Practical Exercises

INTRODUCTION TO STUDY DESIGN

Note that this first exercise involves commenting on some published papers and writing some outline protocols. At this stage of the course it is not envisaged that the student will be able to address all the relevant issues fully. It is suggested that you attempt the questions now and this will help to highlight/focus on important issues re study design. It is also suggested that at the end of the course you return to these questions when you should be better equipped to give more comprehensive answers.

1. Give the PICO for the following research questions:

a) What is the prevalence of pre-school asthma?

P :

I :

C :

O :

b) What is the likely prognosis for newly diagnosed lung cancer patients?

P :

I :

C :

O :

c) Do children with epilepsy have different average BMIs compared to non-epileptic children?

P :

I :

C :

O :

d) Are children who develop epilepsy between 5 and 15 years of age more likely to have been prescribed antibiotics in the first year of life?

P :

I :

C :

O :

e) Are fetuses with head circumferences above the 99th centile at any ultrasound scan more likely to have congenital abnormality? (i.e. Is large head circumference diagnostic of congenital abnormality?)

P :

I :

C :

O :

f) Do steroids improve lung function in mild to moderate asthmatics?

P :

I :

C :

O :

g) Does increasing patient contact with or without further therapy improve skin condition for patients with severe eczema?

P :

I :

C :

O :

2. What study designs might be used to address the research questions in question 1?

a) What is the prevalence of pre-school asthma?

b) What is the likely prognosis for newly diagnosed lung cancer patients?

c) Do children with epilepsy have different average BMIs compared to non-epileptic children?

d) Are children who develop epilepsy between 5 and 15 years of age more likely to have been prescribed antibiotics in the first year of life?

e) Are fetuses with head circumferences above the 99th centile at any ultrasound scan more likely to have congenital abnormality? (i.e. Is large head circumference diagnostic of congenital abnormality?)

f) Do steroids improve lung function in mild to moderate asthmatics?

g) Does increasing patient contact with or without further therapy improve skin condition for patients with severe eczema?

3. How might confounders be present for the study designs decided on in question 2?

a) What is the prevalence of pre-school asthma?

b) What is the likely prognosis for newly diagnosed lung cancer patients?

c) Do children with epilepsy have different average BMIs compared to non-epileptic children?

d) Are children who develop epilepsy between 5 and 15 years of age more likely to have been prescribed antibiotics in the first year of life?

e) Are fetuses with head circumferences above the 99th centile at any ultrasound scan more likely to have congenital abnormality? (i.e. Is large head circumference diagnostic of congenital abnormality?)

f) Do steroids improve lung function in mild to moderate asthmatics?

g) Does increasing patient contact with or without further therapy improve skin condition for patients with severe eczema?

4. How might (f) and (g) be addressed using the different study types given in Chapter 1 of the course notes?

f) Do steroids improve lung function in mild to moderate asthmatics?

g) Does increasing patient contact with or without further therapy improve skin condition for patients with severe eczema?

5. Several published papers (listed below) and associated newspaper articles for some of them are given in the next few pages.

   A: Web addiction and depression

   B: Magnesium and depression

   C: Driving and gambling

You will be asked to review some of these and answer the following key points:

a) What research question did the study hope to answer?
b) What was the target population?
c) How was this population sampled from? Were there any biases in the sampling procedure? Could this affect outcome?
d) What measurements were made on each subject? Were these measurements adequate to address the research question? Were any spurious and were there others that should've been made that weren't?
e) In the light of the study results what appears to be the answer to the research question?
f) Are the authors' conclusions justified?
g) Could the study design have been improved to enable the research question to be answered in a more direct, simple or definite way?

6. Write outline protocols for studies to determine:-

a) Whether a new herbal preparation is effective in the treatment of asthma in children.

b) Whether visual screening of pre-school children (as performed by health visitors using Snellen letter cards) accurately identifies those children with sight problems (as measure by the "gold standard" of ophthalmologists/optometrists using refraction).

Original Paper

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The Relationship between Excessive Internet Use and Depression: A Questionnaire-Based Study of 1,319 Young People and Adults

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Key Words
Internet use, excessive · Addiction · Depression · Suicide

Abstract
Background: There is a growing awareness of a psychiatric construct that needs to be better defined and understood: Internet addiction (IA). Recently there has been much public concern over the relationship between Internet use and negative affect. This study explored the concept of IA and examined the relationship between addictive symptoms and depression. ***Sampling and Methods:*** An online questionnaire was used to measure participants' Internet use, the functions for which they used the Internet, and their depressive tendencies. Three scales were included: the IA Test, the Internet Function Questionnaire and the Beck Depression Inventory (BDI). 1,319 respondents completed the questionnaires, with 18 (1.2%) identified as falling in the IA category. ***Results:*** Correlational analyses were conducted across the whole data sample. In factorial analyses, the 18 IA respondents were compared to a matched group of non-addicted (NA) respondents in terms of their scores on the Function Test and the BDI. Across the whole data sample, there was a close relationship between IA tendencies and depression, such that IA respondents were more depressed; there were also significant differences between the sexes, with men showing more addictive tendencies than women. In addition, young people were significantly more likely to show addictive symptoms than were older people. There was a significant difference between the IA and the NA group in their levels of depressive symptoms, with the NA group firmly in the non-depressed range, and the IA group in the moderately-to-severely depressed range ($F_{1, 34} = 22.35$; $p < 0.001$). In terms of the function for which they used the Internet, the IA group engaged significantly more than the NA group in sexually gratifying websites, gaming websites and online community/chat websites. ***Conclusions:*** The concept of IA is emerging as a construct that must be taken seriously. Moreover, it is linked to depression, such that those who regard themselves as dependent on the Internet report high levels of depressive symptoms. Those who show symptoms of IA are likely to engage proportionately more than the normal population in sites that serve as a replacement for real-life socialising. Further work needs to be done on validating this relationship. Future research is needed to corroborate the existing evidence and address the nature of the relationship between IA and depression: there is comorbidity between these conditions that needs greater investigation.

Introduction

The Internet has become an essential part of modern life, bringing huge benefits in terms of living and working flexibly. However, there is a darker side to the Internet, and a hot social and medical issue currently is the question of whether Internet sites, particularly those involv-

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ing online communities, influence behaviour and induce or support pathological thinking.

Although not a recognised syndrome in ICD-10 or DSM-IV, the term Internet addiction (IA) is commonly used [1]. The definition of IA is 'an individual's inability to control their Internet use, which in turn leads to feelings of distress and functional impairment of daily activities' [2]. A quick Internet search shows that some are cashing in on this concept by offering treatment and remedial programmes for those who fear they have become addicted to the Internet. However sceptical one might be about this, there seems to be a growing awareness in the psychiatric community that there is validity in this construct as a distinct psychiatric condition. Indeed, a recent editorial in the *American Journal of Psychiatry* [3] has called for IA to be recognised as a syndrome in the forthcoming DSM-V. In this article, Block [3] argues that in societies in which the Internet infrastructure is very well developed, i.e. in East Asia, the case for IA is very evident; however, in the West, the prevalence of the condition is less well understood. But with increasingly sophisticated infrastructures developing in the West, it seems fairly certain that where the Far East leads, the West will follow [4, 5].

There is no doubt that some people develop what they and/or others recognise subjectively as compulsive tendencies towards Internet use, and the symptoms they report, including physiological arousal and psychological withdrawal, seem to mirror symptoms that are understood to be related to well-established addictive behaviours. Since the early 1990s there has been a growing body of literature arguing for the acknowledgement of IA as a distinct psychological construct [3, 6, 7]. With DSM-V in development, it is essential that the case for IA as a separate psychiatric condition is made now.

One of the problems in examining IA is that there is a paucity of tools with which to measure this condition, and some inconsistencies between the tools available [8]. The most widely used test of IA was developed by Young [9, 10], and it has been refined to provide a tool for determining whether someone meets the criteria for addiction as identified by Young. We recognise that Beard [11] urged caution in accepting the reliability and validity of the tools currently available, but with that caveat in mind, and in view of the fact that the Young test is widely reported in the literature, we chose this measure in the present study.

In addition to considering time spent online, it is important to bear in mind that the Internet has multiple ways by which people can engage; Young [9] makes the point that it allows for any and every virtual experience. Given the multi-faceted way in which an individual can interact with the Internet, there is a growing appreciation that Internet use needs to be analysed systematically. Hence it is not enough simply to ask people the extent to which they use the Internet, it is important also to ask what they use it for. Recent research has suggested that those who are more dependent on the Internet are likely to engage proportionately more in sites related to sexual gratification, online gaming or e-mail/text messaging [2].

One function of the Internet that seems to have taken a firm grip on young people is the involvement in online, virtual communities such as Facebook, Bebo and, most recently, Twitter. A recent spate of suicides amongst teenagers and young adults in South Wales, UK, has led to questions being raised in the media about the extent to which online communities foster suicidal tendencies in young people [12]. This is one of many reasons why there is a growing public awareness of the existence of online communities, with questions being raised about the extent to which online communities may play some role in encouraging those with suicidal tendencies to follow through on their suicidal thoughts or, indeed, about the possibility that these communities might encourage the development of such thoughts in previously healthy young people [12, 13]. The Internet is coming to be popularly regarded as a breeding ground for dark, depressive thoughts and as providing encouragement to those with suicidal tendencies.

Despite the media speculation, what is not yet evident is whether excessive Internet use is clearly associated with depressive symptoms. The link between IA and depression was first suggested more than a decade ago, when Young and Rogers [14] reported a relationship between high levels of depressions as measured by the Beck Depression Inventory (BDI) and IA as measured by the IA Test (IAT) [9] in a sample of 259 adults. Despite this intriguing evidence, little has appeared in the literature since. However, a recent study of South Korean adolescents added weight to this evidence [15], suggesting that those with a tendency towards IA exhibited more symptoms of depression. However, this study was limited in terms of a low sample size and the fact that only 8 participants were firmly classifiable as Internet addicted.

The present study was a much larger-scale analysis of IA and its relationship to depression in young adults in the UK. We aimed to identify whether there was a link between depressive tendencies and Internet use, and fur-

thermore whether any link was associated with particular aspects of Internet use, in view of the literature outlined above.

Method

Participants

A total of 1,319 respondents completed the questionnaires. Recruitment was via links placed on UK-based social networking sites. The age range of the respondents was 16–51 years, with a mean age of 21.24 years (SE = 0.11). Sixty-three percent of the respondents were women.

Materials

Three questionnaires were applied: Young's IAT [9], the Internet Function Questionnaire and the BDI [15]. The IAT consisted of 20 questions designed to identify people as mildly, moderately or severely addicted. It is scored on a 100-point scale: ≤49 is considered normal, 50–79 is considered problematic and 80–100 is classed as significantly problematic. Questions include items such as 'How often do you find that you stay on-line longer than you intended?' and respondents are required to rate them on a 5-point scale where 1 = rarely and 5 = always. The Internet Function Questionnaire measured the different uses people have for the Internet (eBay/shopping, communities, browsing, games, chat, gambling, e-mail, research and sexually gratifying sites), taking into account the percentage of time spent browsing these respective forms of website. It includes questions such as 'How much of your online time do you spend on e-mail?', again on a 5-point scale: 1 = 0–20%, 2 = 21–40%, 3 = 41–60%, 4 = 61–80% and 5 = 81–100%. The BDI is a long-standing, widely used, self-evaluation depression scale. Online versions of the questionnaires were constructed using UCCASS software and were hosted on a Tsohost server. Data were recorded by the SQL database programme. Ethical approval was obtained from the Institute of Psychological Sciences Ethics Committee and procedures were put in place to offer advice to any respondent who reacted adversely to the questionnaires.

Design

The primary method of data analysis was correlational analysis. Furthermore, we aimed to identify a subgroup of participants in the 'addicted' range as measured by the IAT and match them with 'non-addicted' respondents in a factorial analysis in order to explore the links between Internet dependence, depression and different forms of online activity.

Results

The data were heavily skewed as far as age was concerned, with a range of 16–51, but a mean of 21.24 years (SE = 0.11). Skewness analysis yielded a value of 2.55, indicating a positive skew to the data. The age data were $\log_{10}$ transformed, which reduced the skewness value to 1.40. Correlational analyses of the total data sample showed a close relationship between scores on the IAT and BDI, such that those with more addictive tendencies also tended to be more depressed. This is shown in table 1, with a highly significant positive correlation between IA and BDI. It also seems that there is an age bias, with younger people being more addicted than middle-aged people. There was also, as would be expected, a highly significant correlation between IA score and the average time spent online. And when asked how they apportion time to different activities, those who scored more highly on IA spent proportionately more time on online gaming sites, sexually gratifying websites, browsing, online communities and chat sites. There were only weak negative correlations, though some suggestion that less addicted people use the Internet more for research. These patterns are mirrored, though less strongly, in the BDI scores: people who were more depressed spent proportionately more time on browsing, sexually gratifying sites, chat, online gaming sites and online communities. The lack of any significant negative correlations between BDI and the different activities suggests that non-depressed people did not use the Internet principally for a limited range of activities, but have a broad range of uses. The correlations with age show that older people use chat sites less and gambling sites more than young people. And sex differences are evident in that women use the Internet more for research, e-mail and chat than do men, and less for sexually gratifying sites, games and browsing.

Multiple regression analysis was used to examine the predictors of IA. The independent variables were BDI score, age and sex. The overall equation was highly significant: MS = 16,637; $R^2 = 0.256$; $F_{3, 1,315} = 150.68$, and $p < 0.0001$. The BDI was the best predictor of IA ($t = 20.57$; $p < 0.0001$), such that high IA scores were linked to high levels of depression; the unstandardised coefficient was 0.78 (95% confidence interval: 0.70–0.85). Sex was also significant, such that men reported more addictive tendencies than women ($t = 3.61$; $p < 0.0001$; unstandardised coefficient: –2.25; 95% confidence interval: –3.50 to –1.03). Age was also significant ($t = –3.21$; $p = 0.001$; unstandardised coefficient: –13.40; 95% confidence interval: –21.60 to –5.20), such that young people had higher IA scores than older people.

Of the 1,319 respondents, 18 were classed as being Internet addicted, with a score of ≥75 on the IAT; hence, only a small minority of respondents (1.2%) showed serious addictive behaviour (the IA group). These 18 addicts were matched on age and sex to participants who had low scores for IA by Young's definition (scoring ≤45); they

Table 1. Correlation matrix for measures of IA, BDI, age and sex of respondent, and average time spent online (time) with ratings for percent proportion of time spent on different activities or types of website

	BDI	Age	Sex	Time	eBay/ shopping	Communities	Browsing	Games	Chat	Gambling	E-mail	Research	Sexual gratification	Other
IA	0.493**	–0.103**	–0.073**	0.435**	–0.032	0.169**	0.181**	0.228**	0.159**	–0.015	–0.062*	–0.078**	0.216**	0.164**
BDI	1	–0.058*	0.022	0.255**	0.010	0.075**	0.140**	0.077*	0.120**	0.039	–0.055	–0.010	0.130**	0.064*
Age		1	–0.020	0.015	0.030	–0.052	–0.033	–0.046	–0.234**	0.090**	0.012	0.028	–0.026	–0.032
Sex			1	–0.246**	0.069*	0.004	–0.123**	–0.142**	0.132**	–0.078*	0.177**	0.253**	–0.245**	0.030
Time				1	–0.025	0.047	0.262**	0.239**	0.160**	0.011	–0.180**	–0.148**	0.100**	0.153**
eBay/shopping					1	0.007	0.010	–0.017	0.046	–0.016	0.127**	0.026	–0.011	0.031
Communities						1	0.043	–0.159**	0.080**	0.042	–0.003	0.026	0.089**	–0.016
Browsing							1	0.032	0.136**	0.040	–0.051	0.079**	0.117**	0.153**
Games								1	0.012	0.053	–0.089**	–0.158**	0.113**	0.007
Chat									1	0.022	0.065*	0.125**	0.069*	0.194**
Gambling										1	–0.013	0.076*	0.119**	0.114**
E-mail											1	0.158**	–0.060	0.020
Research												1	0.086**	0.220**
Sexual gratification													1	0.199**

* $p < 0.05$, ** $p < 0.01$ (2-tailed).

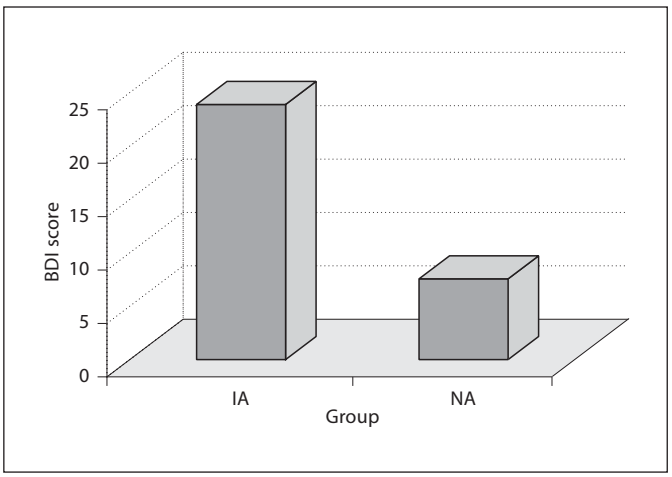

Fig. 1. Difference in BDI score between IA and NA groups.

Table 2. Mean values of time spent and BDI for the IA and NA groups

	IA	NA
Average use (1–5 scale)	3.94 (0.06) 3.83–4.06	2.22 (0.24) 1.72–2.72
BDI	23.89 (3.00) 17.56–30.22	4.06 (1.67) 0.52–7.59

Values in parentheses are SEs. Confidence intervals are listed beneath means and SEs.

formed the matched non-addicted (NA) group. In each group, there were 13 males and 5 females, and the mean age of both groups was 18.3 years. Comparisons were made between the groups on several key measures; summary descriptives are shown in table 2. Not surprisingly, the average use for those in the IA group was significantly greater than for those in the NA group (MS = 26.69; $F_{1, 34} = 50.27$; $p < 0.0001$).

The difference in BDI scores between the groups is illustrated in figure 1; the difference between groups was highly significant ($F_{1, 34} = 33.3$; $p < 0.0001$), such that there was a higher level of depressive symptoms in the IA group than in the NA group. This mean score for the IA group puts them in the category of moderate-to-severe levels of depression according to Beck et al. [15].

We also compared the relative proportions of time spent on different activities, and the results are shown in

Table 3. Comparison of proportion of time spent on different Internet activities for IA and NA groups

	NA group	IA group	Summary statistics		
			MS	F	p
Sexually gratifying sites	1.36 (0.169) 0.99–1.72	3.33 (0.513) 2.23–4.43	28.28	(1, 27) = 12.611	0.001
Games	2.07 (0.474) 1.05–3.10	4.00 (0.412) 3.13–4.87	29.290	(1, 30) = 9.456	<0.005
Chat	2.13 (0.487) 1.09–3.18	4.13 (0.496) 3.07–5.20	30.000	(1, 28) = 8.279	<0.01
Browsing	2.56 (0.353) 1.81–3.32	3.72 (0.360) 2.96–4.48	11.393	(1, 32) = 5.242	<0.05
Community	2.94 (0.431) 2.03–3.85	4.24 (0.442) 3.30–5.17	14.568	(1, 33) = 4.37	<0.05
E-mail	2.27 (0.419) 1.37–3.17	1.78 (0.275) 1.20–2.36	1.956	(1, 31) = 1.01	>0.1
Research	2.5 (0.303) 1.85–3.15	2.13 (0.424) 1.22–3.04	1.041	(1, 29) = 0.505	>0.1
Gambling	1.0 (0.000) 1.00–1.00	1.45 (0.455) 0.44–2.47	1.082	(1, 19) = 0.905	>0.1
eBay/shopping	1.12 (0.081) 0.95–1.29	1.07 (0.067) 0.92–1.21	0.021	(1, 30) = 0.23	>0.1
Other	1.67 (0.333) 0.93–2.40	2.50 (0.562) 1.29–3.71	4.487	(1, 24) = 1.492	>0.1

Values in the NA and IA group columns are means (SEs in parentheses), on a scale of 1 = rarely/never to 6 = very frequently. Confidence intervals are listed beneath means and SEs.

table 3. These data back up the evidence from the correlation matrix, showing that the IA group spent significantly more time on sexually gratifying sites, gaming sites, chat sites, browsing and community sites. The activities for which the NA group had a preference did not differ significantly, indicating that the NA group have a more even spread of activities.

Discussion

In summary, we found a clear link between IA and depression, such that those whom we classed as addicted were significantly more depressed than those in the NA group. Hence we have identified a statistically significant relationship between IA and depression. What is not clear from these data is which comes first: are depressed people drawn to the Internet, or does excessive Internet use make one more prone to depression? This needs further work in the future, but it is clear that, for a small subgroup of the population, excessive use of the Internet is a warning signal of depressive tendencies. However, in line with previous studies, this subgroup represents <2% of the population. This is the figure typically reported in the literature, and it is higher than the incidence of gambling in the UK, which stands at around 0.6% [16].

When considering the functions of the Internet, the important point to note is that there was a significant difference between the groups in terms of sexually gratifying websites, online games and chat/community sites, such that the IA group engaged significantly more in these sites than did the NA group. This accords with recent evidence suggesting that those prone to dependence on the Internet are drawn to sites that involve these 3 types of activities [2]. This feeds the public speculation that overengagement in websites that serve/replace a so-

cial function might be linked to maladaptive psychological functioning.

This is the first large-scale study of Western young people to consider the relationship between IA and depression. Much of the research on IA has been carried out in East Asia, where Internet infrastructures are more advanced than in the West. A recent, smaller-scale study of 452 South Korean adolescents [17] presented data that accord with our findings: the authors reported a significant relationship between IA as measured by the IAT and depression as measured by a Korean version of the CES-D (Center for the Epidemiologic Study of Depression). And, similar to the present results, they found a rate of severe addiction of 1.8% (compared to our 1.2%). However, because of the relatively low number of participants in their study, the criteria for classing respondents as addicted were not as stringent as in our study; they simply did a median split of their respondents into 2 groups and classed those who scored more highly on the IAT as addicted, and the rest as non-addicted. The present study adopted a much more stringent method of group allocation, such that we were able to isolate a group we could firmly label as addicted and compare them with a matched control group. Hence, this study provides the first compelling evidence of a clear link between IA and depression.

Where we believe we need to be cautious is with the measures that are currently available to assess IA. In line with most studies on this topic, we used the IAT questionnaire [9]. Whilst this questionnaire appears to capture essential features of what addiction to the Internet might involve, other tools that have been developed subsequently, within different theoretical frameworks, include measures of social isolation [18] and loneliness [19]. Beard [11] has urged caution in accepting the reliability and validity of these tools, and we are at a juncture where, if IA is to be accepted as a distinct disorder, there is an urgent need for a well-validated assessment tool. A recent meta-analysis of the literature also urges caution in drawing conclusions from studies that use inconsistent methods and analysis [20], and an emerging view is that diagnostic tools should be used within a comprehensive framework of clinical assessment [1, 8].

In conclusion, the present data have added to the as yet small but compelling body of evidence on the link between high levels of depression and IA. Furthermore, the present data add weight to the recent suggestion that IA should be taken seriously as a distinct psychiatric construct. We echo growing calls for the inclusion of IA as a distinct disorder in the forthcoming DSM-V [2]. It is vital that this issue receives adequate attention now.

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Mail Online

'Internet addiction' linked to depression, says study

By Jenny Hope
Last updated at 10:27 AM on 03rd February 2010

Surfing the internet can expose a 'dark side' of the soul, with online addicts more likely to be depressed, claim psychologists.

They found the longer people spent on websites, the more unhappy they were.

Those worst affected are both depressed and addicted, possibly because they are substituting the net for normal social activities..

Dependent? Researchers found that the longer people spent on websites, the more unhappy they were

Research leader Dr Catriona Morrison, from the University of Leeds, said: 'The internet plays a huge part in modern life, but its benefits are accompanied by a darker side.'

Researchers questioned 1,319 people aged from 16 to 51 to assess levels of internet dependency and depression.

In general, the longer people spent online the more depressed they tended to be, reported the journal Psychopathology.

Dr Morrison said: 'There was a high correspondence between the amount of time spent on the internet and levels of depression.

'If you look at how dependent people feel they are on the internet, that is likely to correspond with how happy or sad they feel.'

The research team identified 18 hard-core internet users who spent many hours online each day and were classed as 'internet addicted'.

Their average depression score was more than five times higher than that of non-addicted users, and they were more likely to be moderately or severely depressed.

DOES BEING INTER THE NET BRING YOU DOWN LOADS?

By Emily Cook
3/02/2010

Surfing link to depression

Surfing the net endlessly could lead to depression, scientists warned yesterday.

Experts found twice as many people are addicted to the web than gambling and fear overuse may spark mental problems.

Study leader Dr Catriona Morrison urged relatives to keep a close eye on anyone who appears to be hooked for signs of psychological changes.

She added: "The internet's benefits are accompanied by a darker side.

"Our study indicates excessive internet use is associated with depression. What we don't know is what comes first. Are depressed people drawn to the net or does the internet cause depression?" The Leeds University survey, published in the journal Psychopathology, did not quiz surfers on how long they actually spent online - but how it affected their lives. Dr Morrison added: "It can interfere with daily living and lead to abnormal behaviour."

Researchers found those most at risk were young adults and the average age of addicts was 21.

They revealed 1.2% of people were hooked on the net, compared with 0.6% for gambling addicts.

Brainy children are more likely to suffer manic depression, a joint study in London and Sweden found.

No10's web 'too leaky'

Worried web experts have started a Downing Street petition calling for the UK government to drop Microsoft's Internet Explorer 6 because they say it is a security risk.

The petition urges the government to use a more modern browser in the wake of Google's claim IE6 was the "weak link" that allowed China to hack into dissidents' email accounts.

It has been set up by web firm boss Dan Frydman and has been signed by 44 people.

Microsoft has released two updated browsers since IE6 was introduced in 2001.

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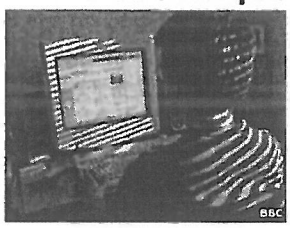
'Internet addiction' linked to depression, says study

There is a strong link between heavy internet use and depression, UK psychologists have said.

The study, reported in the journal Psychopathology, found 1.2% of people surveyed were "internet addicts", and many of these were depressed.



Any direct causal link between internet use and depression remains unclear

The Leeds University team stressed they could not say one necessarily caused the other, and that most internet users did not suffer mental health problems.

The conclusions were based on 1,319 responses to an on-line questionnaire.

Recruitment was via links on social networking sites. People were asked how much they used the internet and for what purposes.

They were also asked a series of questions to assess whether they suffered from depression.

The respondents were aged 16 to 51, with an average age of 21.

The authors found that a small number of users had developed a compulsive internet habit, replacing real life social interaction with online chat rooms and social networking sites.

> **"If a web addict is substituting meaningful friendships and socialising with virtual contact on the internet, this might have an adverse affect on their mental wellbeing"**
>
> Sophie Corlett of the charity Mind

They classed 18 respondents - 1.2% of the total - as "internet addicts".

This group spent proportionately more time on sex, gambling and online community websites.

'Darker side'

Lead author Dr Catriona Morrison said: "The internet now plays a huge part in modern life, but its benefits are accompanied by a darker side.

"While many of us use the internet to pay bills, shop and send e-mails, there is a small subset of the population who find it hard to control how much time they spend online, to the point where it interferes with their daily activities."

The internet addicts were significantly more depressed than the non-addicted group, with a depression score five times higher.

The average score of the internet-addicted group put them in the category of moderate-to-severe levels of depression.

"Our research indicates that excessive internet use is associated with depression, but what we don't know is which comes first - are depressed people drawn to the internet or does the internet cause depression?" said Dr Morrison.

> **"There is no good evidence that the problem is the internet itself"**
>
> Dr Vaughan Bell of King's College London

"Now we need to investigate the nature of that relationship and consider the issue of causation."

'Emotional distress'

Critics of the research say that internet addiction cannot be diagnosed reliably.

Dr Vaughan Bell, from the Institute of Psychiatry at King's College London said that by definition, those identified as "internet addicts" are emotionally distressed, so the conclusions are "not a big surprise".

In terms of cause and effect, he pointed out that previous research has

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suggested that people who are depressed or anxious may be more likely to use the internet rather than the other way round.

He added: "There are genuinely people who are depressed or anxious who use the internet to the exclusion of the rest of their lives, but there are similar people who watch too much TV, bury themselves in books or go shopping to excess.

"There is no good evidence that the problem is the internet itself."

Mental Health charities said the way people spend their time and the kind of social interaction they engage in could well impact on mental wellbeing.

"Social connections"

Dr Andrew McCulloch, chief executive of the Mental Health Foundation, pointed out that, in some ways, the internet can be helpful.

He said: "To the extent that the internet encourages meaningful friendships and social connections it can be a very good influence on people's lives.

"However, social interaction online should not usually replace an offline social life. We should take note of this study's findings - it suggests that further research in the area is needed."

Sophie Corlett, of the mental health charity Mind, said: "Evidence suggests that active pursuits such as exercise and socialising with people face-to-face are among the factors that help us stay in good mental health.

"Although excessive internet use can't be said to cause mental health problems, if a web addict is substituting meaningful friendships and socialising with virtual contact on the internet, this might have an adverse affect on their mental wellbeing."

PLOS ONE

RESEARCH ARTICLE

Role of magnesium supplementation in the treatment of depression: A randomized clinical trial

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Abstract

Current treatment options for depression are limited by efficacy, cost, availability, side effects, and acceptability to patients. Several studies have looked at the association between magnesium and depression, yet its role in symptom management is unclear. The objective of this trial was to test whether supplementation with over-the-counter magnesium chloride improves symptoms of depression. An open-label, blocked, randomized, cross-over trial was carried out in outpatient primary care clinics on 126 adults (mean age 52; 38% male) diagnosed with and currently experiencing mild-to-moderate symptoms with Patient Health Questionnaire-9 (PHQ-9) scores of 5–19. The intervention was 6 weeks of active treatment (248 mg of elemental magnesium per day) compared to 6 weeks of control (no treatment). Assessments of depression symptoms were completed at bi-weekly phone calls. The primary outcome was the net difference in the change in depression symptoms from baseline to the end of each treatment period. Secondary outcomes included changes in anxiety symptoms as well as adherence to the supplement regimen, appearance of adverse effects, and intention to use magnesium supplements in the future. Between June 2015 and May 2016, 112 participants provided analyzable data. Consumption of magnesium chloride for 6 weeks resulted in a clinically significant net improvement in PHQ-9 scores of -6.0 points (CI -7.9, -4.2; $P<0.001$) and net improvement in Generalized Anxiety Disorders-7 scores of -4.5 points (CI -6.6, -2.4; $P<0.001$). Average adherence was 83% by pill count. The supplements were well tolerated and 61% of participants reported they would use magnesium in the future. Similar effects were observed regardless of age, gender, baseline severity of depression, baseline magnesium level, or use of antidepressant treatments. Effects were observed within two weeks. Magnesium is effective for mild-to-moderate depression in adults. It works quickly and is well tolerated without the need for close monitoring for toxicity.

Competing interests: The authors have declared that no competing interests exist.

Introduction

Depression affects 350 million people worldwide and is predicted to be the leading cause of disease burden by 2030, based on disability-adjusted-life-year [1]. Initial antidepressant trials of adequate dose and duration result in only about 50% of patients achieving remission [2]. Even after the addition of other treatments, 20% still suffer from symptoms after 2 years. Non-pharmacologic approaches such as Cognitive Behavioral Therapy and lifestyle interventions require highly trained therapists and several weeks to months to achieve effectiveness [3]. There is a great need for additional treatment options.

The association between magnesium intake and depression is well documented [4–7]. Improvement in depression with magnesium supplementation has been reported inconsistently [8, 9], although few clinical trials exist. One trial found magnesium chloride to be effective for depression in seniors with type 2 diabetes [10] while another trial found magnesium citrate decreased depression in patients with fibromyalgia [11]. One negative trial used magnesium oxide [12], known to be poorly absorbed.

The aim of this study was to test the hypothesis that 6 weeks of oral magnesium chloride ($MgCl_2$) supplementation will improve symptoms of mild-to-moderate depression in a primary care population.

Methods

Trial design

This was a 12-week open label randomized cross-over control trial. Participants were recruited through primary care providers (PCPs) within a single academic medical center and randomized to begin $MgCl_2$ supplementation immediately or at week 7 (delayed). During the other 6-week period, they took no $MgCl_2$. Prior to the start of the study the Institutional Review Board of the University of Vermont approved the study. All subjects provided written informed consent. Trial registry can be found at clinicatrials.gov (Identifier: 02466087).

Participants

The target population was adults with mild-to-moderate depression. Inclusion criteria were: 1) 18 years of age or older; 2) no change in treatment plan for depression for the past 2 months and going forward (including no current treatment, stable use of antidepressant medication, or ongoing nonpharmacologic therapy); 3) Patient Health Questionnaire-9 (PHQ-9) score of 5–19 [13]. Exclusion criteria were: 1) Schizophrenia, bipolar disease, active delirium, dementia, kidney disease (due to the role of the kidneys in magnesium homeostasis), myasthenia gravis (magnesium may worsen symptoms of the disease), or gastrointestinal (GI) disease (diarrhea is a common side effect of magnesium); 2) pregnant or trying to get pregnant; 3) planned surgery in the next 3 months; 5) taking a medication known to interact with magnesium; 6) unwilling to stop taking non-study magnesium supplements for the duration of the study.

Magnesium supplements

Tablets of $MgCl_2$ (Alta Health Products, Idaho City, ID) were provided free of charge. Participants were instructed to take four 500 mg tablets of magnesium chloride daily for a total of 248 mg of elemental magnesium per day. $MgCl_2$ was used because of its high bioavailability and tolerability compared to other salts [14, 15].

Study procedures and randomization

PCPs reviewed lists of their patients with a diagnosis of depression in their medical record and indicated which ones may be sent a letter describing the study. PCPs were encouraged to remove patients from their list if they knew depression was no longer an active problem, the patient was also suffering from severe mental illness, or the patient was not able to start or stop taking magnesium. Those patients that did not opt out after receiving the letter were contacted by phone to determine interest and eligibility. Eligibility and diagnosis of depression was confirmed with an initial telephone PHQ-9 score between 5 and 19. Participants next met with study staff for a baseline visit during which they provided written informed consent and baseline data including demographics, medication use, the PHQ-9 [13], the Generalized Anxiety Disorders-7 (GAD-7) [16], the Modified Morisky Scale [17] to assess medication adherence behavior, the PhenX Tobacco Smoking Status Questionnaire for Adults, and the PhenX Alcohol 30 Day Quantity and Frequency Questionnaire [18]. Randomization to Immediate and Delayed treatment was stratified based on PHQ-9 score (5–9, 10–14, and 15–19) and blocked in groups of 10. Treatment assignments were sealed in an opaque envelope and shuffled and then numbered and opened in that order. The principal investigator (PI) assigned the participants to their randomization order. The PI also gave the volunteers the supplements at either week 1 or week 7, based on randomization, and educated each participant on the dosage and possible side effects. Data were collected every 2 weeks via telephone and included the PHQ-9, GAD-7, questions about changes in medications, changes in treatment for depression, and side effects.

Outcome measures

The primary hypothesis was that magnesium supplementation decreases symptoms of depression and therefore the primary outcome was the difference in the change in PHQ-9 scores between baseline and the end of each six-week period (difference in differences). The PHQ-9 is a validated questionnaire with high sensitivity and specificity for the diagnosis of depression [13]. The PHQ-9 score can range from 0 to 27, with the following severity scores: 0–4 None; 5–9 Mild; 10–14 Moderate; 15–19 Moderate to Severe; 20–27 Severe. Telephone administration is comparable to in-person tracking [19].

Secondary outcomes were exploratory and included changes in the GAD-7 score as well as adherence to the supplement regimen and intention to use magnesium supplements in the future. GAD-7 score was recorded in the same fashion as the PHQ-9 and has been shown to be a valid indication of anxiety symptoms [16]. The GAD-7 score can range from 0 to 21, with the following severity scores: 0–4 None; 5–9 Mild; 10–14 Moderate; 15–21 Severe. To assess side effects, participants were asked to compare symptoms (headache, diarrhea, nausea, constipation, dizziness, oliguria, and polyuria) to baseline using a standardized 0–4 point scale (none, mild, moderate, or severe). At the end of week 12, a pill count was used to calculate adherence to the supplement regimen and participants were asked whether they planned to continue using magnesium and why.

Data analysis

All data were analyzed based on the intention-to-treat principle. The age and gender of patients who were contacted but ineligible were compared to those who were randomized. Baseline characteristics of eligible participants were compared by randomization group. Student t-tests or Wilcoxon Rank Sum tests were used for continuous values and Chi-square tests for categorical values.

The change in outcome for each patient was calculated as the last value measured during that treatment arm minus the last value measured before that treatment arm. Before crossing

over, this was the week 6 measure minus the baseline measure. After cross-over, this was the week 12 measure minus the week 6 measure. If a week 12 measure was not available, the week 10 or week 8 measure was used. Participants who did not provide at least one outcome measure in each treatment period were excluded. Treatment efficacy was assessed as the net improvement in outcome. The mean change in the outcomes during the 6 weeks of the control (no treatment) period was compared to the change in scores during the 6 weeks of treatment. Linear regression was used to test the significance in the net improvement in the outcome while controlling for potential confounders.

Each potential confounder was tested in a separate univariate linear regression for association ($P<0.05$) with the primary outcome and secondary outcome. Potential confounders were included in multivariate models. We explored the effectiveness of treatment among various subgroups using multivariate models. Linear regression adjusting for randomization and clustering was used to identify adverse effects. Cuzick's test of trend [20] was used to explore the relationships between both the Modified Morisky score and treatment response with adherence. A two-sided $P<0.05$ was considered statistically significant. All analyses were completed using Stata14·1 (College Station, TX).

The targeted sample size was based on detection of a difference in difference in PHQ-9 scores of 1.5, which was felt to be clinically significant. The calculation, assuming a paired t-test, with 84% power, type I error rate of 5%, and a standard deviation of 5 [21], resulted in a sample size of 50 participants in each group.

Results

Recruitment occurred between June 2015 and May 2016. Of 1,930 patients identified from medical records, 1,340 (68%) were contacted and 126 (7%) were eligible and randomized (Fig 1). The mean age of the contacted patients was 50 years compared to a mean age of 52 years in the randomized group ($P = 0.06$). The randomized group had fewer males than the other contacted patients (38% *vs*.47%; $P = 0.07$).

Sixty-two participants (49%) were randomized to Immediate Treatment and 64 (51%) to Delayed Treatment ($P = 0.95$). The two groups were similar in all baseline characteristics except age. The mean age in the Immediate group was 55.6 versus 49.1 in the Delayed group ($P = 0.006$). All participants commenced treatment based on allocation. Seven participants withdrew from each group before crossing over (11%) (Fig 1). The most common reason was a change in other depression treatment (n = 7) (Table 1). No participants withdrew due to non-compliance. 108 participants completed all 12 weeks of the study. Four withdrew between week 8 and 12; their last results recorded before withdrawal were included in the final sample, resulting in 112 participants analyzed (Fig 1). The characteristics of the final analyzed sample appear in Table 2. The Immediate group was similar to the Delayed group except that they were 5.1 years older ($P = 0.04$).

The characteristics of the 14 subjects who withdrew before crossing over were similar in all measured characteristics to the 112 in the final sample except that they were more anxious (GAD-7 12.5 *vs*. 8.6; $P = 0.01$). There were no significant differences in age, gender, race, smoking, alcohol consumption, baseline PHQ-9 score, Modified Morisky score, or use of depression therapies at the time of randomization.

Outcomes

Unadjusted PHQ-9 depression scores improved during magnesium treatment (-4.3 points; 95% confidence interval (CI) -5.0, -3.6), but not during the control period (-0.1; CI -0.9, +0.7) for the final analyzable cohort of 112 adults. The net improvement was -4.2 points (CI -5.4,

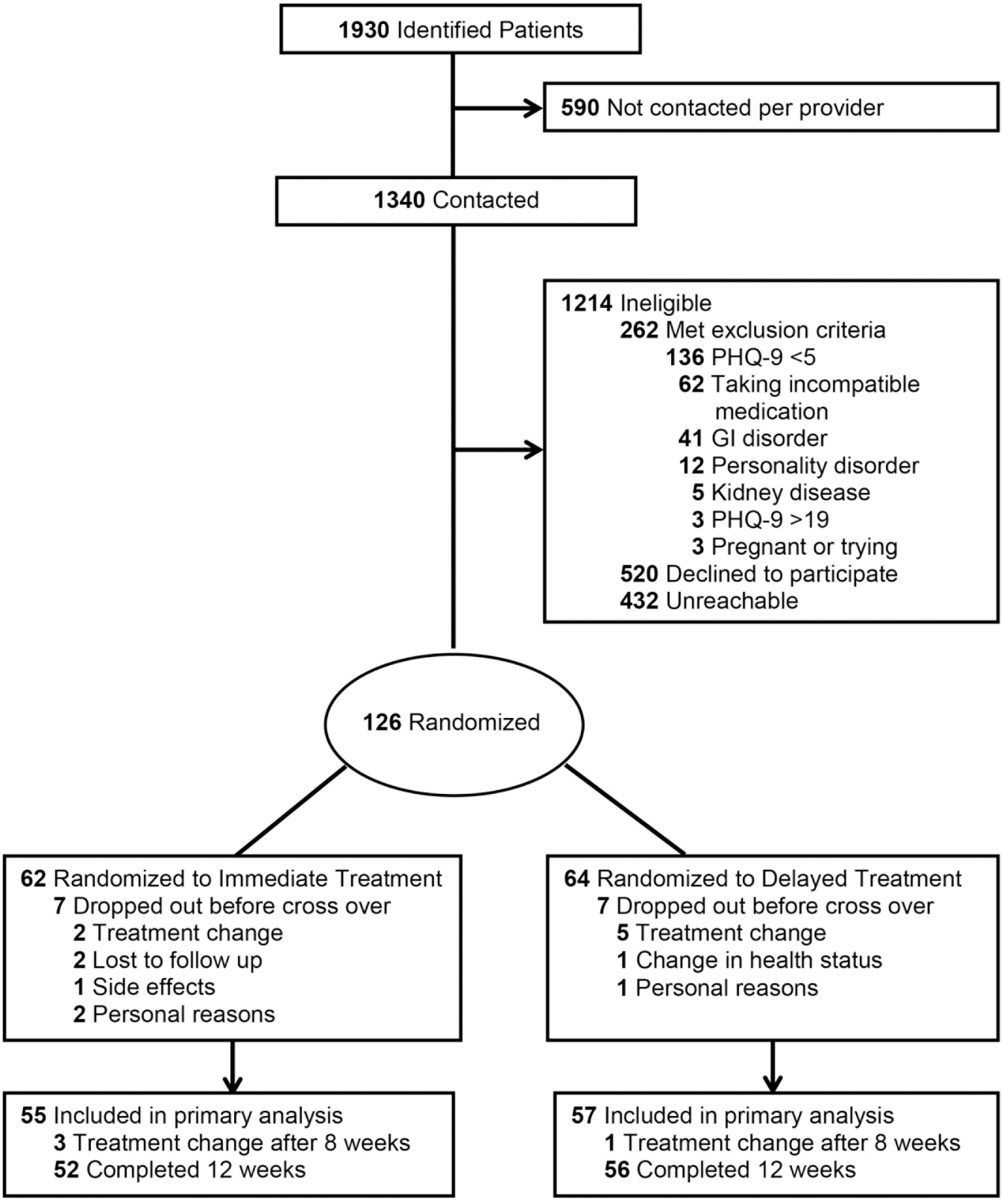

Fig 1. Consort diagram.

https://doi.org/10.1371/journal.pone.0180067.g001

Table 1. Withdrawals by reason and time point.

Reason for withdrawal	*Week 2*	*Week 4*	*Week 6*	*×*	*Week 8*	*Week 10*	*Week 12*	*Total*
Treatment Change for Depression	3	3	1	Cross-over		2[a]	2[a]	11
Side Effects	1							1
Change in Health Status		1						1
Personal Reasons			1					1
No Reason Given		1	1					2
Lost to Follow Up	1		1					2
Total number of withdrawals	5	5	4		0	2[a]	2[a]	18

[a]These participants were included in the final analysis using their last recorded values.

https://doi.org/10.1371/journal.pone.0180067.t001

-2.9; $P<0.001$). Participants who were randomized to Immediate Treatment first experienced a decrease in PHQ-9 score within 2 weeks; their scores increased slightly towards baseline during the 6 weeks of control (Fig 2). Those in the Delayed Treatment group experienced a slight improvement in PHQ-9 score during the control weeks and a further improvement during the active treatment.

Age, gender, race, smoking status, drinks of alcohol per week, adherence to the supplement regimen, and other treatments for depression were not associated with response to treatment and were not included in the adjusted model. Mean PHQ-9 change during the control weeks, randomization order, and use of selective serotonin reuptake inhibitors (SSRI) were retained in the multivariate analyses. When adjusted for these potential confounders, the net

Table 2. Demographic characteristics of final sample (N = 112).

Characteristic	*Randomization Group*		*P-Value*
	Immediate (N = 55)	*Delayed (N = 57)*	
Age, mean (SD)	55.2 (12.3)	50.1 (13.0)	0.038
Male Gender, N (%)	22 (40%)	22 (36%)	>0.99
Self-Report White Race, N (%)	53 (96%)	56 (98%)	0.62
Current Smoker, N (%)	7 (13%)	8 (12%)	>0.99
Servings of Alcohol Per Week, mean (SD)	3.3 (5.0)	4.9 (7.8)	0.19
Current Treatment for Depression, N (%)			
No Treatment	14 (25%)	17 (30%)	0.68
Self-management	1 (2%)	1 (2%)	>0.99
Non-pharmacologic Therapy	14 (26%)	11(19%)	0.50
One or more medications	35 (64%)	35 (61%)	0.85
Selective Serotonin Reuptake Inhibitors	19 (35%)	22 (39%)	0.70
Selective Norepinephrine Reuptake Inhibitors	8 (15%)	8 (14%)	>0.99
Tricyclic	2 (4%)	1 (2%)	0.61
Bupropion	7 (13%)	9 (16%)	0.80
Monoamine Oxidase Inhibitors	0	0	-
Antipsychotic	0	2 (4%)	0.50
Baseline Patient Health Questionnaire-9 Depression Score, mean (SD)	10.7 (3.7)	10.6 (3.8)	0.84
Baseline Generalized Anxiety Disorder-7 Anxiety Score, mean (SD)	8.6 (5.1)	8.7 (5.4)	0.92
Modified Morisky Score, mean (SD)	2.9 (0.9)	2.9 (1.0)	0.91

N = number; SD = standard deviation.

P-values calculated by Chi-square for categorical values and two-sample t-test or Wilcoxon Rank Sum for continuous values.

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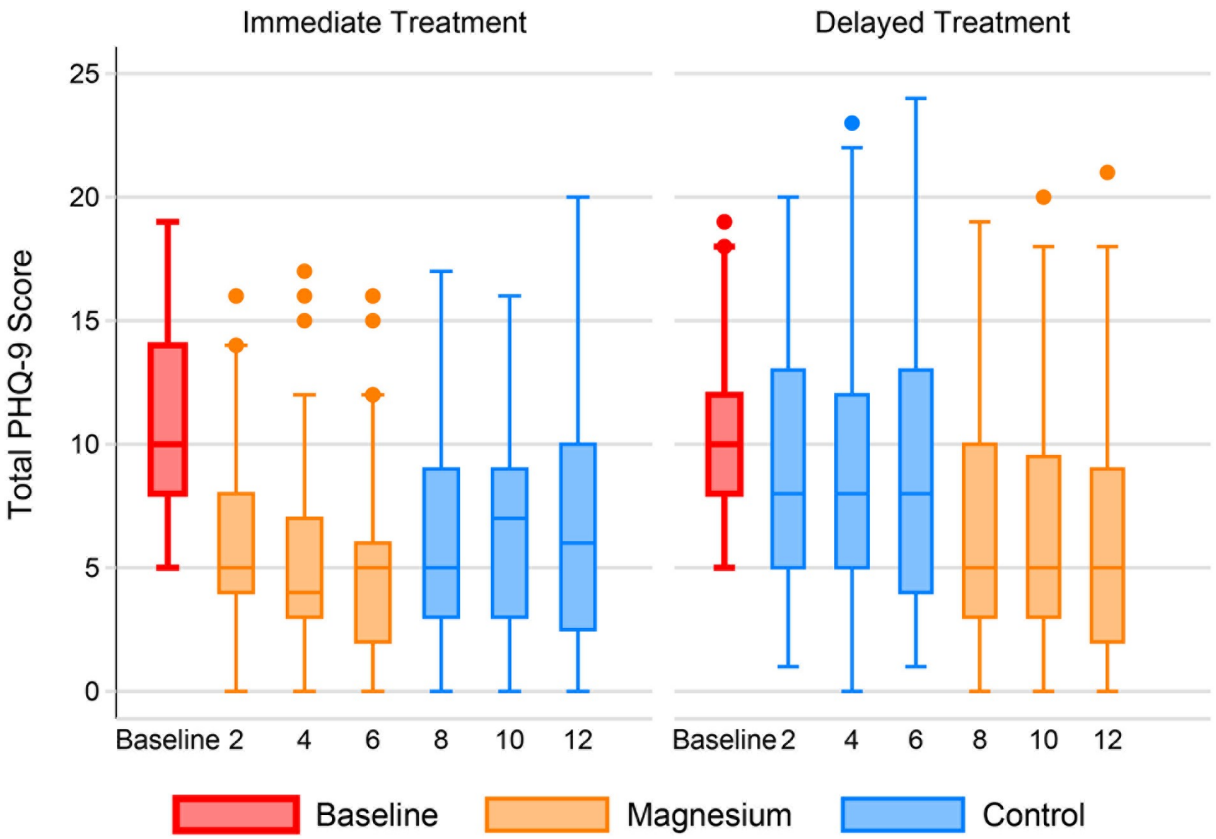

Fig 2. Patient Health Questionnaire-9 over time by group. The individual box plots show the distribution of PHQ-9 scores by week in each randomization group. The middle line of each box represents the median score. The boxes range from the 25th to the 75th percentile. The whiskers demonstrate the range of scores with outliers shown by small circles.

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improvement with supplementation was -6.0 points (CI -7.9, -4.2; $P<0.001$). See Table 3. Data for all participants (N = 126) follow a similar pattern (Table 4).

Unadjusted GAD-7 anxiety scores improved during magnesium supplementation (-3.9 points; CI -4.7, -3.1), but worsened during the control period (+0.8; CI +0.02, +1.6) for a net benefit of -4·7 points (CI -6.0, -3.3; $P<0.001$) (Fig 3). After adjustment for potential confounders (Table 3), the net improvement in anxiety with magnesium supplementation was -4.5 points (CI -6.6, -2.4; $P<0.001$). Again, the data are similar for all participants as well (Table 4).

Subgroup analyses were performed using the adjusted models of the association of magnesium with PHQ-9 and GAD-7 scores. Subgroups were defined by gender, age above or below 55, PHQ above or below 9, GAD above or below 9, use of any antidepressant medications, use of specific medications (SSRIs, selective norepinephrine reuptake inhibitors, bupropion, monoamine oxidase inhibitors, antipsychotics), use of behavioral therapy or counseling, and adherence above or below 80% by pill count. The analyses indicated that magnesium was effective in all subgroups (Table 3).

Participants were less likely to report headaches while taking magnesium compared to the control period (unadjusted mean headache score 0.41 *vs*. 0.57 on the 0–3 scale). The adjusted difference was -0.16 (CI -0.25, -0.03; $P = 0.013$). There was no difference in the reporting of diarrhea, constipation, nausea, dizziness or urinary symptoms (Table 5).

Using the adjusted model, we explored the effect of magnesium supplementation on the answers to individual PHQ-9 and GAD-7 items. All items in the PHQ-9 improved

Table 3. Adjusted net improvement[a] with magnesium.

			PHQ-9			GAD-7		
		N	*Change*	*95% CI*	*P*	*Change*	*95% CI*	*P*
All subjects	Magnesium	112	-4.9	-6.0, -3.9	<0.001	-3.6	-4.9, -2.3	<0.001
	Control	112	+1.1	-0.1, +2.3	0.08	+0.9	-0.4, +2.1	0.17
	Net Improvement		-6.0	-7.9, -4.2	<0.001	-4.5	-6.6, -2.4	<0.001
Subgroups			*Net Improvement*	*95% CI*	*P*	*Net Improvement*	*95% CI*	*P*
Gender	Female	68	-6.6	-9.1, -4.0	<0.001	-3.8	-6.4, -1.1	0.003
	Male	44	-5.3	-7.6, -3.1	<0.001	-5.5	-8.9, -2.1	0.001
Age	≤55 years	55	-5.3	-7.9, -2.8	<0.001	-5.1	-8.6, -1.5	0.002
	>55 years	57	-6.5	-9.0, -4.1	<0.001	-4.0	-6.6, -1.5	0.001
Baseline PHQ-9	≤9	49	-4.7	-6.3, -3.2	<0.001	-3.1	-4.8, -1.3	<0.001
	>9	63	-7.2	-10.1, -4.2	<0.001	-5.6	-9.2, -2.1	0.001
Baseline GAD-7	≤9	68	-4.7	-6.8, -2.6	<0.001	-2.2	-4.0, -0.5	0.005
	>9	44	-8.2	-11.0, -5.3	<0.001	-8.3	-12.6, -3.9	<0.001
Adherence	Low	56	-5.3	-8.2, -2.5	<0.001	-3.3	-5.9, -0.6	0.008
	High	56	-6.6	-8.7, -4.6	<0.001	-5.7	-8.7, -2.7	<0.001

PHQ-9 = Patient Health Questionnaire-9; GAD-7 = Generalized Anxiety Disorder-7; CI = confidence interval.

[a]Net Improvement = change in outcome during magnesium treatment–change in outcome during control.

All results adjusted for mean PHQ-9 score during control weeks, treatment order (Immediate *vs*. Delayed), and selective serotonin reuptake inhibitor (SSRI) therapy.

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significantly during active treatment except question 8 (abnormal movement speed) and question 9 (thoughts of suicide). Of note, question 9 was positive on only 3 of 892 occasions. The only GAD-7 questions that did not improve significantly were questions 1 (feeling nervous, anxious, or on edge) and 5 (experiencing restlessness).

Percent adherence in the Immediate Treatment group (83%) and Delayed Treatment group (82%) were similar ($P = 0{\cdot}85$). Treatment response for both the PHQ-9 and GAD-7 tended to be greater with increased adherence; however, the trend was not significant for either at $P = 0.19$ and $P = 0.64$, respectively.

When asked whether they would take magnesium in the future, 68 (61%) answered yes, 22 (20%) answered maybe and 22 (20%) answered no. The most common reasons for a positive answer were "the magnesium helped my mood" (58%) and "it helped in other ways" (23%), such as by increasing energy, decreasing constipation, and decreasing muscle aches and cramps. The most common reason for a negative response was that "magnesium did not help mood" (46%), followed by side effects (20%). The most common side effect, diarrhea, was reported by 8 participants.

Discussion

This trial was conducted to test the efficacy and safety of over-the-counter magnesium and to determine its role in the treatment of depression. Consumption of 248 mg of elemental $MgCl_2$ daily for 6 weeks improved depression scores by a statistically and clinically significant mean of 6 points and anxiety by over 4 points. This effect was not due to natural history, regression to the mean, or confounding, and was seen in a wide range of patients with varying ages, co-treatments, and severity of baseline symptoms. The similar effects seen in the univariate and multivariate models indicates that the potential confounders had little impact on the estimates of treatment effect.

Table 4. Unadjusted PHQ-9 and GAD-7 scores by event for all participants (N = 126).

	Patient Health Questionnaire-9			*Generalized Anxiety Disorder-7*		
	Randomized Treatment Assignment		*Total*	*Randomized Treatment Assignment*		*Total*
Event	*Immediate*	*Delayed*		*Immediate*	*Delayed*	
Baseline, mean	10.9	10.8	10.8	8.9	9.2	9.0
SD	3.8	3.9	3.8	5.1	5.6	5.3
N	62	64	126	62	64	126
Week 2, mean	7.0	9.1	8.1	5.7	8.3	7.0
SD	4.7	4.9	4.9	4.7	5.4	5.2
N	60	63	123	60	63	123
Week 4, mean	5.8	8.9	7.4	4.9	7.8	6.4
SD	4.3	5.4	5.1	4.4	5.6	5.2
N	59	61	120	59	61	120
Week 6, mean	5.1	9.2	7.1	4.4	9.2	6.8
SD	3.9	5.6	5.2	4.0	5.9	5.6
N	57	57	114	57	57	114
Week 8, mean	6.1	6.8	6.5	5.5	6.2	5.9
SD	4.4	4.9	4.6	4.5	5.5	5.0
N	55	57	112	55	57	112
Week 10, mean	6.5	6.6	6.5	5.3	5.8	5.5
SD	3.9	4.5	4.2	4.3	5.4	4.9
N	52	56	108	52	56	108
Week 12, mean	6.3	6.3	6.3	5.2	5.8	5.5
SD	4.6	5.4	5.0	4.9	5.8	5.3
N	52	56	108	52	56	108

SD = standard deviation; N = number

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As with other studies, [8, 11, 22] the improvement in symptoms was seen within weeks. The effect was somewhat diminished within 2 weeks of stopping supplementation, indicating relatively quick clearance as well. Although females are more likely to be diagnosed with depression [23], there was no difference in effect based on gender. The finding that high and low adherence subgroups had similar improvement suggests that a smaller dose may suffice with less risk for side effects and lower cost.

Adverse effects were not so severe as to lead to discontinuation except in one case in which nausea and lethargy led to withdrawal after two weeks. Participants did report experiencing other clinically significant, and well documented, positive effects of taking magnesium, such as decreases in headaches and muscle cramps [24]. The fact that nearly all specific PHQ-9 and GAD-7 items improved significantly while on treatment corresponds with the qualitative reports.

Although the association between magnesium and depression is well documented, the mechanism is unknown. However, magnesium plays a role in many of the pathways, enzymes, hormones, and neurotransmitters involved in mood regulation [25]. It is a calcium antagonist and voltage-dependent blocker of the *N*-methyl-D-aspartate channel which regulates the flow of calcium into the neuron [26]. In low magnesium states, high levels of calcium and glutamate may deregulate synaptic function, resulting in depression [9]. Depression and magnesium are also both associated with systemic inflammation [27, 28]. The finding that those participants taking an SSRI experienced an even greater positive effect points toward magnesium's possible role in augmenting the effect of antidepressants. Since the mechanism of magnesium's role in

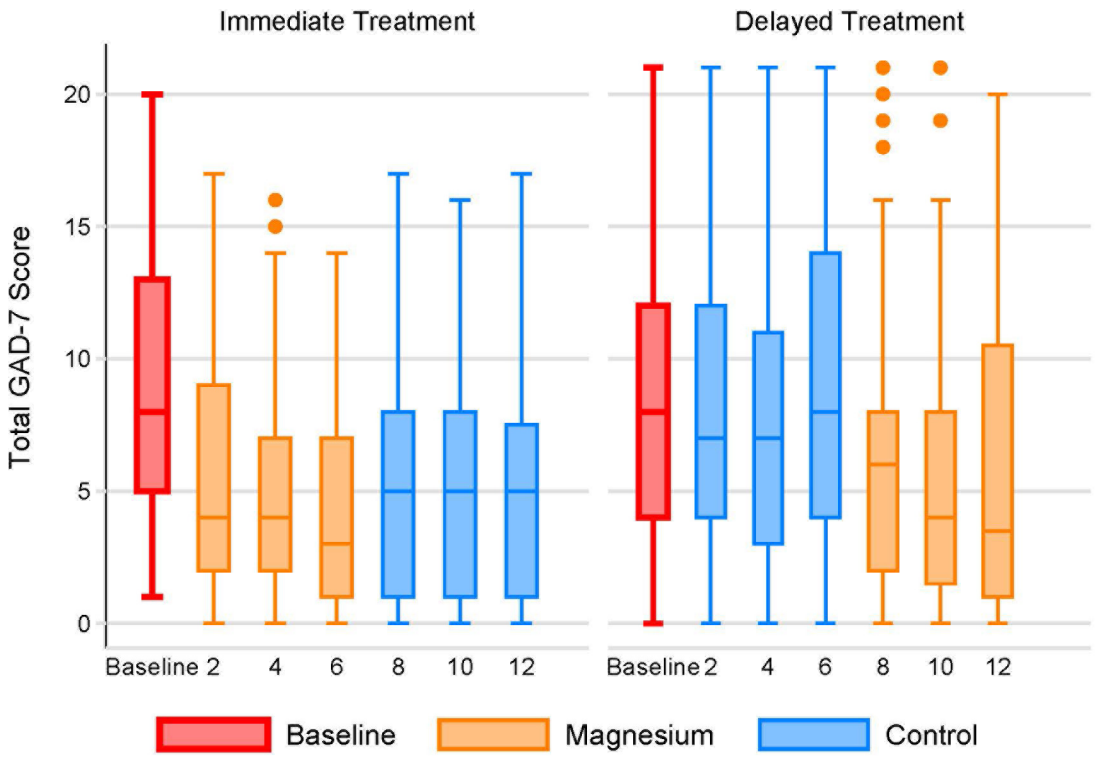

Fig 3. Generalized Anxiety Disorders-7 over time by group. The individual box plots show the distribution of PHQ-9 scores by week in each randomization group. The middle line of each box represents the median score. The boxes range from the 25th to the 75th percentile. The whiskers demonstrate the range of scores with outliers shown by small circles.

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depression is still not clear, it is difficult to say why this relationship with antidepressants may exist. In a sample of treatment resistant depressed patients with normal magnesium levels, those with high normal magnesium levels had a more robust response to antidepressants [29]. In another study, severity of depression correlated with reduced intracellular magnesium, and that cellular levels normalized after successful treatment with antidepressants [30]. Patients may have normal plasma concentration of magnesium yet have depleted intracellular stores

Table 5. Adverse effects during treatment[a].

	Unadjusted			*Adjusted[b]*		
Adverse effect	***Control***	***Magnesium***	***Difference***	***Difference***	***95% CI***	***P***
Headache	0.57	0.41	-0.16	-0.14	-0.25, -0.03	0.01
Diarrhea	0.32	0.29	-0.02	-0.01	-0.11, +0.08	0.79
Nausea	0.22	0.24	+0.02	+0.02	-0.07, +0.11	0.64
Constipation	0.20	0.20	+0.00	-0.00	-0.08, +0.07	0.97
Dizziness	0.24	0.22	-0.02	-0.02	-0.09, +0.06	0.66
Oliguria	0.04	0.07	+0.03	+0.03	-0.02, +0.08	0.19
Polyuria	0.11	0.16	+0.05	+0.05	-0.01, +0.11	0.09

CI = confidence interval.

[a]Mean values of biweekly reports on a 0 to 4 scale.

[b]Adjusted for mean PHQ-9 score during control weeks, treatment order (Immediate *vs.* Delayed), use of SSRIs, and clustering within participant.

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[31]. There may also be differential effects for SSRIs compared to other antidepressants. Some evidence to support adjunctive use of other nutraceuticals with antidepressants exists. The mechanism may be related to their anti-inflammatory properties or role in NMDA and glutamate activity [32]. Magnesium supplementation may allow for lower antidepressant dosage or avoid the need for use of a second medication, both of which could reduce overall side effect burden.

Implications for practice

The net improvement in PHQ-9 score of 6 points is statistically and clinically significant. A change in score of 5 or greater reflects a clinically relevant change in individuals receiving depression treatment. After 6 weeks of psychological counseling, a drop in 5 points from baseline PHQ-9 indicates the treatment response is adequate and no treatment change is needed. The same guidelines can be applied to 4 weeks of an adequate dose of an antidepressant.[33] Magnesium supplementation provides a safe, fast and inexpensive approach to controlling depressive symptoms. Most patients who experience improvement do so within two weeks of starting supplements. Oral magnesium supplementation is safe in adults with normal kidney function who are not taking medications that interact with the supplement and when used in dosages below the upper tolerable limit set by the Institute of Medicine (350 mg elemental magnesium per day) [34]. Hypermagnesemia is most commonly associated with the combination of impaired renal function and excessive intake of nonfood magnesium; few serious adverse effects are reported until very high doses are ingested [34].

Similar to national surveys [35], some participants with depression were not on any treatment. There are many barriers to treatment for depression including stigma associated with diagnosis, cost, side effects, non-adherence, and loss to follow-up [36]. Magnesium supplements do not come with the added stigma associated with other therapies and, while monitoring response is still important, the risk of side effects is not as great as from antidepressants. Over-the-counter magnesium can be offered as an alternative therapy to those patients hesitant to begin antidepressant treatment and is easily accessible without a prescription for around $14.00 per month.

Strengths

This is the first clinical trial done on magnesium for depression in the U.S. Exclusion criteria were minimal, increasing generalizability, and it used a well-absorbed form of magnesium. The paired analysis allowed each subject to serve as his or her own control, minimizing variance and improving statistical power. Random assignment of treatment order allowed for controlling for regression to the mean as an explanation for the apparent treatment effects. Enrolling patients over a full year minimized the effects of seasonal changes in depression. The withdrawal rate was low and adherence was high, confirming patient reports of high acceptability.

Limitations

There was no placebo arm and randomization was not blinded for either the study team or the volunteer. The use of placebo and blinding are essential for a study that seeks to understand the mechanism of action of an intervention. However, they are not useful when the research seeks to assess the presence and magnitude of the effect of an intervention. Whether magnesium works because it induces a physiological change in the subject, or only because of the placebo effect (or a combination of the two), it remains that subjects do report better levels of depression and anxiety when taking magnesium than when not.

Enrolling patients with depression listed on their medical chart resulted in missing people with undiagnosed depression or who do not use Primary Care. PCPs may have introduced

selection bias by differentially disapproving patients they thought were unlikely to be open to alternative treatments. This may not be an important limitation to generalizability since nutraceuticals would probably not be recommended for these patients anyway. The low response rate to our letter of invitation and follow up calls may have also introduced selection bias.

The study excluded subjects with malabsorption because the main known side effect of magnesium is diarrhea. However, because diarrhea was rare in the study, it would be worth determining the tolerance and effect in those with GI disease. Some of the subgroups are small, limiting our ability to detect variation in efficacy, although none was seen. Due to the makeup of the local community, the study population lacked racial diversity.

Although improvement in symptoms occurred within two weeks and was maintained while on treatment, long-term effectiveness is unknown and longer trials are needed.

Measurement of serum magnesium was outside the scope of the study. A recent meta-analysis of observational studies found an overall 1.3-fold increased risk of depression in people with hypomagnesaemia [37] yet a previous met-analysis was inconclusive [38]. It is not clear if hypomagnesaemia influences the efficacy of magnesium supplementation for depression.

Conclusions

Daily supplementation with 248 mg of elemental magnesium as four 500 mg tablets of magnesium chloride per day leads to a significant decrease in depression and anxiety symptoms regardless of age, gender, baseline severity of depression, or use of antidepressant medications. While the cross over design of this trial is robust in controlling for internal biases, it would be reassuring to see the results replicated in larger clinical trials that test long term efficacy and provide additional data on subgroups. However, this efficacy trial showed magnesium supplements may be a fast, safe, and easily accessible alternative, or adjunct, to starting or increasing the dose of antidepressant medications.

Supporting information

S1 File. Consort checklist.
(DOC)

S2 File. Study protocol.
(PDF)

S3 File. Insituttional Review Board approval.
(PDF)

S4 File. Data for all contacted participants.
(XLSX)

S5 File. Data for randomized participants.
(XLSX)

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All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Author Contributions

Conceptualization: ET BL AK.

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Formal analysis: BL.

Funding acquisition: BL.

Investigation: ET BL CM CD.

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Project administration: ET BL.

Resources: ET.

Supervision: BL.

Validation: ET BL.

Visualization: ET BL.

Writing – original draft: ET BL CM AK CD.

Writing – review & editing: ET BL CM AK CD.

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Over-the-counter magnesium tablets can banish the blues in just TWO WEEKS without the side effects associated with antidepressants

www.dailymail.co.uk/health/article-4646528/Magnesium-tablets-significantly-improve-depression.html

Over-the-counter magnesium tablets significantly improve depression in just two weeks, new research reveals.

Unlike antidepressants, taking a daily dose of the mineral eases the mental health condition without causing side effects, the research adds.

Some 61 percent of the study's participants said they would use magnesium supplements to manage their depression in the future.

Magnesium is thought to ease depression by combating inflammation, which is linked to the mental health condition.

Study author Emily Tarleton from he University of Vermont, said: 'The results are very encouraging, given the great need for additional treatment options for depression, and our finding that magnesium supplementation provides a safe, fast and inexpensive approach to controlling depressive symptoms.'

A daily dose of magnesium eases depression without causing serious side effects (stock)

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PARENTS WHO WORRY ABOUT THEIR CHILDREN'S SLEEPING HABITS ARE MORE PRONE TO DEPRESSION

Parents who worry about their children's sleeping habits are more prone to depression, new research suggests.

Educating parents on how to help their youngsters nod off significantly eases the mental health condition, a study found.

Among severe sufferers of the illness, almost 30 percent of mothers and 20 percent of fathers see their symptoms improve after 24 weeks of sleep treatment, the research adds.

Researchers from the University of British Columbia believe their findings demonstrate how treating children's insomnia can give parents a mental health boost.

How the study was carried out

Researchers from the University of Vermont analyzed 126 adults with an average age of 52 and mild-to-moderate depression.

Some of the study's participants were given 248mg of magnesium every day for six weeks. This is generally considered a low dose.

The remaining participants were not treated for their depression.

All of the participants' symptoms were assessed twice a week via phone calls.

Key findings

Results, published in the journal PLOS ONE, revealed taking a daily magnesium tablet significantly improved participants' depression and anxiety symptoms after just two weeks.

Symptom improvement occurred regardless of the participants' age, sex or antidepressant use.

The tablets were well tolerated with no serious side effects. Antidepressants frequently cause nausea, weight gain and insomnia.

Some 61 percent of the participants said they would use magnesium tablets to manage their mental health condition in the future.

Magnesium is thought to ease depression by combating inflammation, which is linked to the mental health

condition.

Ms Tarleton said: 'This is the first randomized clinical trial looking at the effect of magnesium supplementation on symptoms of depression in US adults.

'The results are very encouraging, given the great need for additional treatment options for depression, and our finding that magnesium supplementation provides a safe, fast and inexpensive approach to controlling depressive symptoms.'

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Stress, adrenaline, and fatigue contributing to at-fault collision risk: Quantitative and qualitative measures of driving after gambling

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ABSTRACT

This paper is one of the first to address the important topic of problem gambling and risk of collisions. Two hundred and twenty-six (226) problem gamblers completed a self-administered questionnaire that included questions on their lifetime "at fault" collisions, several psychosocial characteristics and open-ended questions on how their gambling may have been related to these collisions. A scale specifically designed for this study, the Gambling Effects on Driving Scale, was significantly related to increased likelihood of lifetime "at fault" collisions in both bivariate and multivariate analyses. Qualitative analyses indicated that drivers frequently reported being tired, upset, angry or under the influence of alcohol or drugs prior to collisions. They most often attributed gambling related collisions to: (1) being stressed or emotionally upset, (2) being in a hurry or rushed in relation to getting to a gambling venue, or (3) being too tired/fatigued. The results from this study suggest a relationship between gambling and risky driving behavior that should be examined in more detail in the future.

1. Introduction

Elevated rates of automobile collisions have been associated with a distinct set of psychosocial characteristics including risk taking, adventure seeking, higher levels of arousal, distress, and lowered inhibitions (Trimpop and Kirkcaldy, 1997). Moving violations are also correlated with driver fatigue and stress as it can have a negative impact on driving capabilities (Desmond and Matthews, 2009; Connor et al., 2001). In one review of the literature, Connor et al. (2001) found most fatigue related to shift work, sleep deprivation/fragmentation, and excessive daytime sleepiness contributed to the burden of fatigue-related crashes in the population. A more recent study found frustration and distress caused aggressive and risky driving among college students (Beck et al., 2014). Other literature shows individuals who use emotion-focused or confrontational coping strategies make more mistakes on driving tasks and tend to have more moving violations (Kontogiannis, 2006; Hill and Ng Boyle, 2007).

This same set of psychosocial characteristics is observed amongst problem gamblers. Evidence shows that compulsive gamblers differ from the general population in terms of numerous psychosocial characteristics such as impulsivity, sensation seeking, and increased risk taking behaviors (Kraplin et al., 2014; Loxton et al., 2008; Maccallum et al., 2007). Interestingly, sensation seeking and risk taking has been correlated and studied in risky driving and drunk driving literature (Jonah, 1997; Dahlen et al., 2005; Jonah et al., 2001), but has not made the connection in gambling literature.

Studies have shown post-gambling wins or losses are related to aggression, fatigue and chronic stress (Korman et al., 2008, Parke and Griffiths, 2005; Coman et al., 1997; Hartley and Hassani, 1994). Fatigue in particular has been studied in detail in transport literature; Connor et al. (2001) found irregular sleep patterns and sleep deprivation were related to increases of car collisions in a review of the literature. Casinos in North America tend to stay open 24 h a day, and are often located away from the city, in areas that people must drive to. Arguably, these emotional states could negatively influence driving behavior after leaving a gambling venue.

In one review of the literature, Spurrier and Blaszczynski (2014) found individuals with higher gambling severity had lower risk awareness, adding evidence that supports the assumption that attitudes influence behavior, and vice versa. Their review also shows that this poor risk estimation and cognitive impairments that inhibit risk perception among gamblers leads to increased risk taking behavior

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and higher rates of harm (Spurrier and Blaszczynski, 2014). While research often relates risk-taking behavior to the slots or poker table, these same behaviors should be considered among individuals behind the wheel of an automobile.

Despite these parallels between risky drivers and compulsive gamblers, a review of the literature revealed no studies to date have been published on this topic. One unpublished study has examined the relationship between problem gambling and adverse driving outcomes (Littman-Sharp, 2003). In this exploratory study conducted by Littman-Sharp (2003) at the University of Toronto, 66 gambling clients had high rates of drowsy driving and falling asleep at the wheel, as well as a substantially high collision rate when compared to the general population. This study also found over half of problem gamblers admitted that the frustration, anger, and fatigue from gambling negatively affected their driving (Littman-Sharp, 2003). While the author has presented on this topic, but no literature has been published on it – likely due to its small sample size and lack of statistical significance. Unfortunately no studies to date have empirically examined the relationship or scale of this important issue.

The objective of this study is to address this gap in the literature by examining driving behavior among a treatment sample of self-identified problem gamblers. Subjects were asked questions on incidents of motor vehicle collisions in which they were charged (i.e. at fault). We also asked them to report and describe any collisions they felt were related to their gambling and to describe how their gambling contributed to the crash. Both quantitative and qualitative analyses were conducted to best examine and identify any potential causal mechanisms or relationships that may explain the factors related to adverse driving outcomes among this population. To our knowledge, this paper will be the first to explore the important topic of problem gambling and risk of collisions.

2. Methods

2.1. Study subjects

Adults aged 18 years and older were recruited from six problem gambling treatment centres in Ontario, Canada from 2003 to 2005. Participants ($n=226$) were clients whose primary reason for seeking treatment was gambling. Participants were among a treatment population originally recruited for a larger study (Macdonald et al., 2008) looking at collision risk related to substance abuse. However, only those participants whose primary problem was gambling were included in this study.

2.2. Procedures

Procedures used to collect the data were similar for all subjects to ensure comparable quality of data (MacMahon and Pugh, 1970). Participants were given a $20 gift card for completing a 45-min self-administered questionnaire at the time of recruitment. All participants provided written informed consent. Data collection procedures were approved by the ethics committee at the Centre for Addiction and Mental Health (CAMH) and the treatment sites, as required. The response rate was 93.6%.

2.3. Measures

The study consisted of both quantitative and qualitative measures. In total, we collected (1) basic demographic information, (2) six validated psychosocial scales related to problem gambling, (3) the Gambling Effects of Driving Scale, and (4) open-ended questions on driving after gambling. Since the relationship between problem gambling and driving has not been examined in the past, the Gambling Effects on Driving Scale was designed specifically for this study. This scale was derived after an examination of the literature to identify causal factors related to collisions that might also be consequences of chronic gambling. These items were derived from the literature and include fatigue, eyestrain, aggression, risk taking/impulsiveness, chronic stress and fatigue. Consequently, these traits were used to develop the items that we asked on the Gambling Effects on Driving Scale (Table 1).

In addition to the Gambling Effects on Driving Scale, six other psychosocial scales that may be related to adverse driving outcomes were administered to participants. These included scales on aggression, risk taking/impulsivity, perceived stress, sleepiness, and social supports. The aggression scale, developed by Buss and Perry (1992), had a test–retest correlation of .80, and good validity based on both self-reports and peer-reports of aggressive acts. The risk taking/impulsivity scale was developed by Cherpitel (1999) is a valid scale with a Cronbach's alpha of .80 in one study. The perceived stress scale (Cohen et al., 1983) has alpha reliabilities in different samples between .84 and .86. For sleep we used the Epworth Sleepiness Scale (Johns, 1991) and the sleep problems scale (Jenkins et al., 1988). Social supports were assessed using a shortened version of the Kaplan Scale. Finally, an assessment of problem gambling based on the DSM-IV was also included.

Finally, the qualitative component consisted of semi-structured, open-ended interviews conducted individually with all participants. In addition to being asked to describe their gambling and other risk taking behaviors, participants were asked to report whether they ever had a collision where they were charged (i.e. “at fault”). If they had a collision, they were asked to indicate how they were feeling just before their most recent collision (e.g. upset, angry or tired), whether they were smoking or gambling, or under the influence of alcohol, cannabis or cocaine. They were also asked whether they ever had a collision they thought was related to their gambling and if yes, to explain in their own words how they felt their gambling had increased the likelihood of the incident. Respondents were able to report on any gambling and driving events they and witnessed among other persons.

3. Results

The first analyses were conducted on the Gambling Effects on Driving Scale to assess the inter-reliability of the items selected for the scale. The scale items can be found in Table 1. Cronbach's alpha for the gambling group was .86, indicating that the scale has excellent internal consistency. Next, *t*-tests were conducted to identify significant differences between scale scores for those who reported any

Table 1
The gambling effects on driving scale.

	Strongly disagree	Disagree	Neither	Agree	Strongly agree
I found that fatigue or sleepiness due to extended periods of gambling negatively affected my driving	1	2	3	4	5
I found it difficult to concentrate while driving because I was thinking about gambling	1	2	3	4	5
Eye strain caused by computerized gambling negatively affects my driving	1	2	3	4	5
I have been so upset or excited by gambling that I have driven recklessly	1	2	3	4	5

Chronbach's alpha=.862, $n=199$.

Table 2
Means and probability levels for comparisons of averages of those with and without "at fault" collisions.

	Mean scores and (sample sizes)		
	At fault collisions	Not at fault collisions	Probability value
Age	44.12 (52)	45.16 (156)	.560
Social support	21.67 (52)	21.92 (153)	.694
Sleep problems	9.72 (51)	10.10 (154)	.691
Chronic stress	28.42 (49)	29.36 (145)	.389
Risk-taking/impulsivity	11.42 (51)	14.32 (146)	.178
Aggression	22.32 (53)	19.91 (146)	.036*
Gamble effects on driving scale	12.96 (49)	11.06 (145)	.008**
Gambling problem scale	7.85 (46)	8.04 (134)	.497

S separate variance estimates used, Levene's $p < .05$.

* $p < .05$.

** $p < .01$.

Table 3
Multivariate logistic regression analysis of "at fault" collisions.

Variables	B	Probability value
Risk taking/impulsivity	.028	.605
Aggression	−.006	.862
Sleep problems	−.053	.219
Chronic stress	−.007	.856
Social support	−.037	.522
Gambling effects on driving	.114	.049*
Gambling problem	−.103	.446
Age	.006	.777
Sex	.684	.158

* $p < .05$.

"at fault" collision versus those who reported none. Results are presented in Table 2. Those who reported "at fault" collisions differed significantly from those who did not on two scales ($p < .05$). Those reporting collisions reported significantly higher scores on the aggression scale ($p < .05$). They also reported significantly higher scores on the negative effects on driving scale ($p < .05$).

Next, a multivariate logistic regression analysis was conducted with at fault collisions as the dependent variable and the psychosocial variables and demographic characteristics as covariates (Table 3). Included in the analyses were demographic measures (age and sex) and the scale measure reflecting potential influences on collisions (risk taking/impulsivity, aggression, sleep problems, chronic stress, social support, gambling effects on driving, and gambling problems). The only variable that significantly increased the odds of being in an "at fault" collision was the Gambling Effects on Driving Scale ($p < .05$).

In order to understand better the mechanisms that might have contributed to the "at fault" collisions, respondents reports of factors that preceded their most recent "at fault" collision were examined (see Table 4). Nearly one half (47.7%) indicated they were feeling tired before the collision. Being upset (28.9%) or angry (23.4%), which were significantly associated with one another ($p < .001$, Fisher's exact test) were also common responses. Being under the influence of alcohol (27.1%) was also frequently reported. Traveling to or from gambling activities was reported by 21.3% of respondents.

The final analyses were descriptive, specifically designed to better understand the likelihood that gambling might contribute to collisions. Eleven clients (5.0%) reported a collision directly related to their gambling. Three types of responses were most likely. Respondents most frequently attributed the collision to (1) being stressed or emotionally upset so that they did not pay enough attention to driving, (2) being in a hurry or rushed in relation to getting to a gambling venue, or (3) being too tired/fatigued after gambling to drive properly (one person reported falling asleep while driving). Common statements regarding driving patterns included "reckless" and "very aggressive and unsafe," that were often attributed to "adrenaline rushes." One woman describes it as "a high after they win so they shake, speed…" Only one female stated that she was also using alcohol at the time of the incident, and two males mentioned use of cocaine along with their gambling, but were not necessarily driving that occasion.

Three people commented on being drowsy or "tired and falling asleep" while driving. One subject indicated that the combination of frustration, fatigue and rushing contributed to the collision:

> "Yes, I was over tired, mentally frustrated and fatigued; I was running late for an appointment as a result of being unorganized due to my gambling binge." (40-year-old male)

Some respondents who did not attribute a collision to gambling described the behaviors of others, or reflected on their own "close calls." One older woman describes how her friend would "gamble twelve hours and drive," and then explains she has also driven in a bad snowstorm to gamble but in comparison would not have driven in the same conditions to visit a friend. More frequently, gamblers chose to comment on the behaviors of others:

> "…when losing people get very upset. I've seen many people race out of casino parking lots and speed dangerous out into the street… very aggressive and unsafe driving." (42-year-old female)

Table 4
The frequency of various driver conditions immediately prior to the most recent "at fault" collision.

Condition of driver	Valid percent (*n*)
Feeling tired	47.7% (21)
Feeling upset	28.9% (13)
Feeling angry	23.4% (11)
Going to or from gambling	21.3% (10)
Smoking a cigarette	14.9% (7)
Under the influence of alcohol	27.1% (13)
Under the influence of cocaine	12.8% (6)
Under the influence of marijuana	6.4% (3)

"Don't know" and missing data excluded.

"Gambling and speeding likely go hand in hand – due to either anger for losing, the wish to get to the casino, or adrenaline rushes… also careless driving due to preoccupation with gambling. Sleepiness is less likely a factor as a gambler is generally 'wired.'" (33-year-old male)

Sometimes, clients reflected on their own "close calls":

"I have driven after an overnight stretch of gambling… I intended to pull over… but I was completely awake the entire trip, perhaps adrenaline… I do realize it was a stupid thing to do… very lucky I didn't get into an accident." (51-year-old male)

4. Discussion

Although there are psychosocial parallels between gambling problems and increased collision risk (e.g., Trimpop and Kirkcaldy, 1997; Korman et al., 2008, Parke and Griffiths, 2005; Littman-Sharp, 2003), the connection between gambling and elevated collision risk is not well studied. The results of our study identify three major mechanisms by which gambling may increase collision risk: emotional stress, excitement and fatigue/sleep disruption. Of particular value, this study identified temporal factors directly related to at-fault collisions and conditions thought to be related to gambling, such as fatigue (Littman-Sharp, 2003) and anger (Parke and Griffiths, 2005). To our knowledge, this is the only study that specifically addresses the relationship between gambling and increased collision risk.

As part of the investigation of collision risk factors among gamblers, the Gambling Effects on Driving Scale was used to assess participants' perceptions of how gambling might affect their driving. The scale had excellent internal consistency (.86) and appeared to have excellent validity as a predictor of collision risk in this population. It was the only variable to significantly differentiate those with and without at fault collisions in the multivariate analysis, after controlling for demographic factors and other traits, attitudinal and behavioral measures thought to be related to both gambling and collision risk. Although aggression was related to collisions in a bivariate analysis, this variable became non-significant in the multivariate analysis, possibly because the Gambling Effects on Driving Scale also included this dimension of driving risk and linked the characteristic more closely with gambling activities. These preliminary findings suggest that additional research to determine the ability of the Gambling Effects on Driving Scale to predict hazardous driving and collision risk among gamblers is warranted.

While the quantitative portion of this study only revealed significance on the Gambling Effects on Driving Scale and aggression scale, qualitative analyses revealed important factors associated with collision risk that are critical to consider. Our study found that "feeling tired," "feeling angry," "feeling upset," and "going to/from gambling" were the most reported immediately before "at fault" collisions (Table 4). Some clients commented that "adrenaline" was more of a contributor to collisions than being drowsy after a gambling binge, noting that "gambling and speeding go hand-in-hand." However, other respondents indicated that fatigue could contribute to collisions as well, particularly after a gambling binge. Some respondents noted that aggression related to gambling also could be manifested in reckless driving, comments that are similar to those seen in studies that have examined gambling related risk factors for violence (Korman et al., 2008; Parke and Griffiths, 2005). For example, after a loss of money, problem gamblers can exhibit a significant amount of aggressive behavior (Parke and Griffiths, 2005). These results, taken into consideration with eleven (22%) respondents stating their at-fault collision was immediately before "going to/from gambling," should raise considerable questions about the safety of driving among gamblers.

While these results are of substantial interest, they are affected by important limitations. First, the data are based on self-report, and thus may be subject to associated forms of bias. As well, the sample in this study is from a population in treatment and the results may not be generalizable to the larger gambling population. It was interesting that our study failed to find significance for age and sex and other variables on the scales. It is possible that the relationships between these variables are masked by gambling effects, or other unaccounted for variables, such as number of years gambling, number of years or frequency of driving, gambling severity, length of time since the collision events, and income. Most importantly, this study is the first to highlight through both qualitative and quantitative that there may be an association between gambling and adverse driving outcomes. As such, future studies, such as a thorough examination of police reports, a cohort study, or a comparison of gamblers and a general population of drivers, are warranted.

Nevertheless, the convergence of quantitative and qualitative findings in our study implicates problem gambling as risk factor for motor vehicle collisions. Most of the negative influences on driving were associated with casino gambling. Thus, in order to reduce the potential collision risk of customers, casinos could better educate their clients on the driving risks related to gambling for extended periods. Alternatively, clients who gamble for extended periods could be encouraged to take breaks or find a designated driver, much like drinking and driving campaigns.

Since this study is the first to examine the relationship between gambling and adverse driving outcomes, more research is needed to understand the causal pathways and increased collision risk among problem gamblers and among the general gambling population.

We hope to highlight that an association may exist between gambling and driving and urge future research that considers the scale of this problem and the association between gambling and collision risk among a non-treatment sample.

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TYPES, STORAGE AND GRAPHICAL DISPLAYS OF DATA

1. Are the following variables numeric or categoric? If categoric, state whether binary, nominal or ordinal.

    a) Height
    b) Blood pressure
    c) Number of male siblings
    d) Customer service satisfaction rated as very unsatisfactory/ unsatisfactory/ average/ satisfactory/ very satisfactory
    e) Number of female siblings
    f) Family history of asthma
    g) Hair colour
    h) Lung function
    i) Music volume (number of decibels)
    j) Country of birth
    k) Tolerance rated as Very Low /Low/ Medium/ High/ Very high

2. The weight of an individual may be recorded using either a numeric, ordinal or binary scale. Explain how this can happen. Which is the best method to use? Why?

3. What factors should be considered when deciding on how to display a set of data?

4. In the following examples:

    a) State the variable(s) being shown. What type of variables are they? What values do they take?
    b) Is the display appropriate for this type of data?
    c) Are there alternatives? Would a different display have been better? Why?

i) Management of Acute Otitis Media After Publication of the 2004 AAP and AAFP Clinical Practice Guideline, Andrew Coco, Louis Vernacchio, Michael Horst and Angela Anderson, Pediatrics 2010;125;214-220;

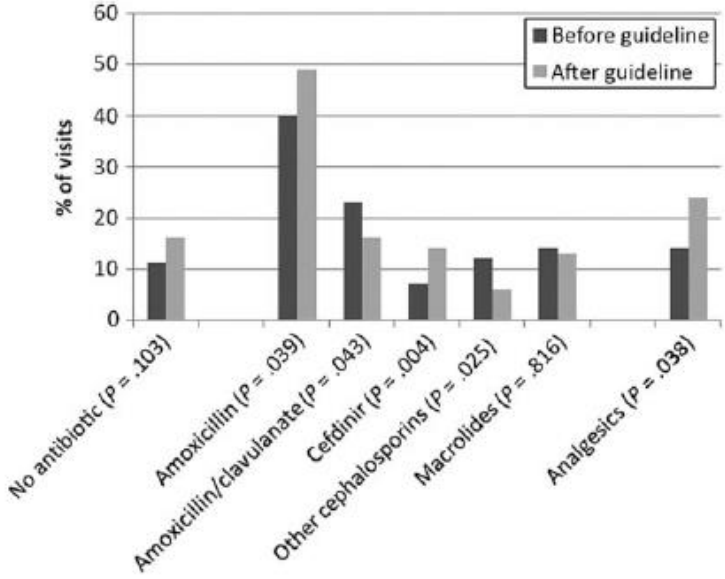


FIGURE 1
Comparison of prescribing choices in visits for children with a diagnosis of AOM to US physicians' offices before and after publication of the AAP/AAFP 2004 clinical practice guideline ($N = 1114$).

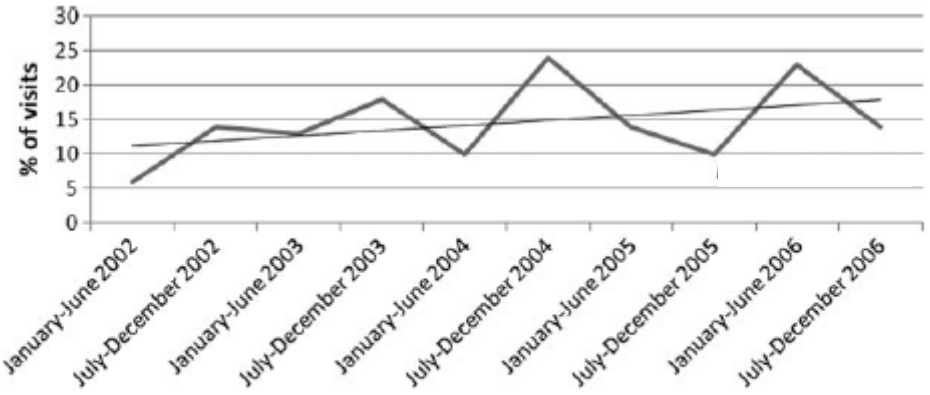


FIGURE 3
Trend in the rate of visits at which no antibiotic-prescribing was reported for children with a diagnosis of AOM to US physicians' offices before and after publication of the AAP/AAFP 2004 clinical practice guideline ($N = 1114$).

ii) Colonic wall thickness, pancreatic enzyme dose and type of preparation in cystic fibrosis, W H Ramsden, E F Moya and J M Littlewood, Arch Dis Child 1998 79: 339-343

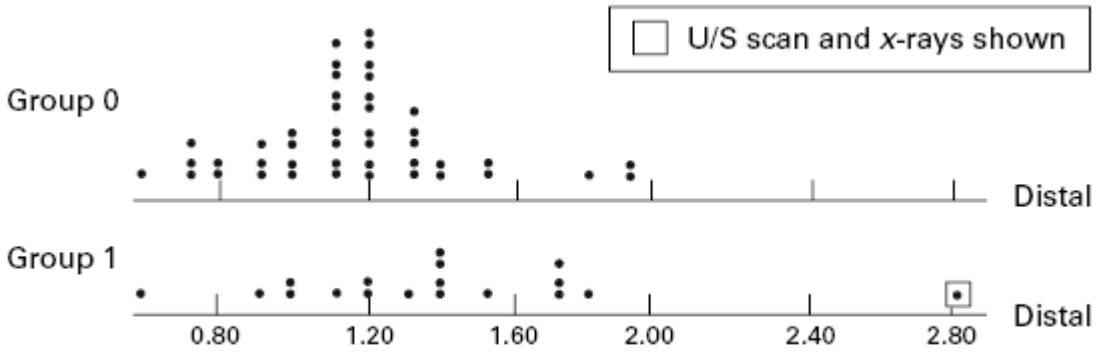


Figure 4 Comparison of distal ascending colon thickness and previous exposure to copolymer.

iii) Hemophagocytic Lymphohistiocytosis in Texas: Observations on Ethnicity and Race, J. Allyson Niece, Pediatr Blood Cancer, 2010;54:424–428.

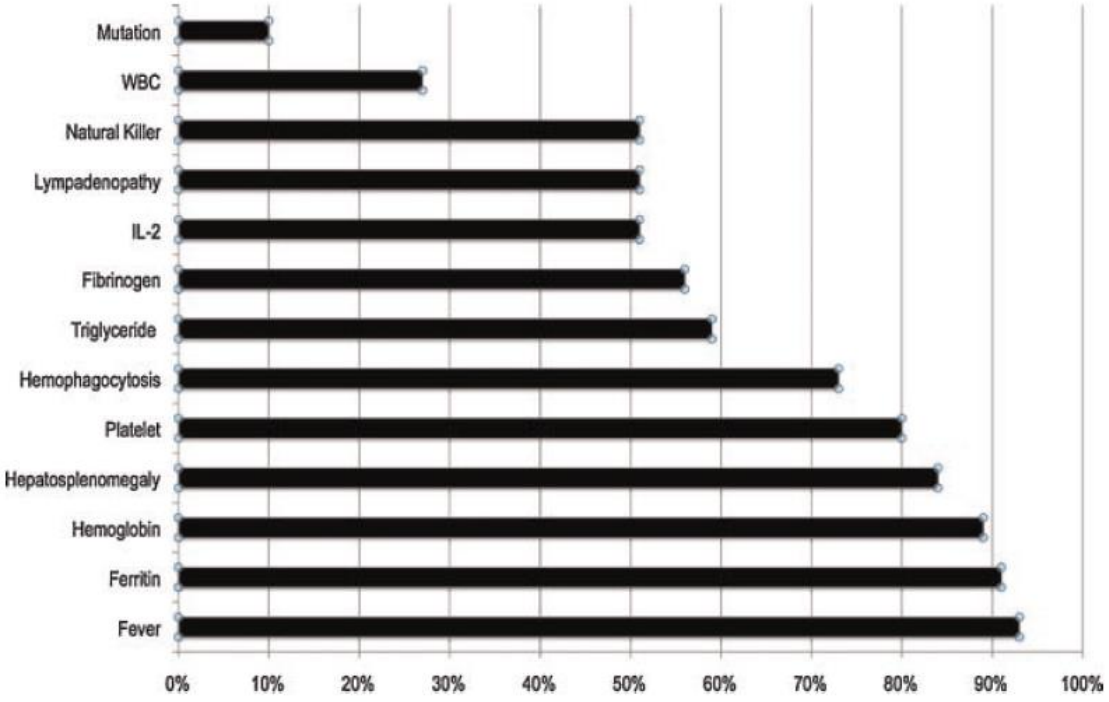


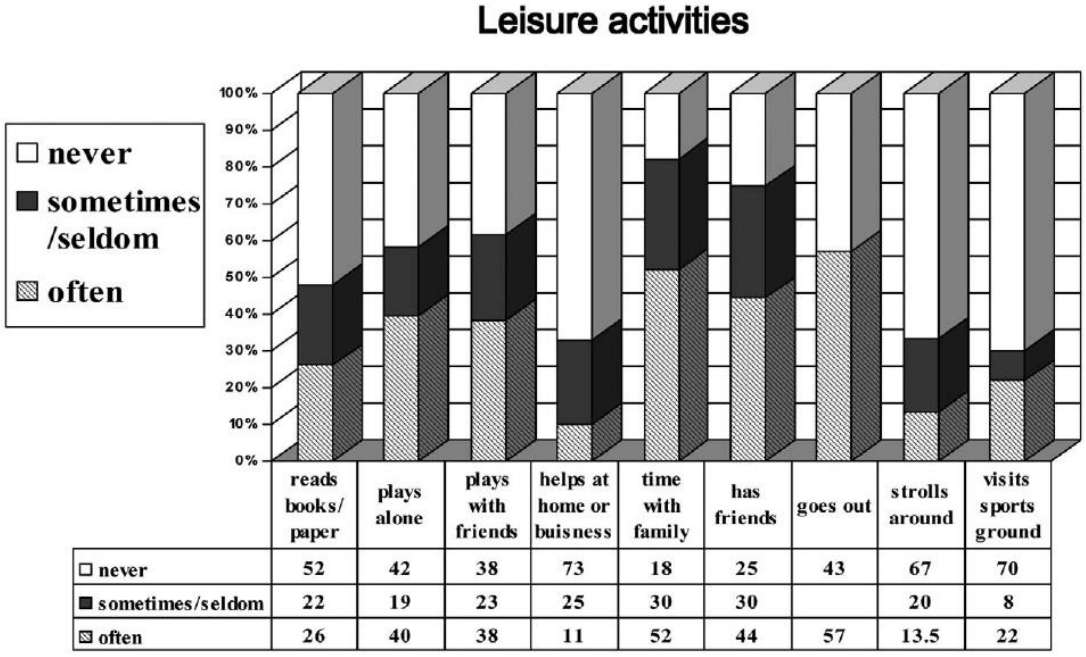
Fig. 1. Frequency of HLH diagnostic criteria.

TABLE II. Ethnicity for HLH and Cancer Diagnoses

	Dallas		San Antonio	
	HLH	Cancer	HLH	Cancer
Ethnicity (%)				
Caucasian	3 (27%)	103 (45%)	1 (25%)	33 (31%)
Latino	6 (55%)	78 (35%)	1 (25%)	68 (64%)
African-American	1 (9%)	23 (10%)	2 (50%)	6 (5%)
Asian	1 (9%)	7 (3%)	0	0
Middle Eastern	0	0	0	0
Other	0	16 (7%)	0	0
Total	11	227	4	107

The Dallas and San Antonio cancer registry statistics were provided for 2006, and contains two HLH patients.

iv) Cerebral Palsy_Long-Term Medical, Functional, Educational, and Psychosocial Outcomes, Ronit Mesterman et al, J Child Neurol 2010; 25; 36.



	reads books/ paper	plays alone	plays with friends	helps at home or buisness	time with family	has friends	goes out	strolls around	visits sports ground
never	52	42	38	73	18	25	43	67	70
sometimes/seldom	22	19	23	25	30	30		20	8
often	26	40	38	11	52	44	57	13.5	22

Figure 1. Distribution of leisure activities.

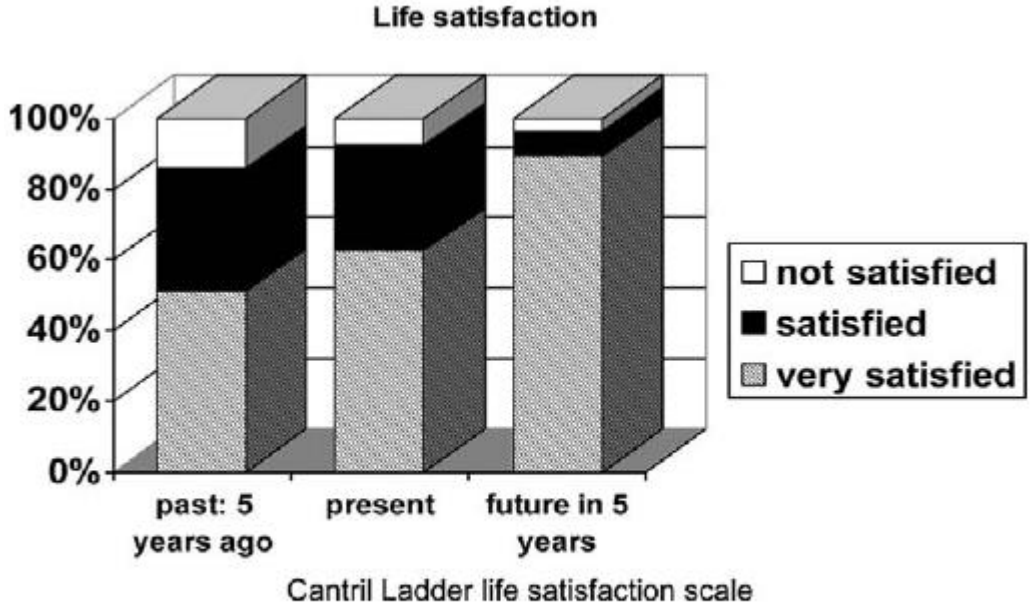


Figure 2. Life satisfaction in persons with cerebral palsy.

v) Characteristics associated with maltreatment types in children referred to a hospital protection team, Andreas Jud & Ulrich Lips & Markus A. Landolt, Eur J Pediatr (2010) 169:173–180.

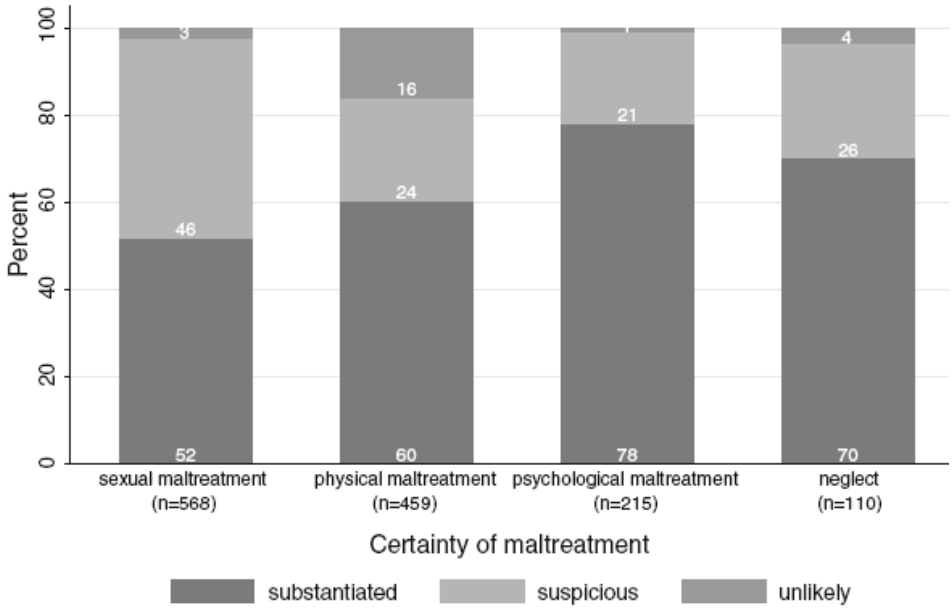


Fig. 1 Substantiation rate for the different types of maltreatment (N=1,358)

vi) Pharmacokinetics of Daunorubicin and Daunorubicinol in Infants with Leukemia Treated in the Interfant 99 Protocol, Georg Hempel et al, Pediatr Blood Cancer 2010;54:355–360.

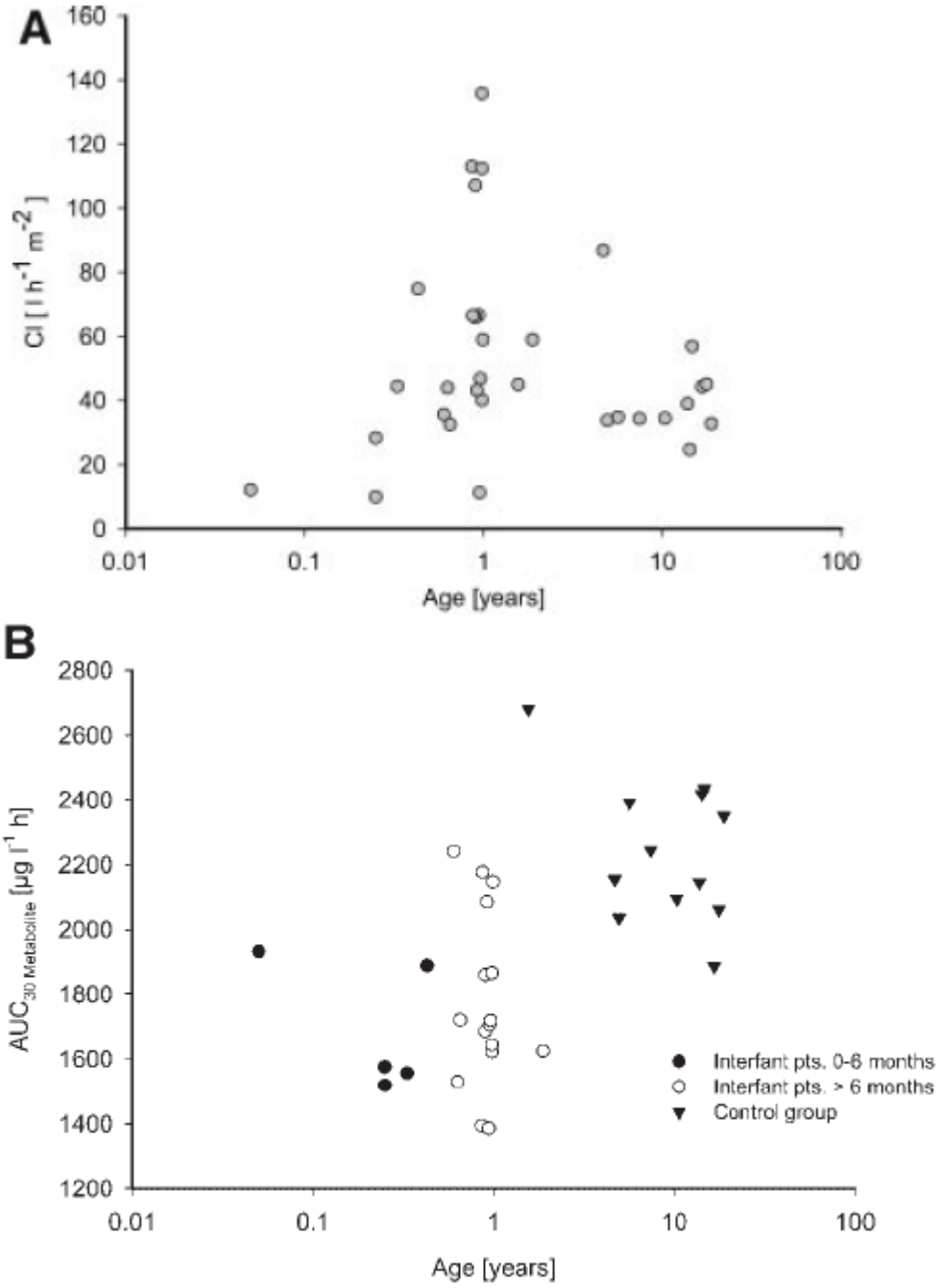


Fig. A: Plot of the CI pharmacokinetic parameter versus age of the patients.
Fig.B. Age versus AUC of daunorubicinol after the first dose in each patient. For a better comparison, the AUC of the older patients was calculated as if they had received 30 mg/m2 (actual dose was 45 mg/m2).

vii) Placental Features of Chorioamnionitis Colonized With Ureaplasma Species in Preterm Delivery, Fumihiko Namba, Pediatric Research, Vol. 67, No. 2, 2010.

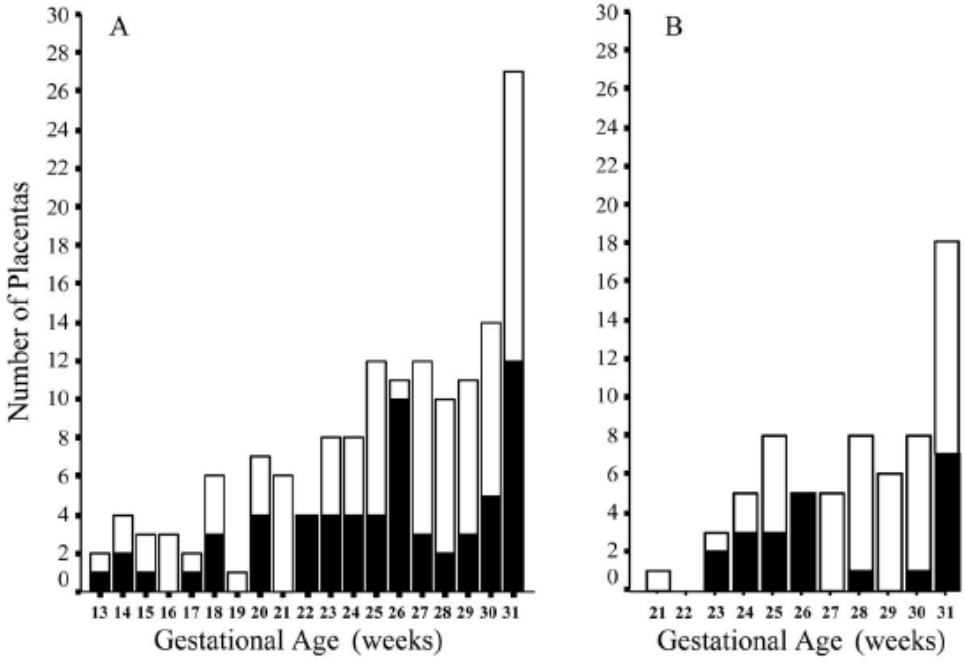
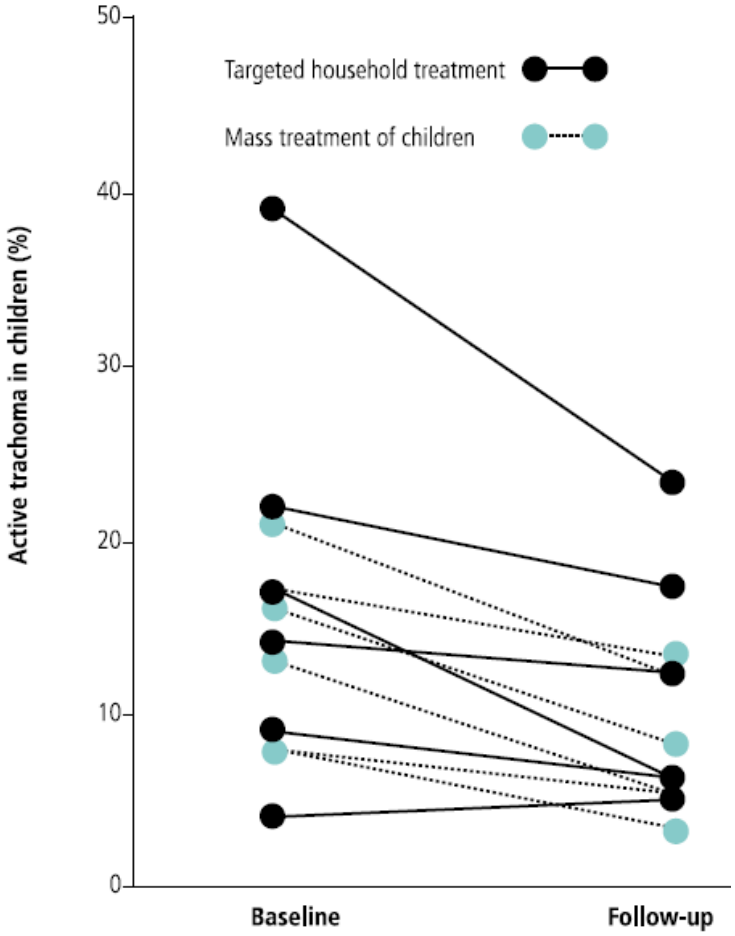


Figure 1. Isolation of *Ureaplasma* spp. from preterm placenta. Forty-two percent (63/151) of wk) were culture posi-. (*A*), and 33% (22/67) livery, (*B*) black bars, *reaplasma* spp.; white r *Ureaplasma* spp.

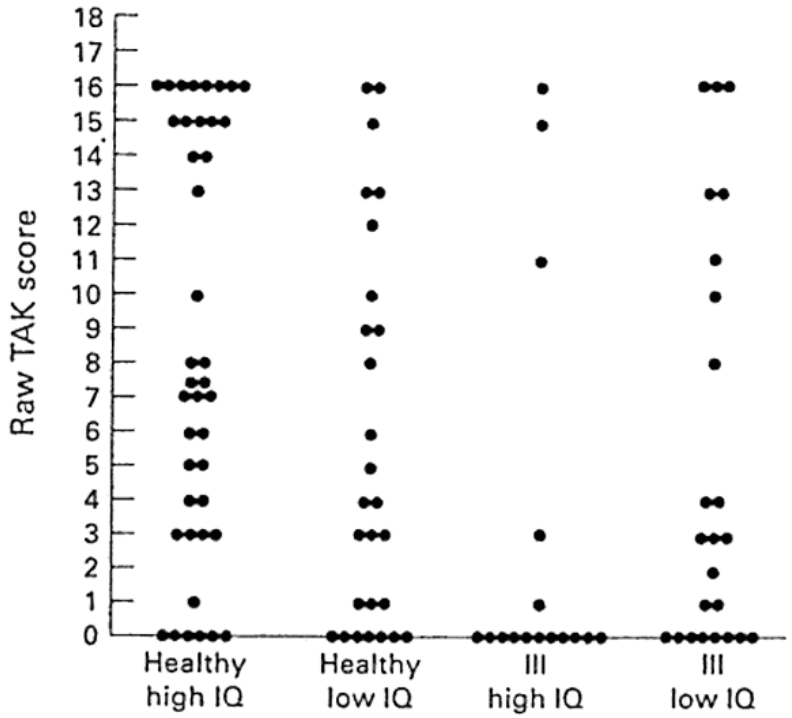
viii) Comparison of two azithromycin distribution strategies for controlling trachoma in Nepal. Holm So et al. Bulletin of the World Health Organisation, 2001, 79(3).

12 units (each consisting of one or more wards) were randomly assigned to mass treatment or targeted intervention.

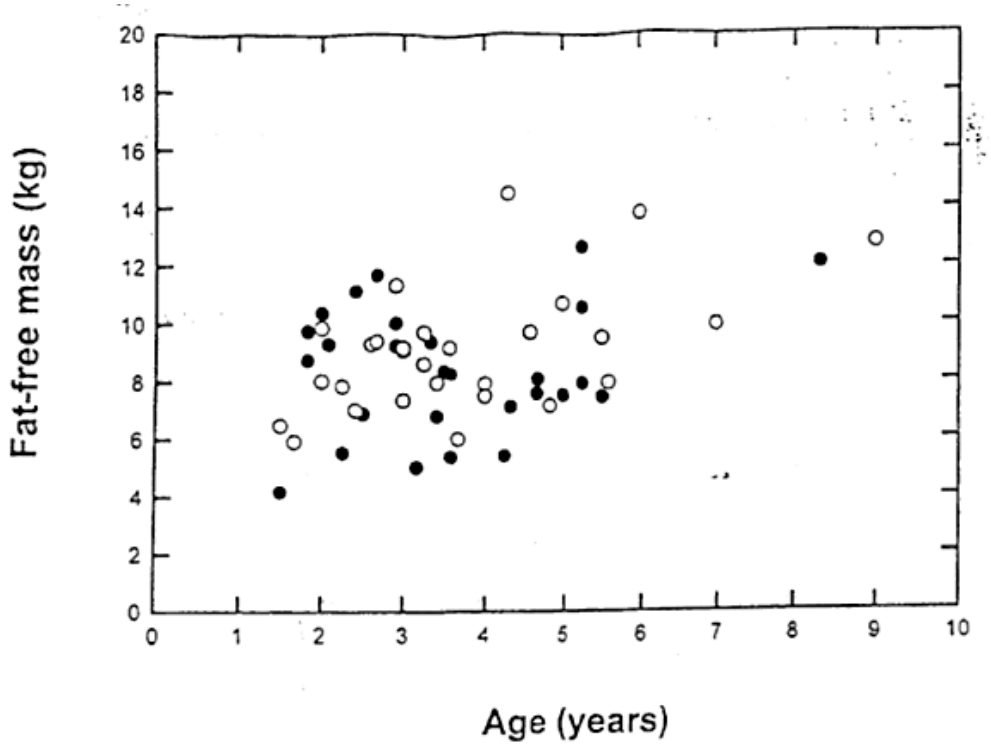


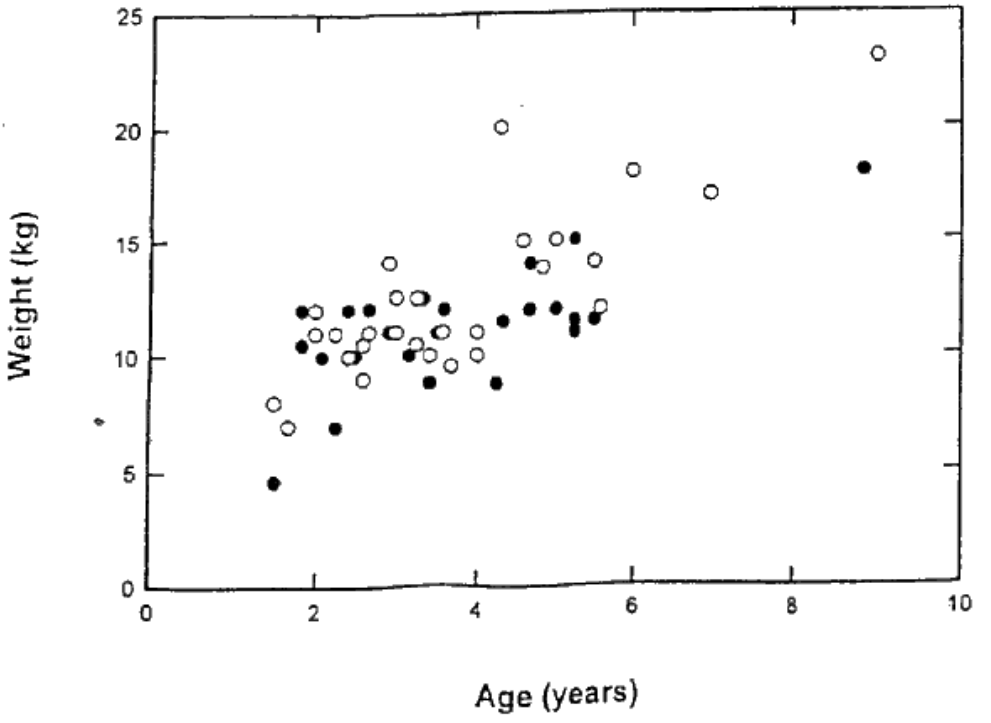
ix) Krishnan B, Glazebrook C, Smyth A. Does illness experience influence the recall of medical information? Arch Dis Child, 1998; 79, 514-515.

Forty children with a chronic illness were recruited from specialist pediatric outpatient clinics. An age stratified, random sample of 66 children with no chronic health problems were recruited from one primary school, in a socially mixed catchment area.

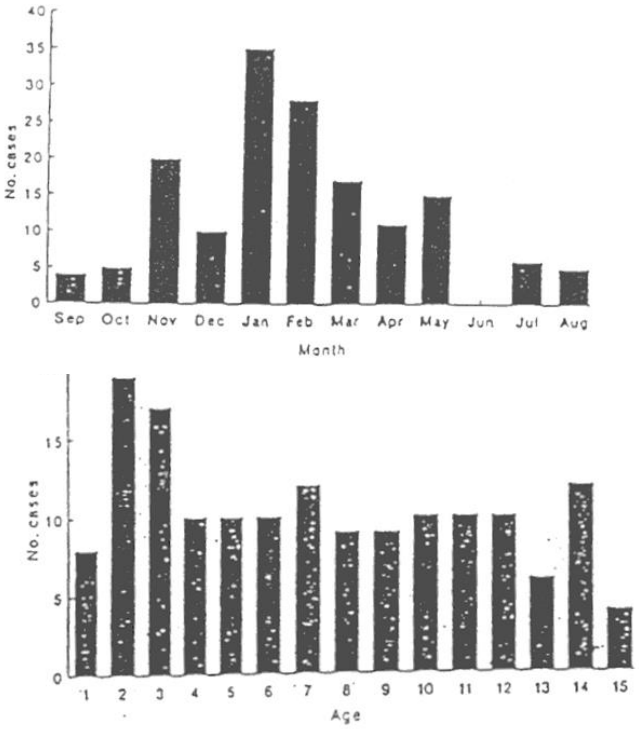


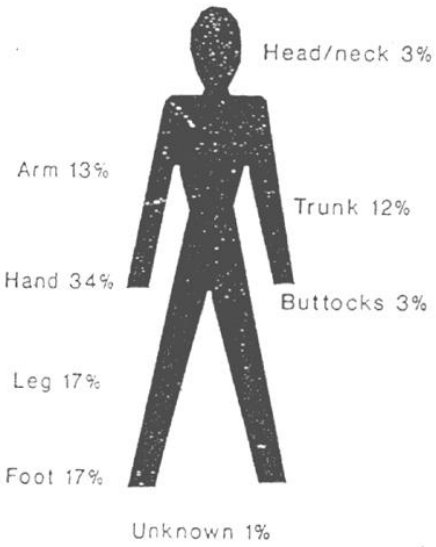
x) VanderJagt DJ et al. Bioelectrical impedance analysis of the body composition of Nigerian children with calcium-deficiency rickets. Journal of Tropical Pediatrics, 2001, 47, 92-97.





xi) Mead HJ and Jelinek GA, Red-back spider bites to Perth children,1979-1988,J Ped Chld Hlth,1993;29,305-308.





xii) Kapur D et al. Iron status of children aged 9-36 months in an urban slum integrated child development services project in Delhi. Indian Pediatrics, 2002, 39, 136-144.

The following show how haemaglobin levels relate to age and to morphology:

Table I__Hemoglobin Distribution and Prevalence of Anemia Among Children

	Percentage of children in the following age-group (months)					
Hb (g/dl)	9 – 12 (n = 91)	13 – 18 (n = 148)	19 – 24 (n = 119)	25 – 30 (n = 117)	31 –36 (n = 70)	Total (n = 545)
< 7.0	3.4	13.3	6.8	7.4	4.5	7.8
7.0 – 9.9	31.5	36.4	35.0	44.4	31.8	36.1
10.0 – 10.9	29.2	17.5	18.8	13.9	19.7	19.5
11.0 or above	36.0	32.9	39.3	34.3	44.0	36.5
Total children	89	143	117	108	66	523
Mean ± (SD) hemoglobin	10.2 ± 1.7	9.7 ± 2.1	10.2 ± 2.0	9.9 ± 2.2	10.5 ± 1.9	10.1 ± 2.0
Hb <10.0 g/dl (%)	35	50	42	52	35	44
Hb <11.0 g/dl (%)	64	67	61	66	56	64

Table II__Morphology of Anemia in Relation to Hemoglobin Levels

Hb (g/dl)	Normocytic normochromic	Microcytic hypochromic	Dimorphic	Macrocytic normochromic	Significance
<7.0 (n = 37)	1 (2.7)	22 (59.5)	14 (37.8)	–	
7 – 10.0 (n = 171)	7 (4.1)	69 (40.4)	94 (55.0)	1 (0.6)	
10.1 – 10.9 (n = 74)	20 (27.0)	32 (43.2)	20 (27.0)	2 (2.7)	
Total anemic (n = 282)	28 (9.9)	123 (43.6)	128 (45.4)	3 (1.1)	p <0.001
Non-anemic >11.0 (n = 166)	95 (57.2)	29 (17.5)	38 (22.9)	4 (2.4)	
Total	123 (27.5)	152 (33.9)	166 (37.1)	7 (1.6)	

SUMMARISING DATA

1. Fisch et al, Autism and fragile X syndrome, Am. J. Psychiatry, 1986;143:1,71 73.

Of the 398 male subjects screened for fragile X syndrome, 144 met the DSM-III criteria for infantile autism. The results of the analysis of their blood samples showed that 18 of the 144 had the fragile X chromosome... Of the 254 non-autistic subjects, 52 had the fragile X chromosome.

According to the information above, fill in the following table with the correct frequencies and percentages (out of total autistic/non-autistic, i.e. the column percentages should add to 100%).

	Autistic	Non-autistic	Totals
Fragile X syndrome			
No fragile X syndrome			
Totals			

2. Barrett D and Rutter N, Percutaneous lignocaine absorption in newborn infants, Archives of Disease in Childhood, 1994; 71,F122-F124.

24 infants were studied; here is the distribution of their gestational ages:

Gestational Age (weeks)	Frequency
25	4
26	3
27	-
28	-
29	-
30	1
31	-
32	3
33	1
34	3
35	2
36	4
37	-
38	2
39	-
40	1

The sum of the 24 gestational ages = 769

a) Calculate both the mean and the median gestational age in this sample.

b) What is the difference between the mean and the median?

c) Does this tell us anything about the distribution? What?

3. Cragg DK et al, Comparison of out of hours care provided by patients' own general practitioners and commercial deputising services: a randomised controlled trial. 1: The process of care, BMJ, 1997;314,187-9.

Response to call, time to visit, prescribing and hospital admissions were recorded for 2152 patients who requested out of hours care from 49 practice doctors and 183 deputising doctors.

"For patients visited at home the median and mean times to arrival for practice doctors were 35 and 55.4 minutes and for deputising doctors 52 and 65.9 minutes."

Were the times to arrival symmetrically distributed? Are they upwardly or downwardly skew?

4. Ballotta E, Da Giau G, Renon L, Narne S, Saladini M, Abbruzzese E, Meneghetti G, Cranial and cervical nerve injuries after carotid endarterectomy : A prospective study, Surgery, 1999;125,85-91.

This study reviewed the outcome of patients who had cranial and cervical nerve injuries after carotid endarterectomy (CEA). From 200 CEAs, 25 nerve injuries were identified. None of the patients were lost to follow up. Table II shows the number of the different types of injury observed, the surgical procedures (CEAP or CEE) and the recovery interval in months.

Table II. Results (cranial and cervical dysfunctions and recovery intervals)

	Surgical procedure (n)		
Nerve (n/%)	CEAP	CEE	Recovery interval (mo)
HN (11/5.5)	6	5	0.25, 0.25, 0.5, 1, 1, 2, 3, 3, 4, 5, 6
RLN (8/4)	4	4	1.5, 2, 2, 3, 10, 12, 31, 37
SLN (2/1)	2	0	4, 6
MMN (2/1)	1	1	2, 2.5
GAN (2/1)	1	1	3, 4
Total (23/12.5)	14	11	

Mean time to recovery was 5.8 months (3.4 months if 31- and 34-month extremes are excluded. CEAP, Carotid endarterectomy with patch; CEE, carotid eversion endarterectomy.

a) For all 25 injuries combined, calculate the median time to recovery.

b) The sum of the injury times is (0.25 + 0.25 + 0.5 + ...+ 4) = 146. Calculate the mean recovery time. Compare this to the median and comment.

c) Comment on the statement at the foot of the table.

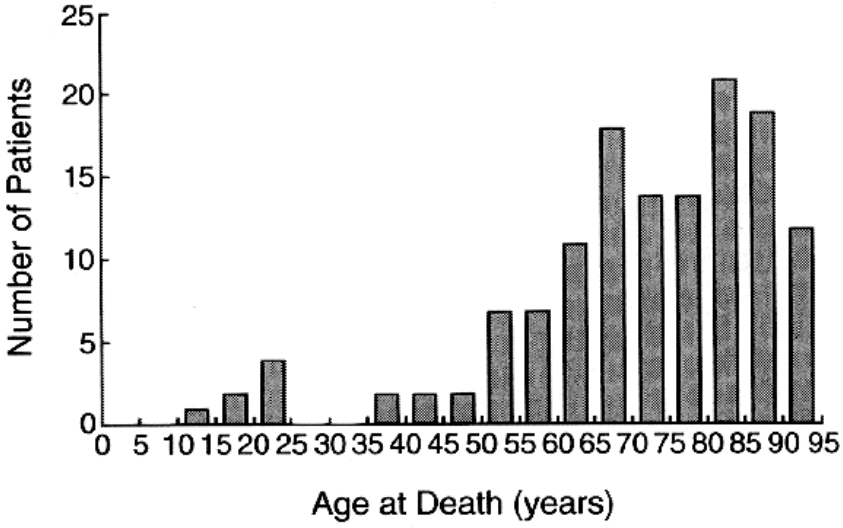
5. Calculate the range and interquartile range of the ages given in question 2.

The standard deviation of the ages is 4.84, calculate the variance. How would you expect the distribution to have changed if the standard deviation had been 1.73?

6. Calculate the range and interquartile range of the recovery times given in question 4. The variance of these times is 80.39, calculate the standard deviation.

   How would you expect the distribution to have changed if the variance had been 120.47?

7. Silverstein MD et al, Long-term survival of a cohort of community residents with asthma, New Engl J Med, 1994; Vol.331,No.23, 1537-41.-



a) Comment on the distributions of the age of onset of asthma and of the age of death in this cohort. What would be suitable measures of centre and spread to summarise each of these distributions?

b) Could the ages of asthma onset and the ages at death of the asthma cohort (shown below) be transformed to normality? If so, suggest possible transformations to try.

8. Logie LJ, Porteous MEM, Intelligence and development in Aarskog syndrome, Arch Dis Child,1998;79,359-360.

Table 1 IQ in boys with Aarskog syndrome

Case	*Age (years)*	*Method*	*IQ*
1	0.7	Griffiths	97
2	1.2	Griffiths	98
3	1.3	Griffiths	104
4	1.4	Griffiths	92
5	2.3	Griffiths	68
6	2.3	Griffiths	102
7	2.4	Griffiths	104
8	3.8	Griffiths	81
9	4.3	Griffiths	102
10	5.2	BAS	128
11	5.8	BAS	107
12	7.5	BAS	116
13	7.9	BAS	103
14	8.8	BAS	109
15	9.6	BAS	105
16	10.5	BAS	117
17	13.4	BAS	127
18	13.4	BAS	112
19	13.5	BAS	109
20	14.3	BAS	125
21	16.7	BAS	118

Mean IQ, 106; Mean IQ for Griffiths mental development scales (Griffiths), 94; Mean IQ for British activity scales (BAS), 115.

a) Calculate the median IQ for all 21 boys, for those assessed using the Griffiths scale and for those assessed using the BAS scale.

b) Compare these to the mean values given at the foot of the table.

c) Calculate the ranges for all 3 groups.

9. If we accept that the gestational ages of the infants included in the study presented in Exercise 2 are normally distributed, within what range do we expect approximately 95% of the gestational ages to lie? (Note: The standard deviation of the measurements was given in exercise 5).

How many of the sample values are above the upper age, how many are below the lower limit? Express both these numbers as a percentage of the total number of infants and comment.

10. The apparent permeability coefficient (cm/hour x 10-4) of each of the 24 infants was as follows:

388.4, 120.0, 67.0, 62.5, 55.0, 27.0, 19.3, 8.5, 7.4, 6.6, 6.4, 6.0, 4.4, 3.8, 3.5, 2.9, 2.6, 1.0, 0.9, 0.7, 0.5, 0.5, 0.3, 0.044;

$\Sigma x = 795.24$; Standard deviation = 81.224

a) Calculate the mean and the median and the difference between them and comment.

b) Calculate the range within which 95% of the values are expected to lie if the permeability coefficients are normally distributed. How many values lie outside this range in either direction? Express these numbers as a percentage of the total and comment.

11. Harms L et al, Decreased N-acetyl-asparate/choline ratio and increased lactate in the frontal lobe of patients with Huntington's disease: a proton magnetic resonance spectoscopy study, J Neurol Neurosurg Psychiatry,1997;62,27-30.

Proton magnetic resonance spectoscopy was carried out on a frontal region of the cortex in 17 patients with clinically overt Huntington's disease and 4 asymptomatic gene carriers. NAA/Ch and Lactate/Ch values are given below:

NAA/Ch	Lactate/Ch
1.50	0.35
1.51	0.89
2.35	0.39
1.59	0.81
1.73	0.00
2.00	0.25
1.62	0.13
2.34	0.00
1.63	1.12
1.63	0.00
1.50	0.00
1.66	0.15
1.23	0.00
1.67	0.63
1.11	0.00
1.27	0.56
0.95	0.00
1.18	0.35
1.24	0.00
1.40	0.34
1.55	0.00

Mean NAA/Ch can be calculated to be 1.56, standard deviation 0.36. The values for lactate/Ch are 0.28 and 0.34 respectively.

For each of the variables calculate the median values. Calculate the ranges within which 95% of the values are expected to lie if the variables are normally distributed. How many values lie outside the range in either direction? Express these numbers as a percentage of the total. Comment on the distributions of NAA/Ch and Lactate/Ch.

12. Ramsden WH, Moya EF, Littlewood JM, Colonic wall thickness, pancreatic enzyme dose and type of preparation in cystic fibrosis, Arch Dis Child,1998;79,339-343.

Table 1 Present enzyme doses used in the paediatric cystic fibrosis clinic in units of lipase/kg/day

Age (years)	*n*	*Median*	*Mean*	*Maximum*	*Minimum*	*> 10000*	*> 15000*	*> 20000*
0–5	35	9036	9972	21407	3113	16 (46%)	6 (17%)	2 (6%)
5–10	38	9393	10024	25397	2848	19 (50%)	5 (13%)	2 (5%)
10–15	44	7853	7458	16667	1564	10 (23%)	3 (7%)	0
> 15	22	5047	5047	12880	1339	3 (14%)	0	0

Table 2 Mean (range) regional colonic thickness in cystic fibrosis patients and controls

	Ascending	*Transverse*	*Descending*
Patients (n = 86)	1.2 (0.7–2.5)	1.2 (0.9–2.5)	1.2 (0.9–2.2)
Controls (n = 12)	1.0 (0.6–1.2)	1.1 (0.9–1.3)	1.1 (0.8–1.4)

The table tells us that 2 (5%) of the 5-10 years age group have enzyme doses >20000. The mean enzyme dose for each age group is also given.

Estimate the standard deviation of the measurements in the 5-10 year age group. Calculate the interval within which approximately 95% of the measurements for that age group would be expected to lie if the values are normally distributed.

13. Eregie CO, Assessment of gestational age: the value of a maturity scoring system for head circumference and mid-arm circumference, Journal of Tropical Pediatrics, 1991; 37: 182-184.

Table 2 Gestational age groups and the corresponding mean values, 95 per cent confidence intervals, maturity scores, and their definitions for head circumference measurements.

Gestational age group Maturity (completed weeks)	No.	Mean±SEM (cm)	95%CL (cm)	95%CI (cm)	Definition (cm)	score
<28	32	23.3±0.4	±0.8	22.5-24.1	<25.4	0
28-30	38	26.4±0.5	±1.0	25.4-27.4	≥25.4 & <28.8	1
31-33	35	29.6±0.4	±0.8	28.8-30.4	≥28.8 & <30.7	2
34-36	41	31.3±0.3	±0.6	30.7-31.9	≥30.7 & <33.4	3
37-39	308	34.0±0.3	±0.6	33.4-34.6	≥33.4 & <34.7	4
≥40	54	34.9±0.1	±0.2	34.7-35.1	≥34.7	5

SEM, standard error of the mean: CL, confidence limits; CI, confidence intervals; r=0.867 (P<0.001).

The table shows various statistics for each of 6 different gestational age groups. Column 6 (definition) gives a range of head circumferences found to be compatible with each of the gestational age groups. The head circumferences increase with gestational age. The final column (maturity score) gives a score based on head circumference to be used in the assessment of gestational age. E.g. A baby with a head circumference of 32.9 cm would be given a score of 3, indicating a gestational age of between 34 and 36 weeks.

The standard deviation of the head circumferences of babies born between 28 and 30 weeks gestation can be calculated to be 3.1 cm (details not given).

Assuming that head circumference measurements are normally distributed (an assumption made by the author in using this presentation of the data), what proportion of babies born between 28 and 30 weeks gestation would you expect to have head circumferences:

i) Greater than 28.8 cm?
ii) Smaller than 25.4 cm?

What proportion of these (28-30 weeks gestation) babies would you expect to receive a maturity score of 1?

14. Love RR et al, Effect of tamoxifen on lumbar spine bone mineral density in postmenopausal women after 5 years, Arc Intern Med,1994;Vol.154,2585-2588.

Characteristics of the Study Groups at Baseline*

Characteristics	No Tamoxifen (n=70)	No Tamoxifen (n=32)	Tamoxifen (n=70)	Tamoxifen (n=30)
Age, y	58.2±4.0	57.9±4.1	58.1±4.4	57.3±4.2
Time since menopause, y	9.5±6.3	9.7±6.7	10.2±7.4	9.9±8.2
Subjects postmenopausal for <4 y	13	8	14	7
Body mass index†	27.6±6.0	28.7±6.0	26.2±4.3	26.1±4.8
Current smokers	11	4	10	3
Aerobic exercise, h/wk	3.7±2.1	3.0±2.6	3.0±1.2	3.2±1.5
Lumbar spine bone mineral density, g/cm²	1.15±0.15	1.17±0.16	1.14±0.15	1.12±0.14
Serum osteocalcin, ng/mL	13.32±5.99	14.1±6.3	13.02±5.38	12.9±5.1

**Plus-minus values are means±SD.*
†Calculated by dividing the weight in kilograms by the square of the height in meters.

Arfken CL et al, Retinopathy in African Americans and whites with insulin-dependent diabetes mellitus, Arch Intern Med,1994;Vol.154,2597-2602.

Table 2. Characteristics at First Visit, by Race

	African Americans (n=58)	Whites (n=142)	P
Age, y	20.7±10.0	17.2±8.7	.01
Diabetes duration, y	5.0±4.1	5.0±3.7	.89
Hemoglobin A_1, %	11.0±3.0	10.2±2.0	.06
Blood pressure, mm Hg			
Systolic	115.4±14.6	110.8±13.5	.04
Diastolic	71.5±12.3	70.4±8.9	.77
Serum creatinine, μmol/L (mg/dL)	64±19 (0.72±0.22)	63±14 (0.71±0.16)	.73
Fasting cholesterol, mmol/L (mg/dL)	4.66±0.85 (180.1±32.7)	4.51±0.99 (174.3±38.3)	.32
Fasting triglycerides, mmol/L	1.02±0.019	1.005±0.019	.85
Desirable weight,* %	111.8±35.6	94.0±16.6	.003
Female subjects, %	71	57	.07
No retinopathy, %	64	67	.67

**Body mass index (weight in kilograms divided by height in meters, squared) ×4.39 (for male subjects) or ×4.76 (for female subjects). All values expressed as mean±SD.*

Comment on the displays of data in the above 2 tables.

15. Choo KE et al, Serum lipid profiles in Malay mothers and neonates: A cross sectional study, J Paeditr Child Health, 1996;32,428-432.

Comment on the figures and data summaries shown in the table:-

Table 2 Serum lipid results from 487 Malay mothers and neonates

	Maternal	Neonatal
Total serum cholesterol (mmol/L)	7.46 ± 2.50	1.69 ± 1.02
Serum HDL-cholesterol (mmol/L)	1.33 ± 0.80	0.61 ± 0.48
HDL/total cholesterol ratio	0.19 ± 0.07	0.37 ± 0.14
Serum LDL-cholesterol (mmol/L)	4.63 ± 2.88*	0.92 ± 0.88
Serum VLDL-cholesterol (mmol/L)	1.36 ± 0.72	0.17 ± 0.40
Serum triglycerides (mmol/L)	3.18 (2.08–4.86)	0.32 (0.20–0.51)

Data are mean ± SD or, in the case of triglyceride concentrations, geometric mean (−1 SD–+1 SD).
*(n = 408; excludes mothers with serum triglycerides > 4.5 mmol/L.

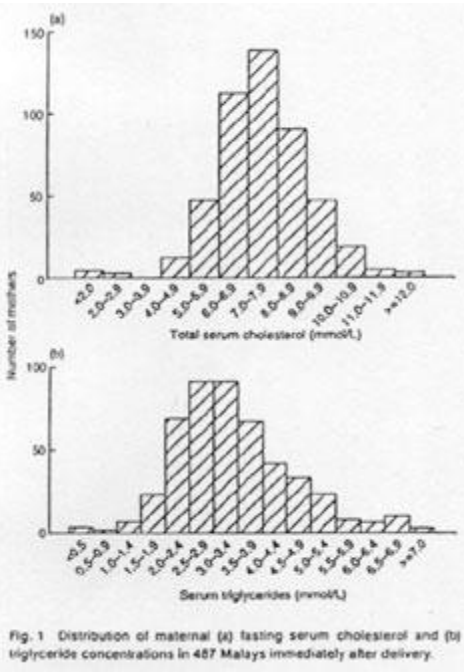


Fig. 1 Distribution of maternal (a) fasting serum cholesterol and (b) triglyceride concentrations in 487 Malays immediately after delivery.

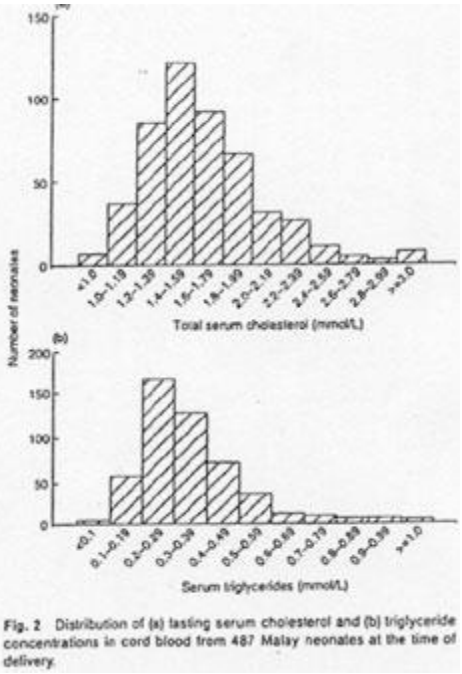


Fig. 2 Distribution of (a) fasting serum cholesterol and (b) triglyceride concentrations in cord blood from 487 Malay neonates at the time of delivery.

16. Krishnan B, Glazebrook C, Smyth A, Does illness experience influence the recall of medical information? Arch Dis Child, 1998;79,514-515.

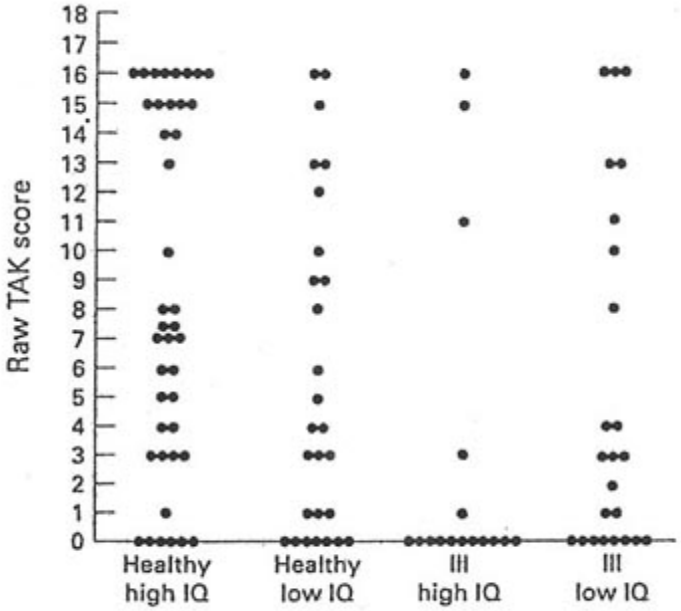


Figure 2 Total anaemia knowledge scores for all subjects.

Comment on the use of the log transformation prior to analysing the anaemia knowledge scores.

17. Colonic wall thickness, pancreatic enzyme dose and type of preparation in cystic fibrosis, W H Ramsden, E F Moya and J M Littlewood, Arch Dis Child 1998 79: 339-343

Age (years)	*n*	*Median*	*Mean*	*Maximum*	*Minimum*
0–5	35	9036	9972	21407	3113
5–10	38	9393	10024	25397	2848
10–15	44	7853	7458	16667	1564
> 15	22	5047	5047	12880	1339

Comment on the plausibility of the normality assumption of the age variable based on the summary measures presented at the table above.

18. Very preterm birth: who has access to antenatal corticosteroid therapy? Antoine Burgueta, Paediatric and Perinatal Epidemiology, 24, 63–74.

Calculate the odds of not receiving antenatal therapy for those in level III of the maternity unit of pregnancy follow up and level I-II of the maternity ward of birth

.

		Antenatal therapy	
	N (790)	No (*n* = 153) %	Yes (*n* = 637) %
Level of the maternity unit for pregnancy follow-up			
III	(135)	17.8	82.2
I-II	(655)	19.7	80.3
Antepartum transfer			
Follow-up and delivery in level III	(135)	17.8	82.2
Follow-up in level I-II, delivery in level III	(492)	6.3	93.7
Follow-up and delivery in levels I-II	(163)	60.1	39.9
Level of the maternity ward of birth			
III	(627)	8.8	91.2
I-II	(163)	60.1	39.9

Table. Delivery and pregnancy follow-up in a non-level-III maternity ward, associated with the probability of not receiving antenatal corticosteroid therapy

19. Effects of calcium supplementation on fetal growth in mothers with deficient calcium intake: a randomised controlled trialppe, Edgardo Abalos, Paediatric and Perinatal Epidemiology, 24, 53–62.

Table 1: Maternal characteristics at baseline

	Calcium ($n = 251$)			Placebo ($n = 259$)		
	n	Mean	(SD)	*n*	Mean	(SD)
Age (years)	251	20.8	(4.7)	259	20.2	(4.5)
Education (years attended)	250	10.1	(2.9)	259	9.7	(2.7)
Weight (kg)	249	57.9	(12.1)	259	58.3	(11.9)
Height (cm)	245	158.8	(6.2)	256	158.9	(6.0)
Body mass index (kg/m^2)	245	22.9	(4.4)	256	23.1	(4.1)
Gestation on enrolment (weeks)	251	12.6	(3.8)	259	12.9	(3.7)
SBP at admission (mmHg)	251	104	(11.4)	259	103	(11.4)
DBP at admission (mmHg)	251	59	(8.8)	259	58	(9.4)
Gravidity (≥1)	23/251 (9.2%)			20/259 (7.7%)		
Smoking during pregnancy	41/251 (16.3%)			55/258 (21.3%)		
Proteinuria at admission[a]	6/245 (2.4%)			14/246 (5.7%)		

Comment on the summary measures used in the table above. What can you infer about normality? State the odds of a mother smoking during pregnancy if she is in the calcium group. How does this compare to the odds if in the placebo group?

QUANTIFYING DIFFERENCES AND ASSOCIATIONS

1. Very preterm birth: who has access to antenatal corticosteroid therapy? Paediatric and Perinatal Epidemiology, 24, 63–74

Table: Delivery and pregnancy follow-up in a non-level-III maternity ward, associated with the probability of not receiving antenatal corticosteroid therapy

	N (790)	No ($n = 153$) %	Yes ($n = 637$) %
Level of the maternity unit for pregnancy follow-up			
III	(135)	17.8	82.2
I-II	(655)	19.7	80.3
Antepartum transfer			
Follow-up and delivery in level III	(135)	17.8	82.2
Follow-up in level I-II, delivery in level III	(492)	6.3	93.7
Follow-up and delivery in levels I-II	(163)	60.1	39.9
Level of the maternity ward of birth			
III	(627)	8.8	91.2
I-II	(163)	60.1	39.9

(i) Calculate the odds of <u>not</u> receiving antenatal corticosteroid therapy in the top two and bottom two rows in the table (i.e. levels III and I-II of the maternity unit for pregnancy follow up and maternity ward at birth). Then, calculate the odds ratio of this event for levels I-II vs III.

(ii) Calculate the equivalent relative risks.

2. What would be suitable ways to quantify the differences described in the following examples?

   a) Heights of normal and diseased children

   b) The chances of an individual becoming obese in UK vs. USA

   c) Brain weight of small and big sized animals

d) Number of people that use public transport in UK compared to those in Germany
e) Number of people that go on holidays within their countries vs. abroad

MAKING INFERENCES

1. This exercise refers back to the data introduced in exercise 13 of Chapter 3. The standard deviation of the head circumferences of babies born between 28 and 30 weeks gestation was calculated to be 3.1cm. Details were not given. Check the calculation using the information shown in the table (i.e. the standard error and sample size for that group). Calculate the standard deviation of the head circumference of babies born between 34 and 36 weeks gestation and also for those born between 37 and 39 weeks.

What information do the standard deviations of the head circumferences give us? What do the standard errors tell us?

2. Cohen et al, Peripartum cocaine use: estimating risk of adverse pregnancy outcome, Int. J. Gynecol. Obstet., 1991, 35, 51-54.

   Table III. Obstetrical and neonatal outcome: cocaine only versus cocaine plus other drugs.

	Cocaine only (n=56)	Cocaine plus (n=27)	p-value
Preterm delivery (%)	22 (39)	13 (48)	NS
Mean gestational age at delivery *	36.7 ± 3.0	35.7 ± 3.9	NS
Mean birthweight (g)*	2648 ± 597	2358 ± 698	NS
Low Birthweight (<2500g) (%)	18 (32)	13(48)	NS
Premature separation of placenta (%)	4(5)	1(1)	NS
Apgar score <7 (%)			
1 min	16 (28)	8 (30)	NS
5 min	6 (11)	6 (22)	NS

*Means ± SD

Calculate 99% confidence intervals for mean birthweight in each group separately. Do the intervals overlap? What does this tell us?

3. Calculate the standard error of the gestational ages of the 24 infants given in exercise 2 of chapter 3. NOTE: The standard deviation of the ages is 4.84.

Calculate a 95% confidence interval for the population mean gestational age. Could average gestational age in the population from which this group was sampled be 40 weeks? Does it seem likely given the present sample?

Calculate the 80% confidence interval for the mean. How does this compare with the 95% confidence interval? Why?

4. Calculate 80, 95 and 99% confidence intervals for the population mean from the sample of NAA/Ch values given in exercise 11 of Chapter 3.

5. Zenewicz D, Kuhn PJ, Routine meconium screening versus drug screening per physician order: detecting the true incidence of drug-exposed infants, Pediatric Nursing,1998;24(6),543-6.

Only 2 of 22 mothers identified as having drug-screen positive babies during the 1994 meconuium screening agreed to use rehabilitative services. Express this as a percentage and present it with 95 and 99% confidence intervals.

6. Petter LPM, Hourihane J O'B and Rolles CJ, Is water out of vogue? A survey of the drinking habits of 2-7 year olds, Archives of Disease in Childhood,1995;72,137-140.

39 preschool and 66 infant schoolchildren were surveyed. The pie diagrams show the plain water consumption over 48 hours:-

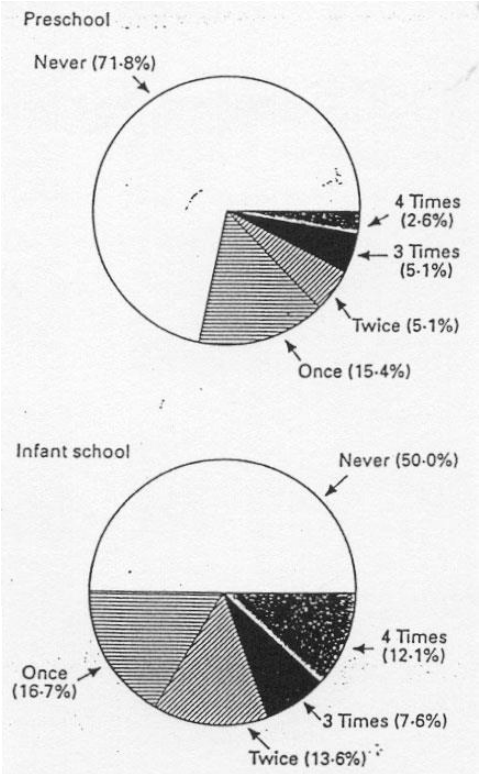


Figure 1 Frequency of plain water consumption over 48 hours in the preschool and the infant school groups.

Comment on these displays of the data.

"Of the preschool group, nine were recruited from two health centres while attending their two year check up with the health visitor, and the rest were recruited while attending four different mother and toddler groups. In the infant school group, parents of each child in the middle two classes of three different local infant schools were contacted by letter."

Comment on the study groups.

Construct 80, 95 and 99% confidence intervals around the percentages in each group who never drank plain water.

Interpret these intervals.

7. Till SH and Grundman MJ, Prevalence of concomitant disease in patients with iron deficiency anaemia, BMJ,1997;314,206-8.

89 consecutive patients referred with iron deficiency anaemia and at least two positive faecal occult blood results were studied.

"The prevalence of colonic cancer among patients presenting with iron deficiency anaemia varies considerably, with outpatient studies suggesting rates of 4-11%. We diagnosed malignant disease of the colon in 14(15%) patients. .. The high prevalence of colonic cancer in our audit might be attributed to our use of faecal occult blood loss as a selection criteria, in contrast to other studies.."

Table 1 Results of investigations (89 patients)

Diagnosis	No of patients
Oesophagitis	14
Colonic cancer	13
Gastric erosion	13
Erosive gastritis	7
Benign colonic adenomatous polyp	6
Duodenal ulcer	5
Gastric cancer	3
Coeliac disease	3
Colonic angiodysplasia	2
Gastric adenomatous polyp	2
Ulcerative colitis	2
Oesophageal cancer	1
Gastric ulcer	1
Barrett's ulcer	1
Gastric angiodysplasia	1
Crohn's disease	1
No diagnosis	14

Calculate a 95% confidence interval for the percentage with colonic cancer in this sample.

8. Messer J et al, Early treatment of premature infants with recombinant human erythropoietin, Pediatrics,1993; 92(4),519-523.

One of the main objectives of this study was to assess the safety of recombinant human erythropoietin (rhEPO) when used in premature infants of less than 33 weeks gestation to reduce postnatal hemoglobin decline.

31 infants were given treatment, none suffered adverse side effects. It was concluded that 'rhEPO therapy is safe in premature babies when given in the three dosages used in this study'.

Construct 95 and 99% confidence intervals for the percentage who suffer adverse effects when taking the drug and comment.

9. Calculate a 95% confidence interval based on the standard error formulae presented in Chapter 5 for each of the summary measures mentioned in the next six questions.

a) For the OR of the gestational age group 28-29 of those that have **not** received antenatal therapy against those that have.

	Antenatal therapy			
	N (790)	No ($n = 153$) %	Yes ($n = 637$) %	OR
Gestational age (weeks)				
24–25	(69)	33.3	66.7	2.3
26–27	(126)	14.3	86.7	0.8
28–29	(231)	19.9	80.1	1.1
30–31	(364)	18.1	81.9	1.0

(The next 4 questions refer to the table seen in the next page)

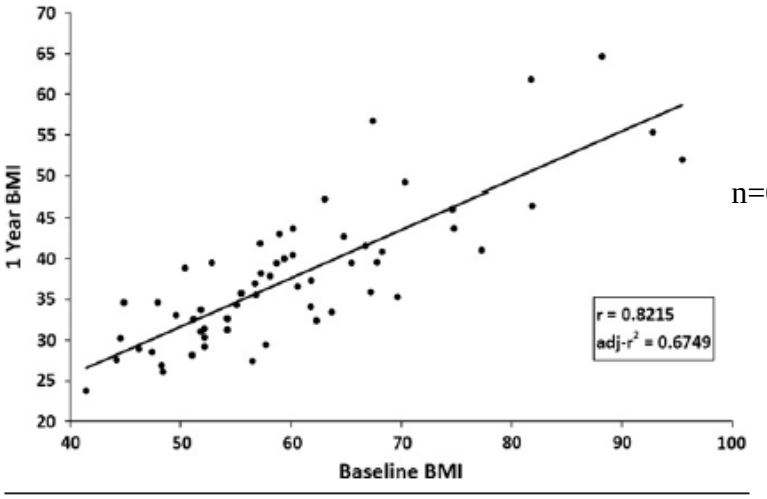
b) For the average daily intake for the calcium group
c) For the difference in average daily intake between the calcium and the placebo groups.
d) For the percentage that complied with ultrasound scans at week 28 at the calcium group
e) For the difference in percentages at week 28 between the calcium and the placebo groups.

Table: Compliance with treatment and ultrasound scans

Compliance with treatment	Calcium ($n = 237$)		Placebo ($n = 237$)	
	Mean	(SD)	Mean	(SD)
Tablets taken	389.0	(143.7)	412.0	(142.5)
Tablets expected	545.3	(91.0)	538.1	(91.3)
Taken/expected	0.718	(0.245)	0.767	(0.237)
Average daily intake	2.15	(0.735)	2.30	(0.711)

Compliance with ultrasound scans	Calcium			Placebo		
	Performed	Expected	%	Performed	Expected	%
Week 20	194	237	81.9	206	237	86.9
Week 24	196	237	82.7	204	237	86.1
Week 28	192	237	81.0	203	236	86.0
Week 32	186	234	79.5	191	232	82.3
Week 36	184	221	83.3	176	211	83.4
Total	952	1166	81.6	980	1153	85.0

f) For the correlation coefficient – r.



n=61 subjects

Figure 1. Plot of baseline and one year post-operative BMI values.

SIGNIFICANCE TESTS

1. The following are the heights in cms of a random sample of 20 Jamaican boys with homozygous sickle cell disease at age 2 years:

84.4	87.0	80.6	83.4	85.0
85.4	89.2	78.5	80.0	89.8
82.5	85.0	89.0	84.1	81.3
85.4	80.7	85.5	81.9	86.3

Mean = 84.25 cm Standard deviation = 3.16 cm

The Tanner and Whitehouse height standards for the United Kingdom give a mean height of 86.5 CMS for boys aged 2 years. Test the hypothesis that the Jamaican boys have the same average height as the UK boys. Give a p-value. Interpret the result. If there is any evidence of a difference, suggest possible reasons.

2. Using the sample given above, calculate 95% and 99% confidence intervals for the mean height of Jamaican boys with sickle cell disease. Interpret these intervals.

If we wanted to estimate mean height more precisely, would we need to increase or decrease the width of the confidence intervals? How could this be achieved?

3. Use a formal significance test to determine how likely the sample from exercise 3 of Chapter 5 was to come from a population with an average gestational age of 40 weeks. Interpret the p-value. How does this value relate to the confidence intervals already constructed for the population average?

4. Refer to exercise 11 of Chapter 3 and exercise 4 of Chapter 5.

Test the hypothesis that the population average NAA/Ch for carriers (those with disease + asymptomatics) is 1.67. Compare the p-value with the confidence intervals previously obtained. Comment on the interpretation of both the p-value and the confidence intervals and how they relate to each other.

5. Check that the confidence intervals that you calculated at exercise 9 of Chapter 5 match the p-values that are now presented.

Table: Compliance with treatment and ultrasound scans

Compliance with treatment	Calcium ($n = 237$)		Placebo ($n = 237$)		*P*-values
	Mean	(SD)	Mean	(SD)	
Tablets taken	389.0	(143.7)	412.0	(142.5)	0.088
Tablets expected	545.3	(91.0)	538.1	(91.3)	0.388
Taken/expected	0.718	(0.245)	0.767	(0.237)	0.031
Average daily intake	2.15	(0.735)	2.30	(0.711)	0.031

Compliance with ultrasound scans	Calcium			Placebo			*P*-values
	Performed	Expected	%	Performed	Expected	%	
Week 20	194	237	81.9	206	237	86.9	0.164
Week 24	196	237	82.7	204	237	86.1	0.376
Week 28	192	237	81.0	203	236	86.0	0.173
Week 32	186	234	79.5	191	232	82.3	0.480
Week 36	184	221	83.3	176	211	83.4	1.000
Total	952	1166	81.6	980	1153	85.0	0.030

6. Ref:- Rogers et al, Kupffer cell depletion in vivo results in clearance of large-sized IgA aggregates in rats by liver endothelial cells, Clin. exp. Immunol., 1991; 85: 128-136.

Normal and macrophage depleted rats were injected intravenously with monomeric IgA and assessed for blood clearance and tissue distribution. The following table gives the clearance half-lives (t½) of different sized IgA in the two groups.

Ig A size	Normal rats	Macrophage depleted	P
1	26.8 +/- 3.6	23.7 +/- 3.2	NS
2	246 +/- 35.8	455 +/- 226.0	NS

Data are mean ± 1 s.d. of five different rats.

Results were analysed for statistical significance using Student's t-test for unpaired samples. Comment on the use of students t-test in these 2 cases.

7. Cohen et al, Peripartum cocaine use: estimating risk of adverse pregnancy outcome, Int. J. Gynecol. Obstet., 1991, 35, 51-54.

	Cocaine only (n=56)	Cocaine plus (n=27)	p-value
Preterm delivery (%)	22 (39)	13 (48)	NS
Mean gestational age at delivery *	36.7 ± 3.0	35.7 ± 3.9	NS
Mean birthweight (g)*	2648 ± 597	2358 ± 698	NS
Low Birthweight (<2500g) (%)	18 (32)	13(48)	NS
Premature separation of placenta (%)	4(5)	1(1)	NS
Apgar score <7 (%)			
1 min	16 (28)	8 (30)	NS
5 min	6 (11)	6 (22)	NS

(This data was used in exercise 2 of Chapter 5).

The standard error for the difference between the mean birthweights of the two groups can be calculated to be 147.8. Which numbers from the table were used to calculate this?

Test the difference in mean birthweight between babies born to the 2 groups 'cocaine only' and 'cocaine plus'. Does your answer agree with the authors' p-value? Calculate a 95% confidence interval around the mean difference, what does this tell us?

8. Schopf RE, Naumann S, Rehder M and Morsches B, Soluble intercellular adhesion molecule-1 levels in patients with psoriasis, Br J Dermatology, 1993;128,34-37.

"Concentrations of sICAM-1 were compared by the two-tailed Student's t-test.....The serum concentration of sICAM-1 in 17 healthy controls was 358.8±87.9 ng/ml; in the 17 patients with psoriasis the value was 480.5±133.6 ng/ml serum (mean±standard deviation).....this difference reached statistical significance at the P=0.02 level."

What is the average difference between the sICAM-1 values of patients and controls?

Comment on the analysis performed by the authors.

The standard error of the difference between patients and controls can be calculated to be 38.79. Re-do the t-test and calculate a 95% confidence interval or the difference in mean levels of sICAM-1.

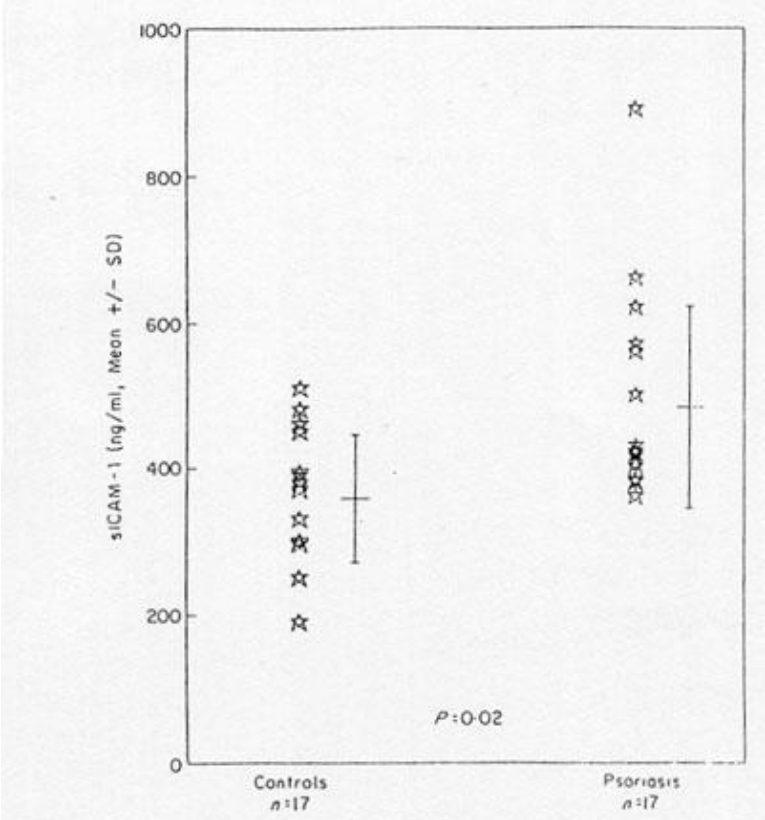


Figure 1. Determination by ELISA-technique of sICAM-1 in healthy control individuals and patients with psoriasis

9. Downie AB et al, Are short normal children at a disadvantage ? The Wessex growth study, BMJ, 1997; 314,97-100.

Two groups were recruited on the basis of their height at age 5-6 years. At approximately 12 years of age the cognitive development (as assessed by measures of intelligence) and the self-esteem of the children in both groups were assessed. Other assessments were also made. The table below gives the results:-

Table 2 Comparison of height group means for all measures

	Short children		Control children		
Measure	Mean (SD)	No*	Mean (SD)	No*	P value
Intelligence	102.6 (16.7)	106	108.6 (15.6)	119	0.005
Reading attainment	44.3 (8.8)	106	47.9 (8.5)	119	0.002
Mathematics attainment	40.2 (7.2)	106	43.5 (9.2)	119	0.003
Locus of control	16.6 (5.0)	98	14.3 (5.1)	115	0.001
Behaviour	6.8 (7.5)	84	5.3 (6.8)	93	0.16
No (%) with disorder score	29 (30.5)	95	29 (27.6)	105	0.77
Self esteem	19.4 (4.4)	106	20.2 (4.0)	119	0.16
Self perception	104.2 (16.8)	103	102.4 (15.3)	117	0.42
Parents' perception	46.9 (7.2)	98	47.0 (6.6)	112	0.92

*Varies according to numbers of incomplete or spoiled forms or non-response rates.

The standard errors for the differences in intelligence and self-esteem are 2.15 and 0.56 respectively.

Perform the appropriate t-tests for these two outcomes. Give confidence intervals.

10. Sriussadaporn S et al, Factors associated with diabetic foot ulceration in Thailand: a case-control study, Diabetic Medicine,1997; 14,50-56.

A case-control study was conducted to determine factors involved in foot ulceration in Thai non-insulin-dependent diabetic patients. 55 patients with foot ulcers and 110 patients without foot ulcers (randomly recruited from the same clinic) were evaluated for 26 factors possibly associated with foot ulceration.

Amongst other results, the differences between the groups with respect to ankle-brachial systolic index (ABI), diabetic knowledge and foot care scores are given in the table :-

Table 2. Clinical characteristics of diabetic patients with and without foot ulcers

	With foot ulcers (55 cases)		Without foot ulcer (110 cases)		*p*-value[a]
	Means	SD	Means	SD	
Age (yr)	57.16	13.66	57.55	10.20	0.84
DM duration (yr)	8.98	6.09	10.80	9.73	0.15
BMI (kg m^{-2})	24.60	4.50	25.37	4.19	0.35
Systolic BP (mmHg)	139.26	21.18	133.30	22.61	0.11
Diastolic BP (mm Hg)	81.51	12.62	79.79	10.07	0.35
ABI[b]	1.070	0.276	1.114	0.234	0.15
Visual acuity[c]	0.347	0.295	0.610	0.301	< 0.001
Diabetic knowledge score	15.04	4.74	16.88	2.32	0.001
Foot-care score	14.50	3.35	15.74	2.31	0.007

[a]Value obtained from Students' *t*-test or chi-square test.
[b]Mean ABI of the legs with foot ulcers in ulcer group vs mean of the lower ABI value between the right and left legs in control group. [c]Mean decimal visual acuity of the better eye.

Comment on the use of t-tests for the comparisons. Calculate 95% confidence intervals for the difference in ABI, diabetic knowledge and foot-care scores between the with and without foot ulcer groups.

(The standard errors for the differences in ABI, diabetic knowledge and foot-care scores can be calculated from the information given as 0.041, 0.549 and 0.446 respectively.)

11. Cragg DK et al, Comparison of out of hours care provided by patients' own general practitioners and commercial deputising services: a randomised controlled trial. 1:The process of care, BMJ, 1997;314,187-9.

Response to call, time to visit, prescribing and hospital admissions were recorded for 2152 patients who requested out of hours care from 49 practice doctors and 183 deputising doctors.

"For patients visited at home the median and mean times to arrival for practice doctors were 35 and 55.4 minutes and for deputising doctors 52 and 65.9 minutes."

The authors log transformed the times to arrival prior to significance testing. Why would they do this? When the 95% confidence limits for the average log time to arrival were antilogged they were 1.19 and 1.64. What information does this give us?

12. Smith SL, Hindmarsh PC and Brook CGD, Compliance with growth hormone treatment - are they getting it ? , Arch Dis Child, 1993; 68,91-93.

Abstract

A study was undertaken to investigate compliance in patients receiving growth hormone treatment. Two hundred patients completed a questionnaire designed to establish understanding about and compliance with treatment; 50% of our patients failed to comply with all aspects of their treatment. Failure to respond to treatment seems to be associated with poor compliance.

Calculate the standard error of the proportion who failed to comply.

A previous study suggested that as many as three-quarters (75%) of patients failed to comply when taking growth hormone. If this were true, how likely is the present sample? Give a p-value.

Calculate 80%, 95% and 99% confidence intervals for the observed proportion. How do they differ? Why?

13. Fisch et al, Autism and fragile X syndrome, Am. J. Psychiatry, 1986;143:1,71 73.

"The fragile X chromosome is an important factor in inherited mental retardation in males. It has also been reported that infantile autism is associated with fragile X. Recently, an article reported an examination of a small sample of autistic children in whom the fragile X chromosome was not found. Its authors concluded that if an association between fragile X and autism exists, it is infrequent. In the present study of 144 autistic male subjects, 18 were found to have the fragile X chromosome, supporting other (epidemiological) findings that the association between fragile X and autism occurs relatively frequently."
(Am J Psychiatry 143:71-73, 1986)

RESULTS
Of the 398 male subjects screened for fragile X syndrome, 144 met the DSM-III criteria for infantile autism. The results of the analysis of their blood samples showed that 18 of the 144 (12.5%) had the fragile X chromosome... Of the 254 nonautistic subjects, 52 (20.6%) had the fragile X chromosome.

The frequency table for the above data was constructed at exercise 1 of Chapter 3.

a) What is the research question? State the null hypothesis.

b) Perform the appropriate test of statistical significance.

   i) Interpret the p value
   ii) Calculate the 95% confidence interval and interpret

c) The authors conclude 'Our investigation ... indicates that the association between fragile X and autism is substantial.' Do you agree? Discuss.

d) Suppose that the sample numbers were halved but that the percentages of fragile X within the groups remained constant, i.e. in the autistic group 9 of 72 (12.5%) had the fragile X chromosome. How would this change your answers to (c)?

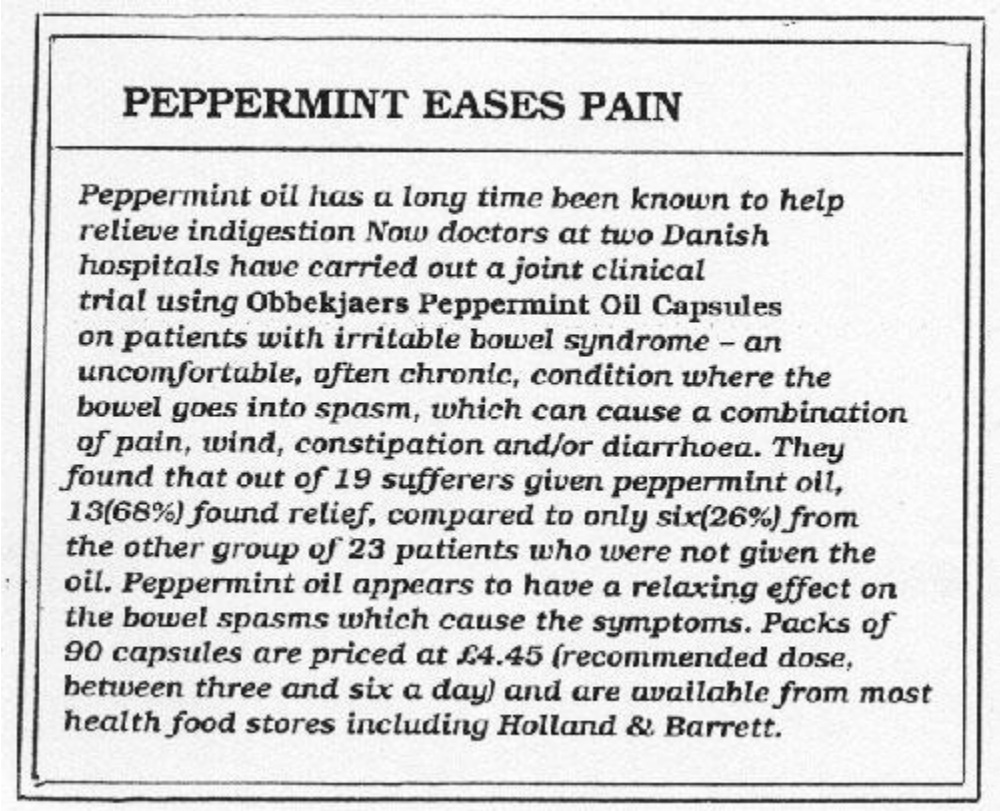
14. Ref: Kumar A et al, The effect of music on ketamine induced emergence phenomena. Anaesthesia 1992;47:438 439.

A study was undertaken to assess the influence of music on emergence phenomena after ketamine anaesthesia. Fifty ASA 1 patients undergoing minor gynaecological procedures were randomly divided into two equal groups. Patients in the treated group were played music of their choice through headphones from 5 minutes before induction of anaesthesia to 15 minutes post operatively. After the operation they were asked whether they would be willing to have a similar anaesthetic in future (given a choice):-

		Music	Control	Total
Willing to have a similar anaesthetic	Yes	20	13	33
	No	5	12	17
Total no of patients		25	25	50

Does the study provide any evidence that playing music changed the women's willingness to have a similar anaesthetic?

15. Report from a magazine:



PEPPERMINT EASES PAIN

Peppermint oil has a long time been known to help relieve indigestion Now doctors at two Danish hospitals have carried out a joint clinical trial using **Obbekjaers Peppermint Oil Capsules** *on patients with irritable bowel syndrome – an uncomfortable, often chronic, condition where the bowel goes into spasm, which can cause a combination of pain, wind, constipation and/or diarrhoea. They found that out of 19 sufferers given peppermint oil, 13(68%) found relief, compared to only six(26%) from the other group of 23 patients who were not given the oil. Peppermint oil appears to have a relaxing effect on the bowel spasms which cause the symptoms. Packs of 90 capsules are priced at £4.45 (recommended dose, between three and six a day) and are available from most health food stores including Holland & Barrett.*

a) Construct a frequency table for the above data.

b) Use an appropriate test of statistical significance to assess the strength of evidence that patients given peppermint oil experience greater relief.

i) State the null hypothesis
ii) Interpret the p value
iii) Calculate confidence intervals and interpret

c) Discuss what design issues need to be considered in assessing the reliability of these data.

16. South Wiltshire Out of Hours Project (SWOOP) Group, Nurse telephone triage in out of hours primary care: a pilot study, BMJ,1997;314,198-9.

Incoming calls to two practices were diverted to an experienced practice nurse during 18 4 hour sessions. In the first nine sessions the nurse managed seven of 29 calls alone. In the second nine sessions this proportion increased to 14 of 27.

This difference could not be explained by differences in the urgency of calls. Calculate 95% confidence intervals around the proportions of calls being managed by the nurse alone in each of the two sets of nine sessions.

Perform a significance test between the proportions managed by a nurse alone in each of the nine sessions. What is the null hypothesis? Calculate a 95% confidence interval around the difference in proportions. Interpret the results.

17. Parker DP et al, Capillary blood sampling: should the heel be warmed ? BMJ,1996;74,F139-140.

"The hypothesis that capillary blood sampling is made easier by warming the heel was examined in a randomised, controlled trial of healthy newborn infants...The time taken to collect a standard volume of blood, the number of repeat procedures needed, and the infants' behavioural responses were measured.....there were no significant differences between the warmed and unwarmed groups in any of the outcome measures....Heel skin temperature is not an important factor in capillary blood sampling. Attention should be directed towards improving sampling devices and techniques."

Sampling time and repeat procedures

	Sampling time (seconds) median (interquartile range)	*No of repeats (%)*
Unwarmed Heels (n=40)	40 (28 to 72)	8/40 (20%)
Warmed Heels (n=41)	44* (25 to 62)	5/41* (12%)

*P>0·05.

Test the hypothesis that the number of repeats is not affected by warming the heel.

Construct a confidence interval for the difference in number of repeats.

Comment on the results in relation to the authors' conclusions.

18. Russell IF and Wang M, Absence of memory for intraoperative information during surgery under adequate general anaesthesia, British Journal of Anaesthesia,1997;78,3-9.

"Two groups of women, studied in a single-blind sequential block design, heard different tapes, either a command and information tape (CG,n=34) or radio static (RSG,n=34) throughout surgery."
The tape played to the RSG group contained a message "here are some special words I would like you to remember - 'sour gooseberry, sharp lemon, green pear'." Several hours after surgery the women were asked to name five fruits. The aim of the study was to determine whether recall of events whilst under anaesthesia was possible.

The 68 women were studied sequentially in the following single-blind manner : 17 command tape, 17 radio static, 17 radio static, 17 command tape.

Table 5: Number of patients who included the "target" fruit in their list of five fruits in recovery. Patients responding with both "pear" and "lemon" are also included in the original counts of "pear" and "lemon"

	Group RSG *(n=30)*	**Group CG *(n=31)***
Pear	**16**	**14**
Lemon	**4**	**3**
Pear and Lemon	**3**	**1**
Gooseberry	**0**	**0**

Is there any evidence that patients in the CG group were more likely to recall at least one of the fruits mentioned under anaesthesia than the RSG group when asked to list 5 fruits shortly after recovery? Give a p-value and confidence interval.

19. Ala TA et al, Hallucinations and signs of parkinsonism help distinguish patients with dementia and cortical Lewy bodies from patients with Alzheimer's disease at presentation: a clinicopathological study, J Neurol Neurosurg Psychiatry,1997;62,16-21.

All 476 cases of dementia received by a brain bank over a 4 year period were reviewed. Medical records were requested for documentation of the patient's medical history. 4 of 60 Alzheimers cases had been treated for depression (AD group) compared with 7 of 39 patients with cortical Lewy bodies (CLB group).

Is this difference significant? Construct a confidence interval around the difference.

4 patients from each group had experienced a fall or syncopal episode in the previous year.

Calculate the difference in percentages between the groups. Construct 80, 95 and 99% confidence intervals around this difference. Perform a significance test of the difference. What is the null hypothesis? What information does the p-value give us?

In the discussion the authors state that **"It must be emphasised that our data collection was retrospective, and the true frequency of occurrence of many of the key symptoms and signs likely was higher...the absence of reports of falls, syncope, and fluctuation cannot be used to argue that they did not occur."** - Comment.

20. Scarfone RJ et al, Controlled trial of oral prednisone in the emergency treatment of children with acute asthma, Pediatrics,1993;92(4),513-517.

"Emergency department patients aged 1-17 years whose chief complaint was acute asthma were assigned a pulmonary index, based on clinical evaluation. Those with a moderate exacerbation (pulmonary index = 9 through 13) received either 2mg/kg of oral prednisone or placebo in a randomized, double-blind fashion. Patients in each group were then treated with an identical regimen of frequent aerosolized albuterol, for up to a maximum of 4 hours...
... These data demonstrate that oral prednisone, within 4 hours of its administration, reduced the need for hospitalization among a subset of children treated in the emergency department for acute asthma."

TABLE 3. Hospitalization Rates*

	Prednisone	Placebo	*P* Value
All patients	11/36 (31)	19/39 (49)	.10
Patients with initial PI > 10	7/22 (32)	13/18 (72)	<.05

* Values expressed as No. hospitalized/total (%). PI, pulmonary index.

For all patients and for the subgroup with initial PI>10 (this subgroup has more severe disease) test the hypothesis that hospitalization rates are different for the placebo and prednisone groups. (Verify the p-values given in the table.)

In both cases, calculate a 95% confidence interval for the difference between the prednisone and placebo patients.

Comment on the results and the authors conclusions.

Calculate the number of patients with initial PI > 10 who would have to be treated with prednisolone to prevent 1 being hospitalised.

Give a 95% confidence interval for this number.

21. Nine out of 150 children receiving a new treatment for eczema developed side effects so severe that they discontinued treatment. Of 139 similar children randomly allocated to the standard protocol, none discontinued usage because of side effects. Is there any evidence that side effects are more commonly attributable to the new treatment?

PAIRED DATA

1. Jayabose A et al, Clinical and hematologic effects of hydroxyurea in children with sickle cell anemia, The Journal of Pediatrics, 1996; 129,559-65.

Patients with SCA and frequent VOCs or severe anemia were eligible for the study. The frequency of VOCs were compared before after hydroxyurea therapy. With regards to the 'before' measurement the authors state "By including a longer period of pretreatment follow-up, one is more likely to obtain a true pretreatment crisis rate. Details of hospitalisation and diagnosis of VOC and ACS before hydroxyurea therapy were obtained from hospital charts and pediatric hematology records."

The results are given below:

Patient	VOCs/yr before therapy	VOCs/yr during therapy
1	3.9	0.8
2	2.9	0.0
3	2.6	0.7
4	3.6	1.9
5	4.2	0.0
6	6.7	7.5
7	2.8	2.6
8	0.6	0.0
9	3.0	0.0
10	0.8	0.0
11	2.2	0.4
12	1.7	0.0
13	0.3	0.0
14	0.7	0.7

Comment on the distributions of VOCs/yr before and during therapy.

Calculate the change in VOCs for each patient from before to during therapy. Comment on the distribution of the differences.

Calculate the average change in number of VOCs/yr. The standard deviation of the differences can be calculated to be 1.42. Is there any evidence that the number of VOCs/yr changed during therapy (from before values)? Give a p-value. Give a 95% confidence interval for the difference. Does hydroxyurea therapy affect the frequency of VOCs/yr?

2. Some of the results of a double-blind cross-over trial of a new drug and an existing drug (Methyldopa) in patients with mild to moderate hypertension are shown below:

Patient	Methyldopa	New drug	Difference
1	+10	-10	+20
2	+ 8	- 9	+17
3	-33	+ 4	-37
4	+19	+ 4	+15
5	+31	-27	+58
6	-30	-12	-18
7	0	-26	+28
8	- 2	-28	+26
9	+ 3	-24	+27
10	-14	- 6	- 8
Mean	-0.8	-13.6	12.8
S.d.	20.21	12.55	27.05

Each patient received each treatment for a period of eight weeks, and the two periods were separated by a two-week "wash-out" period on placebo. The order of administration of the two drugs was randomised, and its effect can be ignored. Note that the standard error of the paired differences is found to be equal to 8.55.

a) Investigate whether there is any evidence of a difference in the effects of the two drugs on systolic blood pressure

b) Find a 95% confidence interval for the mean difference in response to the two drugs.

c) What conclusions can you draw from these data?

3. Landau H et al, Cross-sectional and longitudinal study of the pituitary-thyroid axis in patients with thalassaemia major, Clinical Endocrinology,1993;38,55-61.

Summary

PATIENTS AND MEASUREMENTS ... Longitudinal study: 21 thalassaemia major patients were evaluated with TRH tests in 1976 and again in 1985...

RESULTS ...Longitudinal study: mean TSH response to TRH decreased (P<0.002), and mean T3 levels increased (P<0.001) between 1975 and 1985. These findings are probably related to the initiation of DF treatment in 1981....

.. In 1976, TSH levels were determined using a RIA as previously described (Spitz et al.,1984), and in 1985 using a commercial RIA kit supplied by CIS International, France. Since both assays gave similar results, the data from 1976 and 1985 can be compared directly....

..Mean T3 levels increased from 1976 to 1985 (1.95 ± 0.18 nmol/l; P<0.01) whereas mean peak TSH response to TRH decreased (32.7 ± 3.5 to 17.8 ± 2.2 mU/l; P<0.005). Similarly, mean basal TSH levels decreased significantly from 1976 to 1985 (4.5 ± 0.5 to 2.5 ± 0.3 mU/l; P<0.002)....

Comment on the analysis and interpretation of the results shown.

4. Vainionpaa L et al, Chemotherapy for acute lymphoblastic leukemia may cause subtle changes of the spinal cord detectable by somatosensory evoked potentials, Medical and Pediatric Oncology,1997;28,41-47.

The patient series included 38 consecutive children admitted to the Department of Pediatrics for initial treatment of ALL and who achieved remission during the induction therapy. The SEP recordings were compared with those obtained for control children and were individually matched for age, sex and height.... Differences between the patients and their controls were assessed with the paired t test and confidence intervals.

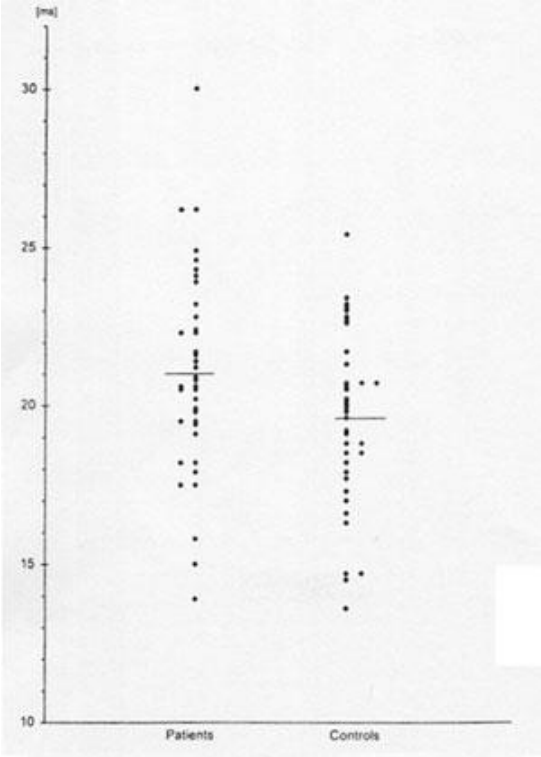


Fig. 1. The data of the latencies from the spinal Th12 to cortex (SP-P40) obtained from the patients after the two therapy phases (induction therapy and CNS therapy) and their controls. Lines show the means of the latencies.

Mean value for the patients was 21.0, standard deviation 3.2. For the controls the values were 19.6 and 2.8 respectively.

The average of the paired differences was 1.4, standard error 0.525

a) Construct a 95% confidence interval for the average difference. Perform a significance test to see whether the average is significantly different from zero.

b) If the pairing between individuals is ignored, the standard error of the difference between the group averages can be calculated to be 0.69. Construct a 95% confidence interval around the average difference between groups. Is the difference significant?

Comment on the difference between the results of (a) and (b).

5. Singh H, Chugh JC, Shembesh AH et al, Hepatotoxicity of high dose salicyte therapy in acute rheumatic fever, Annals Trop Ped, 1992;12,37-40.

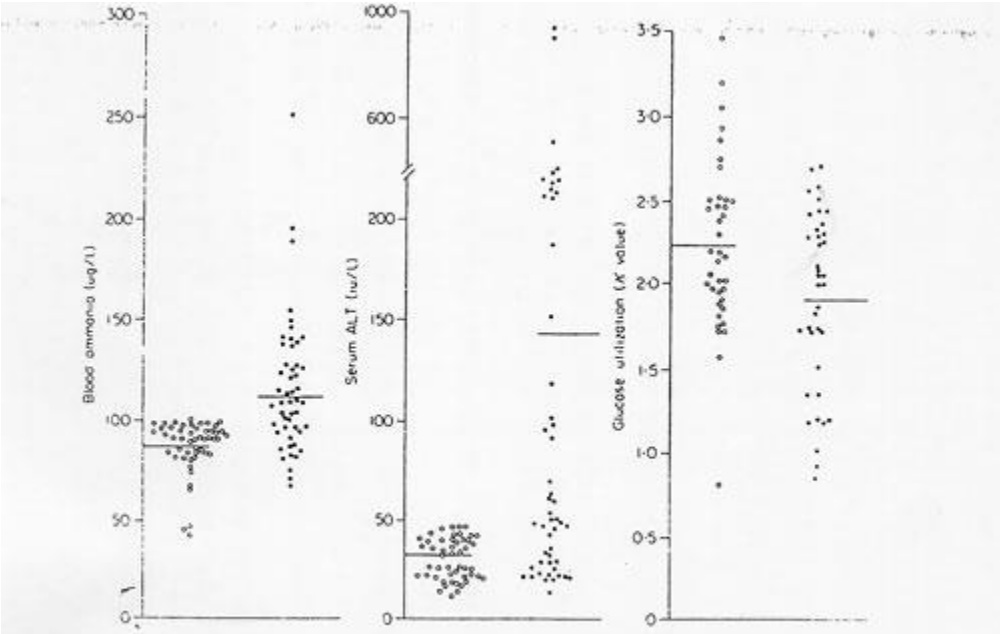


FIG 1 Blood ammonia, serum ALT and glucose utilization coefficients in children with acute rheumatic fever before (○) and after (●) 1 week of aspirin therapy.

TABLE I Liver function tests in children with ARF before and after aspirin therapy

Parameter	Before therapy Range	Before therapy Mean (SD)	After therapy Range	After therapy Mean (SD)	Significance
Blood ammonia (ug dl)	43–99	86.2 (12.6)	69–254	114.8 (32.7)	$p<0.001$
Serum ALT (iu l)	11–45	28.9 (8.9)	13–930	145.4 (189.6)	$p<0.001$
Glucose utilization coefficient (K value $\times 10^{-1}$)	0.8–3.42	2.23 (0.51)	0.85–2.67	1.90 (0.57)	$p<0.02$
Serum alkaline phosphatase (KAU)	5.3–48.6	14.7 (8.5)	6.3–53.1	18.2 (9.0)	$p>0.05$
Serum bilirubin (mg/dl)	0.2–0.8	0.31 (0.1)	0.2–1.1	0.40 (0.26)	$p>0.05$
Serum proteins (g/dl):					
Total	5.4–8.4	7.01 (0.7)	6.0–8.0	6.81 (0.6)	$p>0.05$
Albumin	1.8–4.1	3.01 (0.6)	2.6–4.2	3.33 (0.4)	$p>0.05$
Globulin	2.7–5.8	4.00 (0.8)	2.5–4.3	3.48 (0.5)	$p>0.02$

Comment on the presentation and analysis of the data.

6. In a community trial of the drug Ivermectin for the treatment of onchocerciasis villages were surveyed before being treated and then again 6 months after treatment. The following data show the presence or absence of itching in 470 persons treated with Ivermectin who were observed at both surveys.

Pre-treatment survey	Post-treatment survey	Number of persons
present	present	186
present	absent	85
absent	present	59
absent	absent	140

Construct a frequency table for the above data.

What is the research question? State the null hypothesis. Use the appropriate test of statistical significance to assess the strength of evidence that Ivermectin reduces itching. Interpret the p value. Calculate a confidence interval. Comment on the results.

NON PARAMETRIC TESTS

1. Parra A, Ramirez-Peredo J, Coutino B, Lagunes B, Marin A, Ponce de Leon, S, Ruiz-Arguelles GJ, Impaired metoclopramide-induced pituitary prolactin release in men with human immunodeficiency virus infection, J Lab Clin Med,1999;133,70-4.

Table I. Chronologic age, body mass index, and CD4 cell counts in healthy men (group 1) and HIV-positive men (group 2)

	Group 1			Group 2			
n	Age (y)	BMI (kg/m²)	CD4 (×10⁶/L)	Age (y)	BMI (kg/m²)	CD4 (×10⁶/L)	CDC* classification
1	28	30.0	532	33	19.1	38	C3
2	56	22.8	1504	53	17.2	13	B3
3	28	28.0	756	28	19.5	120	C3
4	36	25.5	946	30	19.7	123	B3
5	26	23.5	870	33	19.4	246	C2
6	30	24.6	811	25	22.5	32	B3
7	33	30.6	1207	30	20.7	421	A2
8	30	26.7	529	24	25.3	570	A1
9	26	25.9	878	23	23.5	547	A1
10	26	24.2	850	27	19.7	380	A2
Mean	32.0	26.1		30.5	20.6		
SD	9.3	2.6		8.3	2.4		

*Atlanta Centers for Disease Control.
BMI, Body mass index. A, Asymptomatic, acute (primary) HIV or persistent generalized lymphadenopathy; A1, A conditions, plus CD4 cells ≥ 500 (×10⁶/L); A2, A conditions, plus CD4 cells 200 to 499 (×10⁶/L); B, symptomatic, not A or C conditions; B3, B conditions, plus CD4 cells < 200 (×10⁶/L); C, AIDS indicator conditions; C2, C conditions, plus CD4 cells 200 to 499 (×10⁶/L); C3, C conditions, + CD4 cells < 200 (×10⁶/L).

Rank the CD4 counts in groups 1 and 2 combined. Calculate the sum of the ranks for each of the groups.

What is the null hypothesis that needs to be tested to determine whether CD4 counts differ between healthy and HIV-positive men?

If the null hypothesis were true what would we expect the sum of the ranks of each of the groups to be approximately equal to?

What would be a suitable test of whether CD4 count and positively are associated? Why? Given the information calculated above would you expect to obtain a large or a small p-value Why?

If a p-value of less than 0.001 were obtained, what would this mean? Would it indicate that HIV-positivity affects CD4 count?

How would the results differ if patient number 2 in group 1 had a CD4 count of 3504 (instead of 1504)?

2. Logie LJ, Porteous MEM, Intelligence and development in Aarskog syndrome, Arch Dis Child,1998;79,359-360.

Table 1 IQ in boys with Aarskog syndrome

Case	*Age (years)*	*Method*	*IQ*
1	0.7	Griffiths	97
2	1.2	Griffiths	98
3	1.3	Griffiths	104
4	1.4	Griffiths	92
5	2.3	Griffiths	68
6	2.3	Griffiths	102
7	2.4	Griffiths	104
8	3.8	Griffiths	81
9	4.3	Griffiths	102
10	5.2	BAS	128
11	5.8	BAS	107
12	7.5	BAS	116
13	7.9	BAS	103
14	8.8	BAS	109
15	9.6	BAS	105
16	10.5	BAS	117
17	13.4	BAS	127
18	13.4	BAS	112
19	13.5	BAS	109
20	14.3	BAS	125
21	16.7	BAS	118

Mean IQ, 106; Mean IQ for Griffiths mental development scales (Griffiths), 94; Mean IQ for British activity scales (BAS), 115.

Rank the IQs for the 21 boys.

What is the average rank for those aged under 5 years (i.e. those tested by the Griffiths scale)?

What is the average rank for the patients who were older than 5 years of age (i.e. those tested using the BAS scale)?

Is there any evidence that IQ improves with age?

Are the Griffiths and BAS scales valid measurements of IQ?

3. Bond CM, Comparison of buccal and oral prochlorperazine in the treatment of dizziness associated with nausea and/or vomiting, Current Medical Research and Opinion,1998;14(4),203-212.

177 patients were randomised to receive buccal (n=89) or oral (n=88) prochlorperazine. Severity was rated as none, mild, moderate or severe and frequency as no symptoms, symptoms some of the time (< 2h per day), most of the time (2-12 h per day) or all of the time (> 12h per day). Comparisons between the groups at the different time points for the different symptoms are given in the table below (significance levels given) :-

Table 2. Buccal and oral prochlorperazine in nausea, vomiting and dizziness

	First progress assessment (24–36 h)		Second progress assessment (7 days)	
	Severity	Frequency	Severity	Frequency
Nausea	NS	0.02*	NS	NS
Vomiting	0.05*	0.07*	NS	NS
Dizziness	NS	NS	NS	NS

*Buccal superior to oral prochlorperazine.
NS = No significant difference between treatments.

What is the appropriate test to use to make these comparisons? Comment on the presentation of the results in the table.

BOOTSTRAPPING

1. The process of finding a bootstrap estimated mean birthweight and confidence interval using 10,000 samples was repeated twice more.
   The results were 3377.3 (3168.7, 3597.4 grams) for the first replication and 3378.4 (3178.2, 3596.8) for the second.

   Comment on the differences.

   Is such replication something that you would do in practice? Why?

A bootstrap sample of 100,000 was taken from the same sample of 30 birthweights and this gave estimates of 3377.4 (3174.2, 3594.4).

Bootstrap samples of size 20 were also tried twice and these gave estimates of 3323.6 (3213.5, 3576.8) and 3348.9 (3202.2, 3458.5).

Comment on the differences between the estimates based on 10000, 100000 and 20 bootstrap samples.

Why use median of distribution, not the mean?

2. For proportion example (7/57), calculate the standard error using the single proportion formula introduced in Chapter 5 and verify the parametric ci. What assumptions is this based on?

BEYOND T-TESTS

1. Ref: Ashby, J., Sadera, W. A., & McNary, S. W. (2011). Comparing student success between developmental math courses offered online, blended, and face-to-face. Journal of Interactive Online Learning, 10(3).

Data Analysis: Comparisons between learning environments on continuous outcomes (unit tests, final exam, course average) were made using one-way ANOVA, with learning environment as the factor, with three levels (Face-to-face, Blended, and Online).

Table 3
Mean and Standard Deviation Percent Correct on Unit Tests, IACE, and Course Average by Learning Environment (Complete Dataset N = 167)

	Face-to-face (N = 58)	Blended (N = 46)	Online (N = 63)	F(2, 164)	p	Pairwise tests of significance[h]
Unit Test #1[a]	70.1 (21.4)	67.9 (32.1)	77.6 (24.6)	2.21	0.113	
Unit Test #2[b]	88.7 (14.7)	69.5 (34.5)	75.0 (32.5)	6.54	0.002*	F>B;F>O
Unit Test #3[c]	50.4 (23.1)	45.4 (32.2)	59.3 (30.3)	3.39	0.036*	O>B
Unit Test #4[d]	67.3 (22.7)	55.6 (33.5)	64.2 (34.1)	2.00	0.138	
Unit Test #5[e]	83.4 (20.2)	62.2 (41.1)	78.2 (35.4)	5.68	0.004*	F>B; O>B
Unit Test #6[f]	63.8 (26.9)	52.8 (38.4)	64.7 (37.7)	1.82	0.165	
Unit Test #7[g]	75.5 (27.0)	54.4 (43.3)	65.0 (43.5)	3.86	0.023*	F>B
IACE	60.2 (22.6)	45.8 (34.6)	50.7 (33.0)	3.13	0.046*	F>B
Course Average	68.1 (18.7)	54.5 (32.0)	63.9 (28.5)	3.40	0.036*	F>B

Note. *$p < 0.05$ for main effect of Learning Environment.[a]Factoring, [b]Function notation and operations, [c]Rational Expressions, [d]Radicals, [e]Complex and Imaginary Numbers, [f]Solving Quadratic Equations, [g]Parabolas and Circles, [h]Pairwise significance tests via Tukey's HSD, $p < 0.05$.

The table gives results from a one-way ANOVA comparing the results of various tests between different learning environments.

i) Comment on the analysis chosen to carry out these comparisons, is it appropriate?

ii) What is the final column, pairwise test of significance, showing?

2. Ref: Tay SH, Ho CS, Ho RC-M, Mak A (2015) "25-Hydroxyvitamin D3 Deficiency Independently Predicts Cognitive Impairment in Patients with Systemic Lupus Erythematosus." PLoS ONE 10(12):e0144149.

Table 4. Results of multiple linear regression analysis between total throughput score and demographic, neuropsychological and clinical variables for 61 SLE patients and 61 healthy controls.

	Independent variable	β (SE)	Beta	P	R^2
Model 1*					0.471
	Age	-4.523 (0.586)	-0.518	0.00	
	Chinese	59.977 (14.509)	0.285	0.00	
	SLE status (yes versus no)	-40.673 (13.778)	-0.206	0.04	
Model 2**					0.441
	Age	-4.495 (0.619)	-0.516	0.000	
	Chinese	58.515 (15.621)	0.274	0.000	
	SLE status (yes versus no)	-40.399 (14.579)	-0.205	0.007	
Model 3***					0.459
	Age	-4.422 (0.611)	-0.508	0.000	
	Chinese	53.511 (15.550)	0.250	0.001	
	SLE status (yes versus no)	-33.242 (14.732)	-0.168	0.026	
	$25(OH)D_3$ deficiency	-46.977 (21.949)	-0.156	0.035	

* Model included age, education, gender, ethnicity, HADS-Total and SLE status; significant variables reported.

** Model included age, education, gender, ethnicity, HADS-Total, SLE status and $25(OH)D_3$; significant variables reported.

*** Model included age, education, gender, ethnicity, HADS-Total, SLE status and $25(OH)D_3$ status; significant variables reported.

The table above gives results from three separate regression models fitted to investigate the relationship between outcome variable total thoroughput score and a number of predictor variables.

i) Comment on the presentation of results.

ii) Why do regression coefficients differ between models for the same predictors?

iii) For model 1 what is the interpretation of the age coefficient if age is recorded in years.

iv) Calculate the 95% confidence interval for this coefficient and interpret

DISPLAYING RESULTS

Comment on the presentation of the results in the following examples; can you pick up flaws in the study design and analysis via these graphs? Suggest potential improvements if possible.

1. Neonatal sepsis, antibiotic therapy and later risk of asthma and allergyppe, Tanja Sobkoa, Paediatric and Perinatal Epidemiology, 24, 88–92.

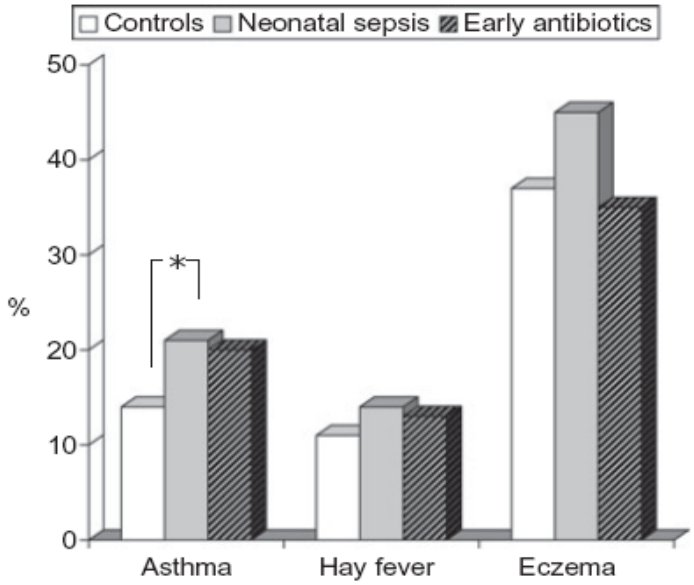


Figure 1. Prevalence of asthma, hay fever and eczema (%) in children and young adults (median 12, range 7–23 years of age) according to neonatal sepsis and early antibiotic therapy (total $n = 831$). Asthma was significantly more common after neonatal sepsis ($^*P < 0.05$).

		Unadjusted OR [95% CI]	Adjusted[a] OR [95% CI]	*P* value
	Asthma *n* (%)			
Sepsis	43/201 (21)	1.73 [1.12, 2.69]	1.63 [1.04, 2.56]	0.035
Antibiotics[b]	40/201 (20)	1.58 [1.01, 2.47]	1.48 [0.93, 2.35]	0.098
Control	57/420 (14)	1.00 Reference	1.00 Reference	
	Hay fever *n* (%)			
Sepsis	28/195 (14)	1.33 [0.80, 2.19]	1.27 [0.76, 2.13]	0.363
Antibiotics[b]	26/196 (13)	1.21 [0.73, 2.02]	1.28 [0.75, 2.17]	0.365
Control	47/419 (11)	1.00 Reference	1.00 Reference	
	Eczema *n* (%)			
[illegible]	[illegible]	[illegible].98, 1.95]	1.39 [0.98, 1.98]	0.063
[illegible]	[illegible]	[illegible].64, 1.30]	0.94 [0.66, 1.36]	0.959
[illegible]	[illegible]	[illegible]eference	1.00 Reference	

Table 2. Risk of asthma, hay fever and eczema according to neonatal sepsis and use of antibiotics

[a]Adjusted for group, birthweight in fifths, gestational age, level of mother's education, sex, number of older siblings and year of birth.

[b]Antibiotic therapy without any infection.

"In conclusion, neonatal sepsis was found to be associated with an increased risk

for later asthma during childhood and in young adults, so our a priori hypotheses was rejected. Neonatal antibiotic exposure may contribute to this association."

2. Colonic wall thickness, pancreatic enzyme dose and type of preparation in cystic fibrosis. W H Ramsden, E F Moya and J M Littlewood, Arch Dis Child 1998;79:339–343.

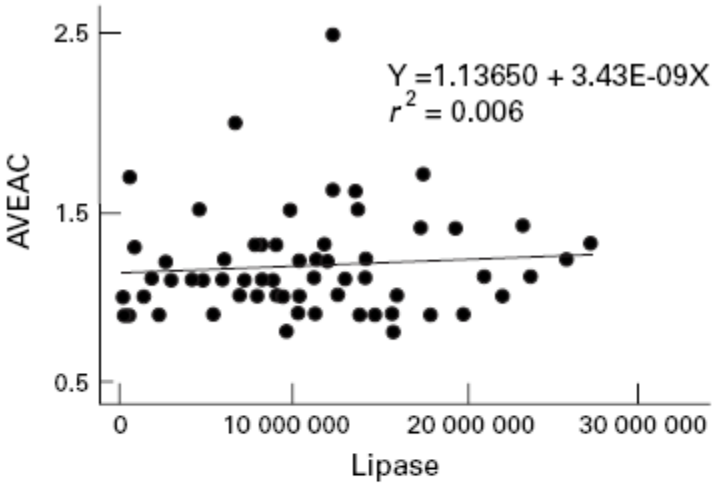


Figure 2 Plot of average ascending colon thickness against lipase use (units/kg).

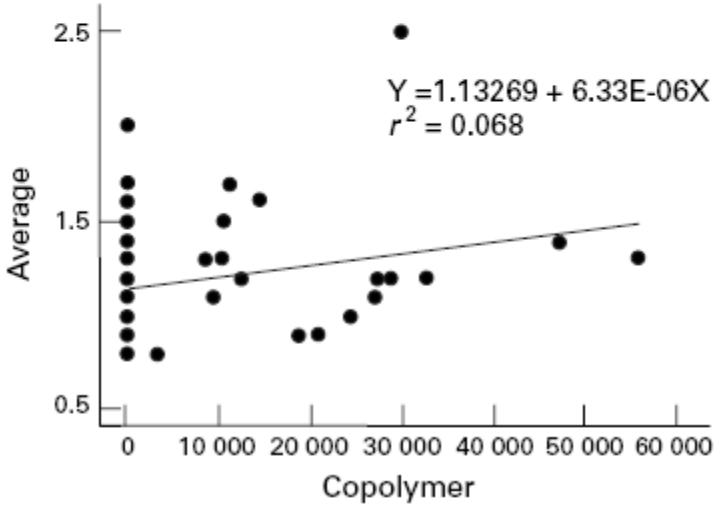


Figure 3 Plot of average ascending colon thickness against copolymer use (mg/kg).

3. Hyperoxia Exposure Alters Hepatic Eicosanoid Metabolism in Newborn Mice, LYNETTE K. Pediatric Research, Vol. 67, No. 2, 2010.

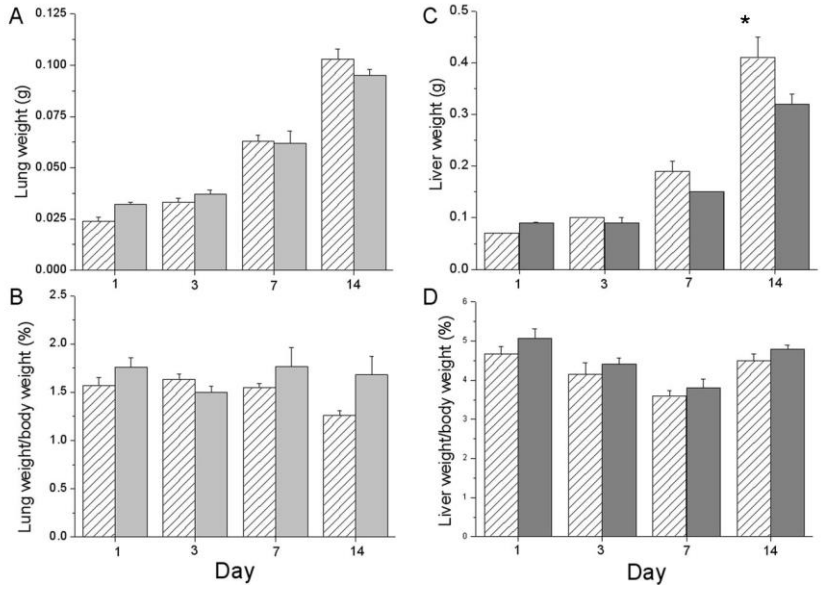


Figure 1. Lung and liver weights in newborn C3H/HeN pups. Pups were exposed to 1, 3, 7, or 14 d of RA (white hatched bars) or _95% O2 (gray bars). Pups were killed at the designated times. Total lung and liver weights were recorded (*A* and *C*). Ratios of lung weight/body weight and liver weight/body weight were calculated (*B* and *D*). Results are reported as mean _ SEM and data were assessed by twoway ANOVA with modified *t* test *posthoc* for individual differences, *n* _ 10 to 18, *p* _ 0.05. An effect of day was observed on lung weights and lung weight/body weight ratios. An effect of day, an effect of exposure, and an interaction were observed on liver weights with an effect of day on the liver weight/body weight ratios. *Indicates different from same day RA.

4. Maternal smoking during pregnancy and intellectual performance in young adult Swedish male offspring, Frida Lundberg, Paediatric and Perinatal Epidemiology, 24, 79–87.

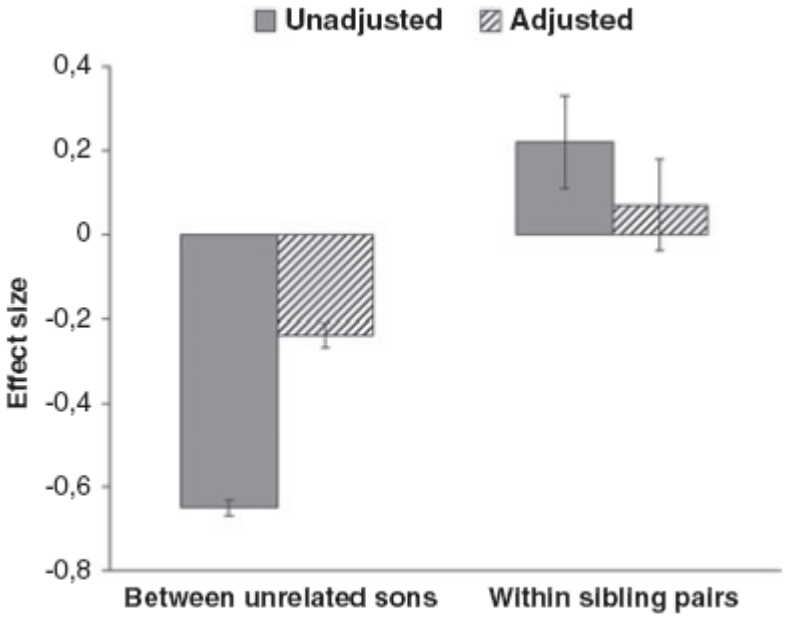


Figure 1. Relationship between prenatal smoking and intellectual performance of sons.

5. Thioredoxin Binding Protein-2 Inhibits Excessive Fetal Hypoglycemia During Maternal Starvation by Suppressing Insulin Secretion in Mice Haruta Mogami et al, Pediatric Research, Vol. 67, No. 2, 2010.

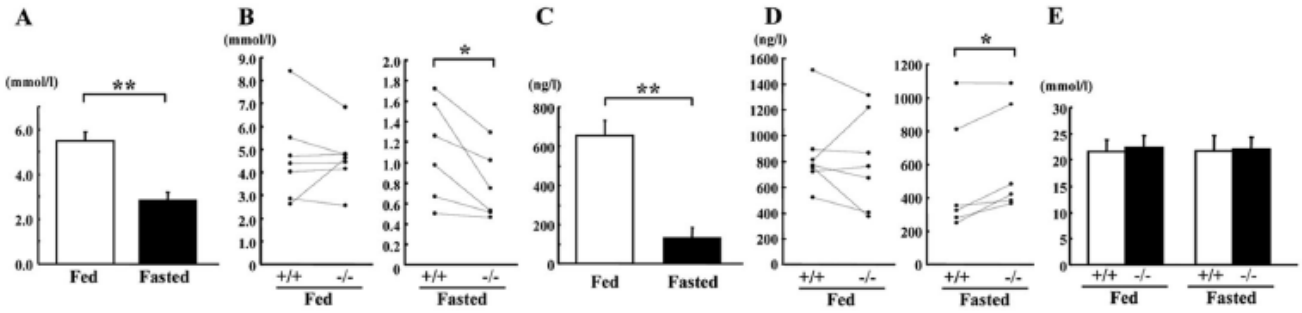
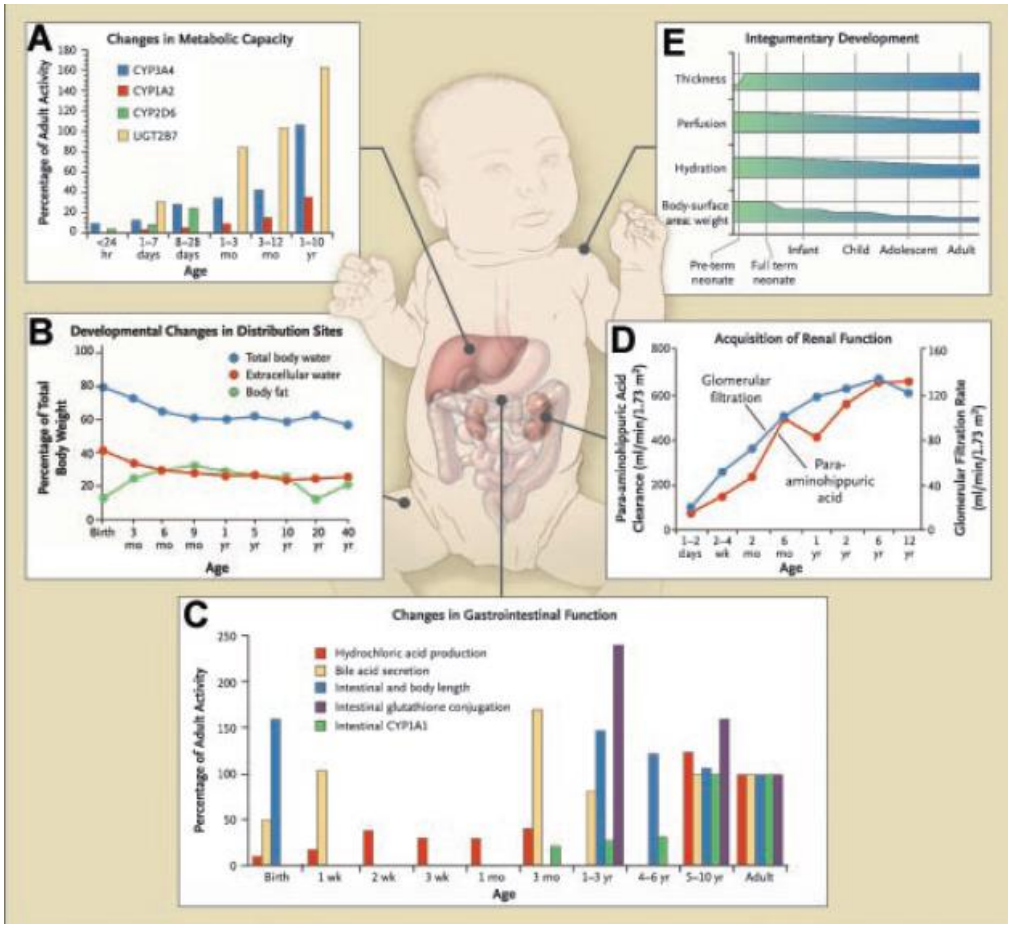


Figure 1. Blood glucose, plasma insulin, and lactate concentrations. (*A*) Maternal and (*B*) fetal blood glucose concentrations in fed ($n = 7$) and fasted ($n = 6$) dams. (*C*) Maternal and (*D*) fetal plasma insulin concentrations in fed ($n = 7$) and fasted ($n = 6$) dams. In (*B*) and (*D*), the concentrations in the thioredoxin binding protein-2 (TBP-2)-deficient (−/−) fetuses were compared with that in the wild-type (+/+) fetuses. *E*, Fetal plasma lactate concentrations in fed ($n = 7$) and fasted ($n = 6$) dams, comparing the wild-type (+/+) fetuses with the TBP-2-deficient (−/−) fetuses. Values are mean +/− SEM in (*A*), (*C*), and (*E*). The data presented in (*A*) and (*C*) were analyzed using *t* test, while those presented in (*B*) and (*D*) were analyzed using paired *t* test. The data presented in (*E*) were analyzed using one-way ANOVA. $*p < 0.05$, $**p < 0.01$.

6. It's Not Easy Being Small, Peter C. Adamson, Pediatr Blood Cancer 2010;54:341–343.



7. Plasma Protein C Is a Useful Clinical Marker for Hepatic Veno-Occlusive Disease (VOD) in Stem Cell Transplantation, Akihiro Iguchi, Pediatr Blood Cancer, 2010;54:437–443.

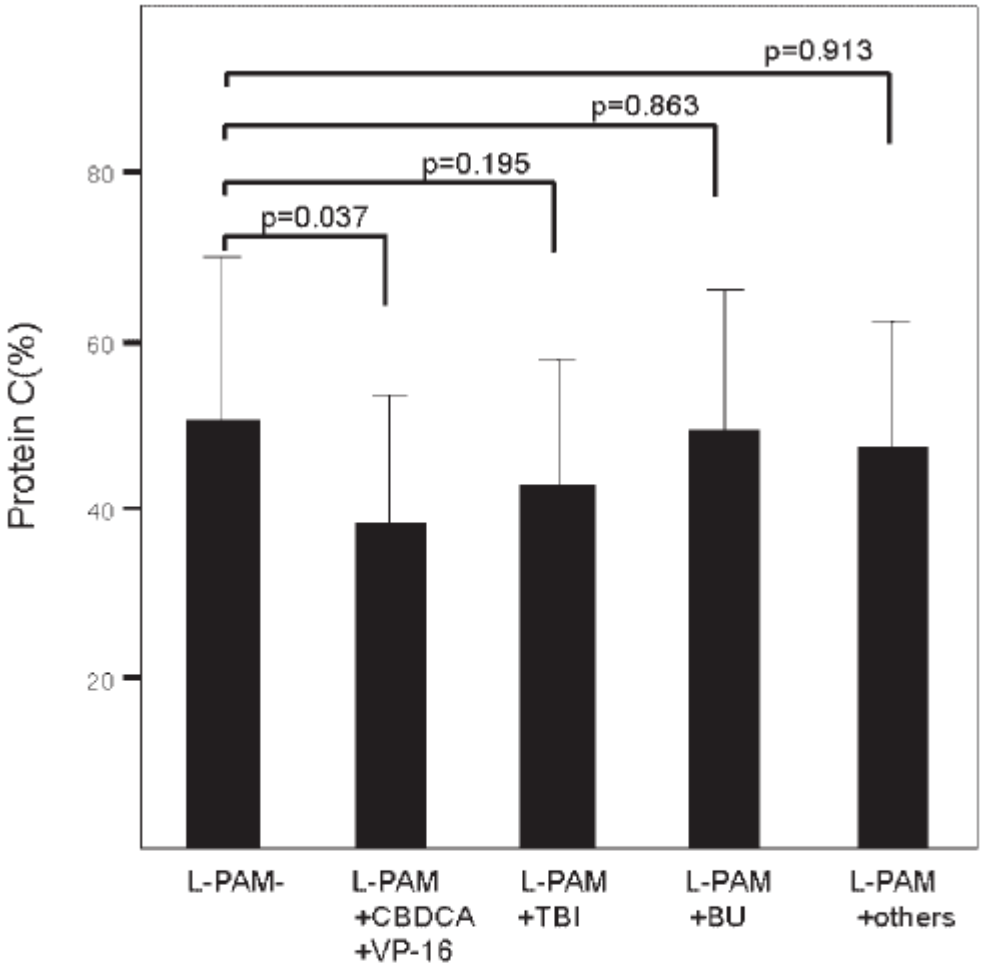


Fig. 4. Comparison of mean minimum plasma protein C levels between patients receiving non-L-PAM containing regimen (n = 101) and those receiving L-PAM + CBDCA + VP-16 (n = 13), L-PAM + TBI (n = 19), L-PAM + BU (n = 16), and L-PAM + others (n = 2). Among the patients receiving four different L-PAM containing regimens, only the patients with L-PAM + CBDCA + VP-16 exhibited significantly lower plasma protein C level compared to those in the non-L-PAM group ($P = 0.037$).