed by a neurologist. Data on exposure to benzodiazepines were collected with a standardised questionnaire at each follow-up visit and validated by visual inspection of the patient's medicine packs.

### Main results and the role of chance

In the main cohort analysis, new use of benzodiazepines was associated with an increased risk of dementia (multi-variable adjusted hazard ratio 1.62, 95% confidence inter-

### Dementia-free survival in new benzodiazepine users and non-users at baseline



val 1.08 to 2.43). The pooled hazard ratio across the five cohorts of new benzodiazepine users (secondary analysis) was 1.46 (1.10 to 1.94). In the nested case-control study, ever use of benzodiazepines was associated with a 50% increase in risk of dementia (adjusted odds ratio 1.55, 1.24 to 1.95) compared with never users. The results were similar in past users (started benzodiazepines at least five years before onset of dementia: odds ratio 1.56, 1.23 to 1.98) and recent users (1.48, 0.83 to 2.63) but reached significance only for past users.

### Bias, confounding, and other reasons for caution

Despite the use of a five year run-in period to exclude prevalent cases of dementia and prevalent users of benzodiazepines, and to allow control for important confounding factors, reverse causation cannot be entirely ruled out (if benzodiazepines were prescribed for early prodromal symptoms of the disease). The size of the exposed groups (new users) did not allow us to compare the effect of different benzodiazepines or dosages.

### Generalisability to other populations

The study was carried out in a large representative cohort of elderly people living in France and confirmed the results of studies previously done in other countries (United Kingdom, Taiwan, Canada). Generalisability to younger people may be limited.

### Study funding/potential competing interests

This research received public funding. See the full paper for funding details for the PAQUID study. BB, HV, J-FD, TK, and AP have received research funding and/or honorariums from various public bodies and drug companies (see full paper for details).

# Calcium intake and risk of primary hyperparathyroidism in women: prospective cohort study

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## EDITORIAL by Norman

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## bmj.com podcast

Listen to Julie Paik, one of the authors of this research paper, talk about a new risk factor for primary hyperparathyroidism at <http://bit.ly/VtStdj>

**STUDY QUESTION** What is the relation between calcium intake and risk of developing primary hyperparathyroidism in women?

**SUMMARY ANSWER** Increased calcium intake is independently associated with a reduced risk of primary hyperparathyroidism in women.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Factors that chronically stimulate parathyroid hormone production, such as low calcium intake, could increase the risk of a parathyroid adenoma, the most common cause of primary hyperparathyroidism; however, this relation has not been explored by prospective studies. Increased calcium intake, including both dietary and supplemental calcium, is independently associated with a reduced risk of developing primary hyperparathyroidism in women.

## Participants and setting

Nurses' Health Study I, which originally recruited 58 354 female registered nurses, aged 39-66 years in 1986 and with no history of primary hyperparathyroidism, from the 11 most populous states in the United States.

## Design, size, and duration

Prospective cohort observational study. Calcium intake was assessed every four years using semiquantitative questionnaires on food frequency. The main outcome measure was incident primary hyperparathyroidism, confirmed by medical record review.

## Main results and the role of chance

During 22 years of follow-up, 277 incident cases of primary hyperparathyroidism were documented. Women were divided into five equal groups, according to intake of dietary calcium. After adjusting for age, body mass index, race, and other factors, the relative risk of primary hyperparathyroidism for women in the group with the highest intake of dietary calcium was 0.56 (95% confidence interval 0.37 to 0.86,  $P=0.009$  for

trend), compared with the group with the lowest intake (table). The multivariable relative risk of primary hyperparathyroidism for women taking more than 500 mg/day of calcium supplements compared with no calcium supplements was 0.41 (95% confidence interval 0.29 to 0.60,  $P<0.001$  for trend). Analyses restricted to participants with regular physical exams did not significantly change the association between calcium intake and risk of primary hyperparathyroidism.

## Bias, confounding, and other reasons for caution

Although our study had an observational design, it had several strengths to minimize the scope for bias and confounding: a follow-up participation rate of more than 90%; repeated, comprehensive assessment of calcium intake and other dietary factors using well validated food frequency questionnaires; confirmation of cases by medical record review; and adjustment for age and other factors. The study also had some limitations. Firstly, we cannot exclude selection bias since we only included primary hyperparathyroidism confirmed by medical record review, and we could not obtain medical records for all women who self reported their condition. Secondly, many cases of primary hyperparathyroidism could be asymptomatic and detected by routine blood work. However, in subanalyses restricted to women who had regular physical exams, the inverse relation between calcium intake and risk of primary hyperparathyroidism remained robust. Thirdly, the magnitude of the association between calcium intake and primary hyperparathyroidism was attenuated in lag analyses; thus, some women with higher values of serum calcium on routine bloodwork could have been told to stop taking calcium supplements before their diagnosis of primary hyperparathyroidism.

## Generalizability to other populations

The study population was female and almost entirely white. Thus, our findings are not necessarily generalizable to men or other races.

**For funding statement see bmj.com**

## Risk of incident primary hyperparathyroidism (PHPT) according to calcium intake

	Group with lowest intake	Group with highest intake	P for trend
Dietary calcium intake			
Group median (mg/day)	443	1070	—
No of PHPT cases	69	44	—
No of person years	290 985	292 944	—
Age adjusted relative risk (95% CI)	1.0	0.61 (0.42 to 0.90)	0.03
Multivariable relative risk (95% CI)	1.0	0.56 (0.37 to 0.86)	0.009
Total calcium intake			
Group median (mg/day)	522	1794	—
No of PHPT cases	86	45	—
No of person years	289 554	295 321	—
Age adjusted relative risk (95% CI)	1.0	0.48 (0.33 to 0.69)	<0.001
Multivariable relative risk (95% CI)	1.0	0.41 (0.27 to 0.63)	<0.001

# Intermediate acting non-depolarizing neuromuscular blocking agents and risk of postoperative respiratory complications: prospective propensity score matched cohort study

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## bmj.com podcast

Listen to Matthias Eikermann, one of the authors of this paper, talk about his research at <http://bit.ly/VtStdj>

**STUDY QUESTION** Does use of intermediate acting neuromuscular blocking agents during general anesthesia increase a patient's risk of postoperative respiratory complications?

**SUMMARY ANSWER** Use of these drugs during surgery, independent of common risk factors of respiratory outcomes, was associated with severe postoperative pulmonary complications.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Long acting non-depolarizing neuromuscular blocking agents increase a patient's risk of developing postoperative respiratory complications, which may be related to residual blockade. This study found that use of modern intermediate acting neuromuscular blocking agents during surgery also increased a patient's risk of severe respiratory complications. In our setting reversal of neuromuscular blockade with neostigmine at the end of surgery to prevent residual effects of these agents also increased a patient's risk for respiratory complications.

## Participants and setting

This propensity score matched cohort study was based on data from medical records of surgical patients who had general anesthesia at Massachusetts General Hospital, Boston, United States. Anesthetists identified variables influencing their decision to administer an intermediate acting neuromuscular blocking agent during surgery. We estimated the probability of a patient receiving such a drug by calculating propensity scores based on the variables age, sex, body weight, body mass index, American Society of Anesthesiologists physical status classification, surgical specialty, duration of surgical procedure, emergency status, Charlson comorbidity index, and use of volatile anesthetics, nitrous oxide, and opioids. We then used the results of this propensity scoring to match each of 18 579 patients undergoing a surgical procedure in whom intermediate acting neuromuscular blocking agents were administered at least once to one reference surgical procedure where the patient did not receive neuromuscular blocking agents.

## Design, size, and duration

A prospective, propensity score matched cohort study of 37 158 surgical procedures where patients underwent surgery under general anesthesia between March 2006 and September 2010.

## Main results and the role of chance

Use of intermediate acting neuromuscular blocking agents was associated with an increased risk of postoperative desaturation less than 90% after extubation (odds ratio 1.36, 95% confidence interval 1.23 to 1.51) and reintubation requiring unplanned admission to an intensive care unit (1.40, 1.09 to 1.80). After surgeries of short duration (<120 minutes) the risk of reintubation was even higher (2.04, 1.44 to 2.90). Strategies to prevent residual post-operative neuromuscular blockade did not decrease this risk, and reversal using neostigmine at the end of surgery increased a patient's risk of developing severe respiratory complications.

## Bias, confounding, and other reasons for caution

This study of medical record data is observational and residual and immeasurable confounding remains a possibility. Despite best efforts to gather complete and accurate data for each patient, it is not possible to rule out potential misclassification, although this should be non-differential.

## Generalizability to other populations

The patients included in the registry were from a specialty medical center in the United States, which may limit generalizability to other settings. Although we have no reason to believe that the effect of neuromuscular blocking agents on our outcomes is largely different in other centers, differences in managing perioperative muscle strength across centers may translate to different effects on respiratory outcome.

## Study funding/potential competing interests

This study was funded by the Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, USA.

Association between use of intermediate acting non-depolarizing neuromuscular blocking agents and outcomes in propensity score matched cohort (n=37 158)

Outcomes	Neuromuscular blocking agents		Odds ratio (95% CI)
	Not received (n=18 579)	Received (n=18 579)	
Desaturation <90%	689	925	1.36 (1.23 to 1.51)
Desaturation <80%	128	212	1.66 (1.34 to 2.07)
Reintubation	108	151	1.40 (1.09 to 1.80)
In-hospital death	48	55	1.15 (0.78 to 1.69)

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## Safe exclusion of pulmonary embolism using the Wells rule and qualitative D-dimer testing in primary care: prospective cohort study

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**STUDY QUESTION** Does a low probability of pulmonary embolism according to the Wells clinical decision rule combined with a negative point of care D-dimer test result safely exclude the condition in primary care?

**SUMMARY ANSWER** Combining a Wells score of  $\leq 4$  with a negative D-dimer test result classified 45.5% of the patients at low risk for pulmonary embolism, with only four (1.5%) actually having a diagnosis of pulmonary embolism. Lowering the threshold of the Wells score to  $< 2$  combined with a negative D-dimer test result yielded an even lower failure rate (1.2%), but at the cost of lower efficiency (28.1%).

**WHAT IS KNOWN AND WHAT THIS PAPER ADDS** Diagnostic management studies in secondary care showed that a Wells score  $\leq 4$  combined with a negative laboratory based quantitative D-dimer test result safely excluded pulmonary embolism without the need for additional imaging. A low Wells score ( $\leq 4$ ) and a negative point of care D-dimer test result safely ruled out pulmonary embolism in primary care.

### Participants and setting

Primary care doctors across different regions of the Netherlands prospectively included 598 adults with suspected pulmonary embolism, based on the presence of at least one of unexplained (sudden) dyspnoea, deterioration of existing dyspnoea, pain on inspiration, or unexplained cough.

### Design, size, and duration

The Wells rule for pulmonary embolism combined with a point of care D-dimer test was validated in a prospective multicentre diagnostic cohort. The primary care doctors applied the Wells rule and carried out the qualitative D-dimer test. All patients were referred to secondary care

and diagnosed according to local hospital protocols. The primary outcome of the study was the presence of venous thromboembolism, based on a composite reference standard, including spiral computed tomography, ventilation-perfusion scanning, pulmonary angiography, leg ultrasonography, clinical probability assessment as done in secondary care (with or without D-dimer testing), and a follow-up period of three months in primary care.

### Main results and the role of chance

73 patients (12.2%) were diagnosed as having pulmonary embolism. Only four of 272 patients at low risk of pulmonary embolism (1.5%) were missed by this combined approach.

### Bias, confounding, and other reasons for caution

The reference standard of pulmonary embolism consisted of various combinations of laboratory and imaging procedures, including three months of follow-up, to diagnose or refute a case of pulmonary embolism. This differential verification depended on our index test under study. This could lead to an over optimistic estimate of the failure rate for detecting pulmonary embolism.

### Generalisability to other populations

Our study followed common clinical practice from both academic and non-academic hospitals in many parts of the world, which increases the generalisability of our results.

### Study funding/potential competing interests

The Netherlands Heart Foundation funded the study (NHS-2006B237). GlaxoSmithKline and Inverness Medical cofunded the study with unrestricted research grants. The funders had no role in the design, conduct, analyses, or reporting of the study or in the decision to submit the manuscript for publication.

Diagnostic variables of Wells rule, combined with a qualitative point of care negative D-dimer test result in primary care. Values are percentages (95% confidence intervals)

Diagnostic variables	Negative D-dimer test result	
	Wells $\leq 4$	Wells $< 2$
Efficiency*	45.5 (41.4 to 49.6)	28.1 (24.5 to 31.9)
Failure rate†	1.5 (0.4 to 3.7)	1.2 (0.1 to 4.2)
Sensitivity	94.5 (86.6 to 98.5)	97.3 (90.5 to 99.7)
Specificity	51.0 (46.7 to 55.4)	31.6 (27.7 to 35.8)
Positive predictive value	21.2 (16.9 to 26.0)	19.8 (15.8 to 24.3)
Negative predictive value	98.5 (96.3 to 99.6)	98.8 (95.8 to 99.9)

\*Proportion of all patients in whom pulmonary embolism was excluded based on Wells score below various cut-off values and a negative D-dimer test result.

†Proportion of patients in whom pulmonary embolism was excluded based on Wells score below various cut-off values and a negative D-dimer test result, with symptoms and proved venous thromboembolism during three months' follow-up.

# Effect of intended intraoperative cholangiography and early detection of bile duct injury on survival after cholecystectomy: population based cohort study

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**STUDY QUESTION** Does bile duct injury at cholecystectomy affect survival after cholecystectomy, and could intraoperative cholangiography prevent postoperative deaths?

**SUMMARY ANSWER** Early detection of a bile duct injury and the intention to use intraoperative cholangiography are associated with improved survival after cholecystectomy.

**WHAT IS KNOWN AND WHAT THIS PAPER ADDS** Bile duct injury is a serious complication of cholecystectomy; its prevention by the use of intraoperative cholangiography has been widely debated. Our results suggest that the routine use of intraoperative cholangiography during cholecystectomy has beneficial outcomes.

## Participants and setting

Prospectively collected data from the Swedish national registry of gallstone surgery and endoscopic retrograde cholangiopancreatography, GallRiks, in relation to all cholecystectomies between 1 May 2005 and 31 December 2010.

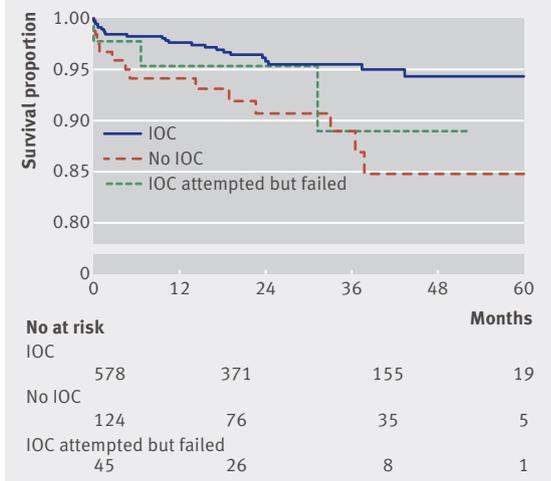
## Design, size, and duration

In this population based cohort study, we analysed the effect of bile duct injury and intended intraoperative cholangiography on survival after cholecystectomy, using a multivariate Cox model. The entire range of severity of bile duct injuries was identified, from minor ductal lesions discovered as postoperative bile leakages to complete transections of the common bile duct or common hepatic duct. We defined the intention to use intraoperative cholangiography as a successful procedure, or an attempted procedure that for any reason was interrupted.

## Main results and the role of chance

During the study, 51 041 cholecystectomies were registered and 747 (1.5%) iatrogenic bile duct injuries identified. Patients with bile duct injuries had a lower survival rate than those without injury (mortality at one year 3.9% v 1.1%). Kaplan-Meier curves showed that early detection of a bile duct injury (that is, during the primary operation) improved survival. The intention to use intraopera-

## Survival in patients with iatrogenic bile duct injury during cholecystectomy



tive cholangiography (IOC) reduced the risk of death after cholecystectomy by 62% (adjusted hazard ratio 0.38 (95% confidence interval 0.31 to 0.46)).

## Bias, confounding, and other reasons for caution

The multivariate Cox analysis allowed us to account for the influence of possible confounders such as age, sex, comorbidity, effect of emergency or elective surgery, and annual caseload of the surgeon and hospital. However, the reasons why surgeons decided to perform or not perform perioperative cholangiography could not be clarified in this study. As a self reported registry, GallRiks was also prone to a risk of selection bias; to minimize the bias, complications and interventions were reviewed 30 days after surgery.

## Generalizability to other populations

Since the coverage of GallRiks is high—about 90% of cholecystectomies in Sweden are registered—these results should have a reliable generalisability to other populations with similar healthcare profiles and resource settings as Sweden.

## Study funding/potential competing interests

The authors have no competing interests.