Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomised clinical trials

Edward Litton,[1 2] Jing Xiao,[1] Kwok M Ho[1 3]

EDITORIAL by McIntyre et al

[1]Department of Intensive Care Medicine, Royal Perth Hospital, Perth, Western Australia 6000, Australia
[2]School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia 6009, Australia
[3]School of Population Health, University of Western Australia, Perth, Western Australia 6009, Australia
Correspondence to: E Litton, Department of Intensive Care Medicine, Royal Perth Hospital, Perth, Western Australia 6000, Australia
ed.litton@health.wa.gov.au

Cite this as: *BMJ* 2013;347:f4822
doi: 10.1136/bmj.f4822

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;347:f4822

STUDY QUESTION

Is intravenous iron effective in reducing the need for blood transfusion and is it associated with an increased risk of infection?

SUMMARY ANSWER

Intravenous iron therapy is effective in increasing haemoglobin concentration and reducing the need for allogeneic red blood cell transfusion and could potentially have broad applicability in a range of acute care settings, though this is counterbalanced by a potential increased risk of infection.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The known benefit of increases in haemoglobin concentration was seen in comparisons with oral iron and no iron supplementation. Intravenous iron therapy was associated with an increased risk of infection.

Selection criteria for studies and potential competing interests See bmj.com.

Main results and role of chance

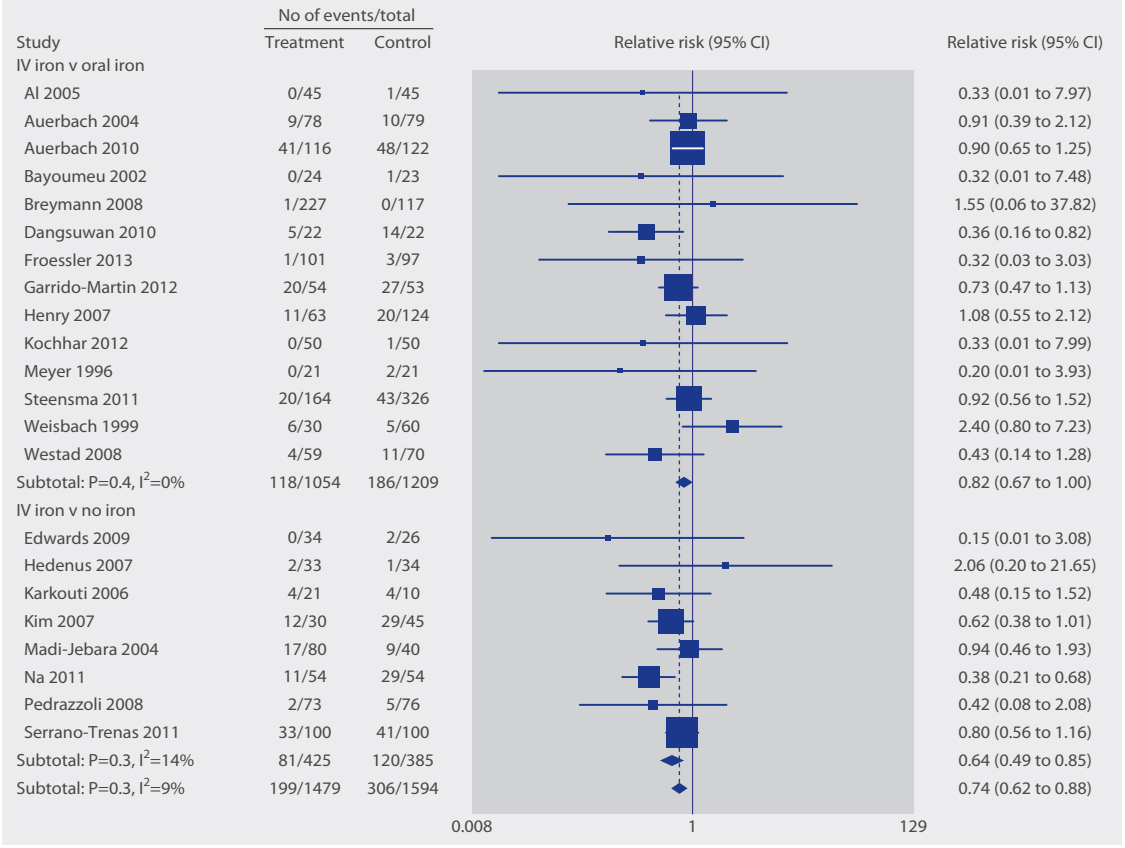
A total of 75 studies including 10 879 participants fulfilled the inclusion criteria and were included in the systematic review. The most common intravenous iron preparations used in the included studies were iron sucrose, iron gluconate, and ferric carboxymaltose. When data were pooled (59 studies, n=7610), intravenous iron was associated with a significant increase in standardised mean haemoglobin concentration (6.5 g/L, 95% confidence interval 5.1 g/L to 7.9 g/L) compared with oral iron or no iron supplementation. Intravenous iron therapy was associated (22 studies, n=3321) with a significant reduction in need for allogeneic red blood cell transfusion (risk ratio 0.7, 95% confidence interval 0.6 to 0.9), with no significant heterogeneity (I^2=9%, P=0.3). This therapy was also associated with a significant increase in risk of infection (24 studies, n=4400) of 1.3 (1.1 to 1.6), with no significant heterogeneity (I^2=22.7%, P=0.2).

Bias, confounding, and other reasons for caution

Overall, the risk of bias was low for 18 studies and high for 57 studies The overall high risk of bias was accounted for by most studies not being blinded to participants or study personnel (n=56). Data on all outcomes were not available from each study and the doses and preparations of intravenous iron used in the pooled studies varied.

bmj.com/multimedia
Watch the authors talk about their findings at bmj.com/multimedia

Risk of red blood cell transfusion in patients who received intravenous iron compared with oral iron and no iron



Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis

Dominik Mertz,[1 2] Tae Hyong Kim,[2] Jennie Johnstone,[2] Po-Po Lam,[3 4] Michelle Science,[5] Stefan P Kuster,[6] Shaza A Fadel,[4] Dat Tran,[5] Eduardo Fernandez,[2] Neera Bhatnagar,[7] Mark Loeb[2 8 9]

[1]Department of Medicine, McMaster University, Hamilton, ON, Canada
[2]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton
[3]Mount Sinai Hospital, Toronto, ON, Canada
[4]Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto, Toronto
[5]Department of Pediatrics, The Hospital for Sick Children, University of Toronto, ON, Canada
[6]University Hospital and University of Zurich, Zurich, Switzerland
[7]Health Sciences Library, McMaster University, Hamilton
[8]Department of Pathology and Molecular Medicine, McMaster University, Hamilton
[9]Michael G DeGroote Institute for Infectious Disease Research, McMaster University, Hamilton
Correspondence to: M Loeb Department of Pathology and Molecular Medicine, McMaster University MDCL 3203, 1200 Main St. W, Hamilton, ON, Canada L8N 3Z5 **loebm@mcmaster.ca**

Cite this as: *BMJ* 2013;347:f5061
doi: 10.1136/bmj.f5061

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;347:f5061

STUDY QUESTION

What are the risk factors for severe outcomes in people with seasonal and pandemic influenza?

SUMMARY ANSWER

The level of evidence to support risk factors for influenza related complications is low. Well accepted risk factors such as pregnancy and ethnicity could not be confirmed, whereas obesity, not yet well established as a risk factor, was among the best supported risk factors.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Certain patient populations thought to be at higher risk for developing complicated or severe influenza illness are prioritised for vaccination as well as for antiviral treatment. While some risk factors could be corroborated, high quality evidence was scarce.

Selection criteria for studies

We searched Medline, Embase, CINAHL, Global Health, and CENTRAL through March 2011 for observational studies published in English, French, Spanish, German, or Korean reporting on risk factor-outcome combinations of interest in participants with influenza.

Primary outcomes

Death, ventilator support, admission to hospital, admission to an intensive care unit, pneumonia, and composite outcomes.

Main results and role of chance

63 537 articles were identified of which 234 with a total of 610 782 participants met the inclusion criteria. The level of evidence was low for "any risk factor" (odds ratio for mortality 2.77, 95% confidence interval 1.90 to 4.05 for pandemic influenza and 2.04, 1.74 to 2.39 for seasonal influenza), obesity (2.74, 1.56 to 4.80 and 30.1, 1.74 to 2.39), cardiovascular diseases (2.92, 1.76 to 4.86 and 1.97, 1.06 to 3.67), and neuromuscular disease (2.68, 1.91 to 3.75 and 3.21, 1.84 to 5.58). The level of evidence was very low for all other risk factors. Some well accepted risk factors such as pregnancy (0.99, 0.67 to 1.46 and 1.07, 0.79 to 1.45) and belonging to an ethnic minority group (for example, Native Americans 0.93, 0.67 to 1.30 for pandemic influenza) could not be identified as risk factors for severe outcomes. In contrast, women who were less than four weeks post partum had a significantly increased risk of death with pandemic influenza (4.43, 1.24 to 15.81) but study quality was very low.

Bias, confounding, and other reasons for caution

The evidence supporting risk factors for severe outcomes of influenza ranged from being limited to absent. This was particularly relevant with respect to the relative lack of data for non-2009 H1N1 pandemics and for seasonal influenza studies. Limitations in the published literature included lack of power to draw definite conclusion for some risk factors. Lack of adjustment for confounders was widespread: adjusted risk estimates were provided for only 5% of risk factor-outcome comparisons in 39 of 260 (15%) studies.

Study funding/potential competing interests

This study was funded by the World Health Organization. Its suggestions were incorporated into the protocol.

Risk estimates of selected risk factors during pandemic (P) and seasonal (S) influenza, and assessment of quality of evidence using an adaption of the GRADE approach

	Pneumonia		All cause hospital admission		Intensive care unit admission		Ventilator support		All cause mortality		
Risk factors	P	S	P	S	P	S	P	S	P	S	GRADE
Elderly *v* non-elderly adults	*	Ntrl	+	+	(+)	NA	Ntrl	NA	+	+	Very low
3rd trimester *v* 1st/2nd trimester	Ntrl	NA	+	NA	+	NA	NA	NA	+	NA	Very low
Any risk factor or comorbidity	Ntrl	+	+	+	+	+	*	*	+	+	Low
Obesity (BMI >30)	Ntrl	NA	+	NA	+	NA	+	NA	+	+	Low
Any chronic lung disease	Ntrl	*	+	+	+	+	Ntrl	+	+	*	Very low
COPD	Ntrl	NA	*	NA	+	NA	*	+	+	Ntrl	Very low
Any cardiovascular disease	Ntrl	+	+	+	+	Ntrl	*	+	+	+	Low
Immunocompromised	(*)	(+)	+	NA	Ntrl	(*)	Ntrl	NA	+	+	Very low
Malignancy	Ntrl	Ntrl	+	+	Ntrl	NA	Ntrl	NA	+	*	Very low
Any neuromuscular disease	Ntrl	*	+	NA	+	NA	*	NA	+	+	Low
Neurocognitive disease	NA	+	+	NA	+	*	+	NA	+	Ntrl	Very low
Diabetes mellitus	Ntrl	Ntrl	+	+	+	NA	*	NA	+	(*)	Very low

GRADE=grading of recommendations assessment, development, and evaluation; BMI=body mass index; COPD=chronic obstructive pulmonary disease; +=significant risk factor; *potential risk factor: odds ratio >1.5, trend; Ntrl=neutral; (*)=potentially protective: odds ratio <0.67, trend, (+)=significant protective factor; NA=not available.

bmj.com Colon cancer updates from *BMJ* are at bmj.com/specialties/colon-cancer

Risk of colorectal cancer after initiation of orlistat: matched cohort study

Jin-Liern Hong,[1] Christoph R Meier,[2 3 4] Robert S Sandler,[1 5] Susan S Jick,[4] Til Stürmer[1]

[1]Department of Epidemiology, UNC Gillings School of Global Public Health, University of North Carolina at Chapel Hill, McGavran-Greenberg, CB # 7435, Chapel Hill, NC 27599-7435, USA
[2]Basel Pharmacoepidemiology Unit, Division of Clinical Pharmacy and Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland
[3]Hospital Pharmacy, University Hospital, Basel, Switzerland
[4]Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Boston, MA 02421, USA
[5]Department of Medicine, UNC School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill NC 27599-7555, USA
Correspondence to: J L Hong
jlhongtw@email.unc.edu

Cite this as: *BMJ* 2013;347:f5039
doi: 10.1136/bmj.f5039

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;347:f5039

STUDY QUESTION

Does starting treatment with orlistat, an anti-obesity drug, increase the short term risk of colorectal cancer?

SUMMARY ANSWER

Initiation of orlistat does not increase the short term risk of colorectal cancer, but the finding is limited by the relatively short mean duration of orlistat treatment and thus absence of data on long term risk of orlistat use.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

An animal study showed that orlistat may induce aberrant crypt foci in rodents, but data from population based post-marketing studies on the risk of colorectal cancer are lacking. This study in the UK population showed no evidence of an increased risk of colorectal cancer associated with use of orlistat in the short term, but the possibility of adverse effects of long term orlistat use on risk of colorectal cancer cannot be excluded.

Participants and setting

We included adults aged 18 years or over and with recorded body mass index in the UK Clinical Practice Research Datalink (CPRD) from September 1998 to December 2008.

Design, size, and duration

This matched cohort study included 33 625 initiators of orlistat and 160 347 non-initiators matched on age, sex, body mass index, and calendar time. We followed up patients without cancer for a diagnosis of colorectal cancer either ignoring changes in treatment (intention to treat analysis in which first treatment was carried forward) or censoring at the time of any treatment change (as treated analysis). We used time to event analysis to compare the risk of colorectal cancer in orlistat initiators with the risk in non-initiators, allowing for a six month induction period (all analyses) and a six month carry-over effect (as treated analysis).

Main results and the role of chance

In the intention to treat analysis, the incidence rate of colorectal cancer per 100 000 person years was 53 (95% confidence interval 41 to 69) for orlistat initiators and 50 (44 to 57) for non-initiators. The hazard ratio of colorectal cancer comparing orlistat initiators with non-initiators was 1.11 (95% confidence interval 0.84 to 1.47) after propensity score weighting. The results were similar in the as treated analysis. Additionally, we observed no increased risk of colorectal cancer in patients who were aged 50 years or over, were morbidly obese (body mass index ≥35), or had a history of diabetes.

Bias, confounding, and other reasons for caution

We controlled confounding by matching our comparison group of non-initiators with orlistat initiators on age, sex, and body mass index and further adjusting for remaining imbalances by using propensity score weighting. Given concerns about detection bias, we also examined the frequency of patients who underwent screening for colorectal cancer within one year before and after cohort entry and found no difference between orlistat initiators and non-initiators. Potential sources of bias may include unmeasured confounding and lack of data on waist circumference. We recognise that the duration of treatment actually observed was not long enough to assess the risk of colorectal cancer in long term users of orlistat.

Generalisability to other populations

The CPRD is representative of the UK population of mainly (92%) European descent. Our findings may not be generalisable to populations with different ethnic backgrounds and patterns of orlistat use.

Study funding/potential competing interests

The study was funded by the population research award from UNC's Lineberger Comprehensive Cancer Center and R01AG023178 from the National Institute of Aging. J-LH and TS receive(d) salary support from the Center for Pharmacoepidemiology funded by GlaxoSmithKline, the current patent holder for orlistat (Alli).

Hazard ratios for colorectal cancer

Cohort	No of colorectal cancers	Median follow-up time—years (interquartile range)	Weighted hazard ratio (95% CI)
Intention to treat analysis			
Orlistat initiators	57	3.0 (1.4-5.4)	1.11 (0.84 to 1.47)
Non-initiators	246	2.9 (1.3-5.2)	1.00
As treated analysis			
Orlistat initiators	14	0.8 (0.6-1.2)	0.99 (0.56 to 1.77)
Non-initiators	230	2.4 (1.1-4.6)	1.00

bmj.com Diabetes updates from *BMJ* are at bmj.com/specialties/diabetes

Fruit consumption and risk of type 2 diabetes: results from three prospective longitudinal cohort studies

Isao Muraki,[1] Fumiaki Imamura,[2] JoAnn E Manson,[3 4 5] Frank B Hu,[1 3 5] Walter C Willett,[1 3 5] Rob M van Dam,[1 6] Qi Sun[1 5]

[1]Department of Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115, USA
[2]MRC Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK
[3]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA
[4]Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
[5]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
[6]Saw Swee Hock School of Public Health and Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore
Correspondence to: Q Sun
qisun@hsph.harvard.edu

Cite this as: *BMJ* 2013;347:f5001
doi: 10.1136/bmj.f5001

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;347:f5001

STUDY QUESTION

Are individual fruits, which vary in composition, differentially associated with risk of type 2 diabetes, and, if so, do the associations depend on the glycemic index or glycemic load of the individual fruits?

SUMMARY ANSWER

Greater consumption of specific whole fruits, particularly blueberries, grapes, and apples, was significantly associated with a lower risk of type 2 diabetes, whereas greater fruit juice consumption was associated with a higher risk. These differences in association were not explained by the glycemic index (quality of carbohydrate) or glycemic load (quality and quantity of carbohydrate and their interaction) values of the fruits.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

In previous studies total fruit consumption was not consistently associated with a lower risk of type 2 diabetes. The current study shows that the inconsistency may be explained by the differences in association between individual fruits, but not by the glycemic index or glycemic load values of specific fruits.

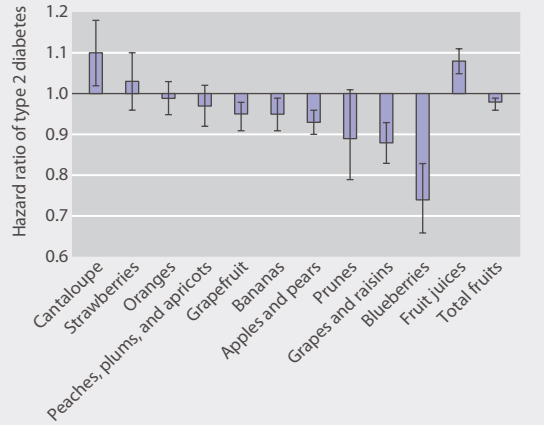
Participants and setting

US adults in three large cohort studies were prospectively followed for incidence of chronic diseases, including type 2 diabetes.

Design, size, and duration

We followed 66 105 women from the Nurses' Health Study (1984-2008), 85 104 women from the Nurses' Health Study II (1991-2009), and 36 173 men from the Health Professionals Follow-up Study (1986-2008). Diet was assessed at baseline and updated every four years using a validated food frequency questionnaire. Ten individual fruits were asked about in the questionnaire: grapes and raisins; peaches, plums, and apricots; prunes; bananas; cantaloupe; apples and pears; oranges; grapefruit; strawberries; and blueberries. Incident cases of type 2 diabetes were identified through self report and confirmed by a supplementary questionnaire.

Pooled multivariable adjusted hazard ratios (95% confidence intervals) of type 2 diabetes for every three servings/week of total or individual fruits, and fruit juices



Main results and the role of chance

During 3 464 641 person years of follow-up, 12,198 participants developed type 2 diabetes. After adjustment for personal, lifestyle, and dietary risk factors for diabetes, the pooled hazard ratio of type 2 diabetes for every three servings/week of total fruit consumption was 0.98 (95% confidence interval 0.96 to 0.99). After mutual adjustment for individual fruits, the pooled hazard ratios of type 2 diabetes (for every three servings/week) were 0.74 (95% confidence interval 0.66 to 0.83) for blueberries, 0.88 (0.83 to 0.93) for grapes and raisins, 0.89 (0.79 to 1.01) for prunes, 0.93 (0.90 to 0.96) for apples and pears, 0.95 (0.91 to 0.98) for bananas, 0.95 (0.91 to 0.99) for grapefruit, 0.97 (0.92 to 1.02) for peaches, plums, and apricots, 0.99 (0.95 to 1.03) for oranges, 1.03 (0.96 to 1.10) for strawberries; and 1.10 (1.02 to 1.18) for cantaloupe. The pooled hazard ratio for the same increment in fruit juice consumption was 1.08 (1.05 to 1.11). The associations with risk of type 2 diabetes differed significantly among individual fruits (P<0.001 in each cohort). Differences in glycemic index or glycemic load of specific fruits did not account for the heterogeneity in associations among the specific fruits.

Bias, confounding, and other reasons for caution

A role of residual or unmeasured confounding, chance, or measurement errors in diet cannot be entirely excluded. Nevertheless, the prospective study design, relatively high follow-up rate (approximately 90%), adjustment for a multitude of lifestyle and dietary confounders, and use of repeated assessments of fruit consumption may help minimize the impact of these biases on the associations. The consistency of most associations across three cohorts also suggested that chance was unlikely to explain these findings.

Generalisability to other populations

Our study participants were primarily of European ancestry, limiting the generalizability to other populations.

Study funding/potential competing interests

This study was funded by research grants CA87969, CA176726, CA55075, CA50385, CA167552, DK58845, and DK082486 from the National Institutes of Health. QS was supported by a career development award R00HL098459 from the National Heart, Lung, and Blood Institute. The funding sources had no role in this study. We have no competing interest.