

# Lifestyles and HCC

Jean-François Dufour

Director

University Clinic for Visceral Surgery and Medicine, Hepatology

University of Berne

Berne, Switzerland

# Disclosures

Advisory committees



Bayer HealthCare



Bristol-Myers Squibb



GENFIT  
TOWARDS BETTER MEDICINE



GILEAD

Intercept



MERCK



NOVARTIS



SILLAJEN

Speaking and teaching



Bayer HealthCare

Intercept

Research grant



Bayer HealthCare

# Outset

---

**The best option regarding hepatocellular carcinoma  
is to...**

# Outset

---

**The best option regarding hepatocellular carcinoma  
is to...**

**AVOID IT !**

# How can you decrease your risk ?

---

# How can you decrease your risk ?

---

**Immunization**

**Lifestyles**

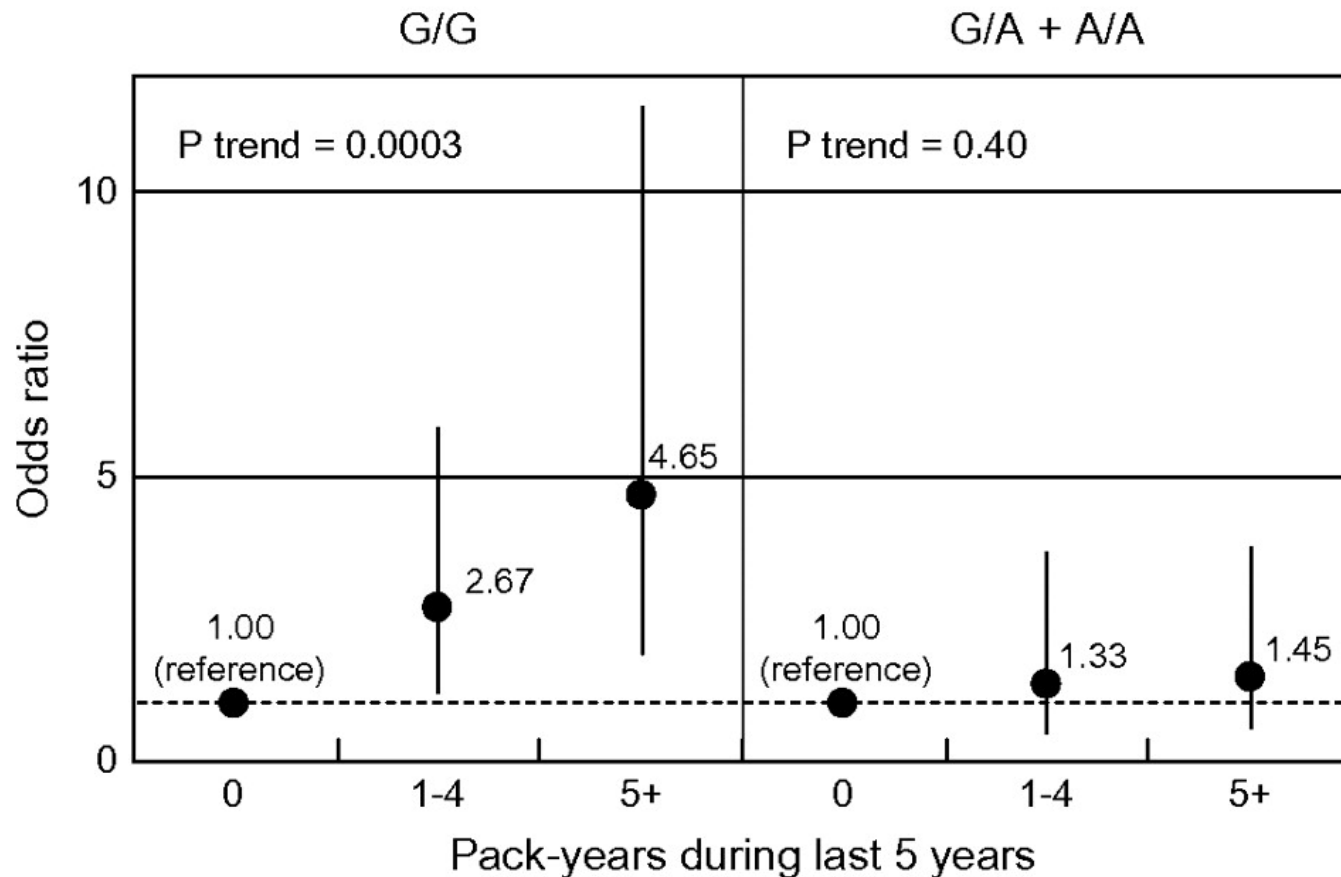
**Drugs**

# Smoking: *CYP1A2* -3860 G>A polymorphism

*CYP1A2* metabolizes polycyclic aromatic hydrocarbons

*CYP1A2*\*1C slow metabolizers (caffeine!)

Comparison was made between 209 HCC cases and 381 patients with CLD



# Smoking and HCC

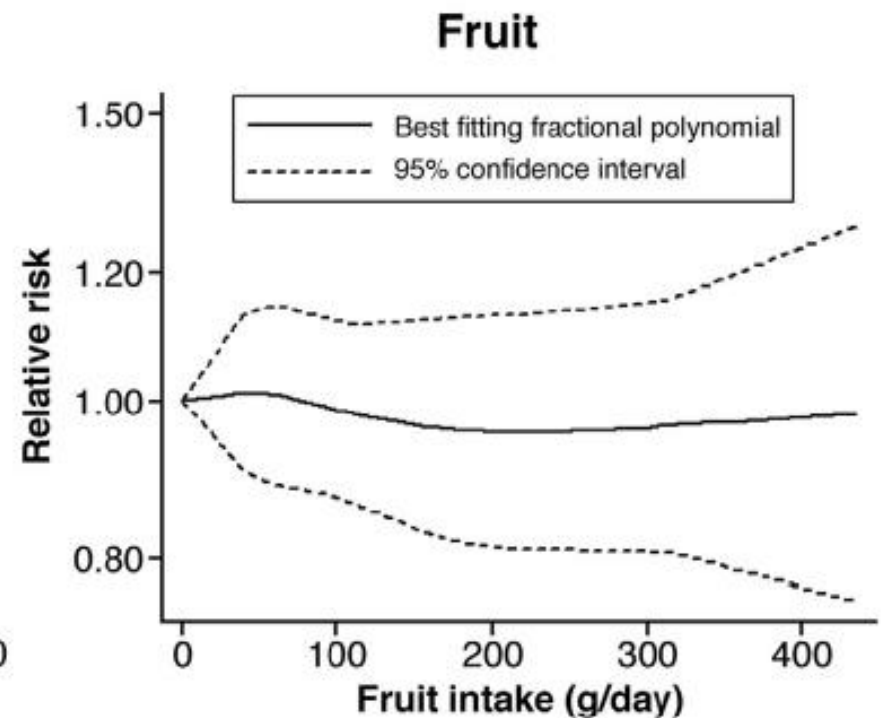
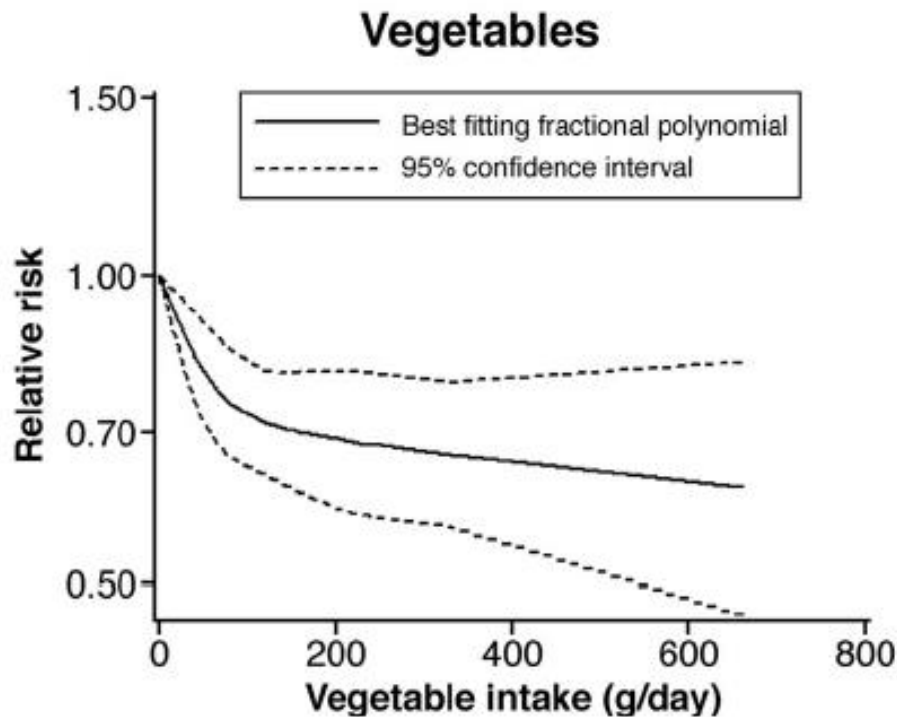
Author, year	Design	N HCC/N Total	Results
Wang 1998	Case study	110/152	OR 4 for medium and OR of 10 for high 4-aminobiphenyl exposure
Chen 2003	Case control	36000/53000	RR 1.36 for ♂, 1.17 for ♀
Koh 2011	Prospective cohort	394/61321	HR 1.63
Shih 2012	Prospective case-control study	115/229	OR 4.55 current smokers OR 1.98 former smokers



# Diet and HCC

Meta-analysis 19 studies with 1290045 participants and 3912 HCCs

RR for HCC 0.72 with high intake vegetables 0.93 with high intake of fruit



# Diet and HCC

---

Two case-control studies (Italy – Greece) 518 HCCs, 772 controls

Mediterranean diet score lowest 0 maximum 9

	<b>≥ 5</b>	<b>0-4</b>
No hepatitis	1 (Odd Ratio)	1.64 (1.07-2.50)
Viral hepatitis	44 (26 -75)	74 (43 – 129)

Indices of departure from additivity of effects

Relative excess risk due to interaction  $p=0.12$

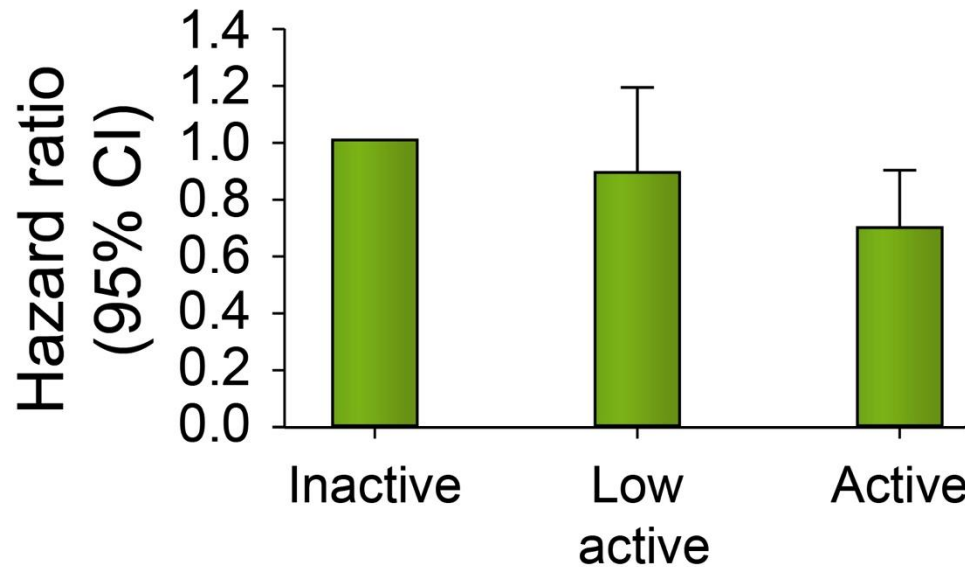
Synergy index  $p=0.08$

# Coffee and HCC

<b>Authors year</b>	<b>Design</b>	<b>Population</b>	<b>Risk of HCC</b>
Larsson 2007	Meta-analysis	2,260 cases 239,146 non cases	RR 0.57
Bravi 2013	Meta-analysis	3,153 cases	RR 0.60
Sang 2013	Meta-analysis	3,622 cases	OR 0.50
Lai 2013	Prospective study	27,037 finnish ♂ smokers	RR 0.82 /cup/day
Bamia 2015	Prospective study	486,799 Europe	HR 0.28 highest vs. lowest
Setiawan 2015	Prospective study	215,000 US	RR 0.62

# Physical activity and HCC

Cohort of 428,584 Taiwanese from a private health screening firm  
Average follow-up 8.5 years, 1668 incident HCC



Physical activity (MET-hr)

<3.57

3.75-7.49

>7.5



# Physical activity and HCC

---

507,897 participants of the NIH-AARP Diet and Health Study

Age 50-71 years at baseline in 1995/6

10 years follow-up

628 incident case of liver cancer

Sessions of 20 minutes vigorous physical activity/week

Relative risk comparing 0 vs.  $\geq 5x$  : 0.6 (0.5 - 0.8) p trend < 0.001

# Physical activity and HCC



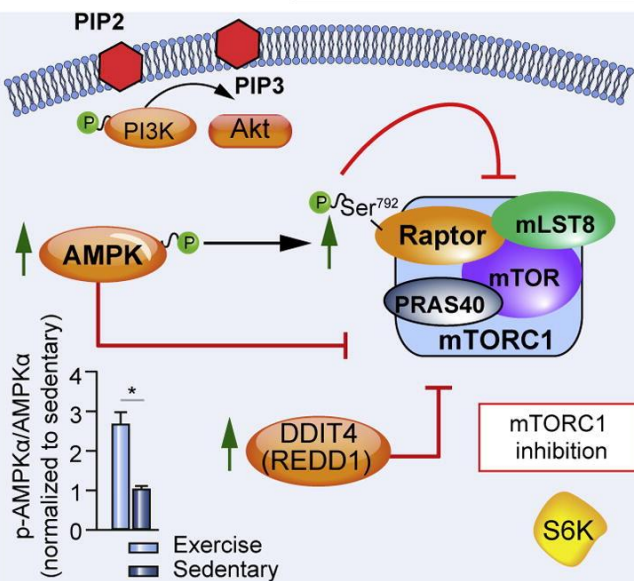
Physical activity

*AlbCrePten<sup>fllox/fllox</sup>*

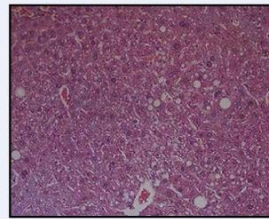
Mouse model of NASH



Sedentary



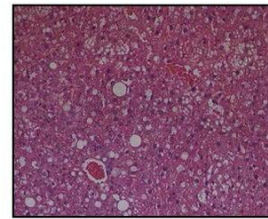
Development of NASH



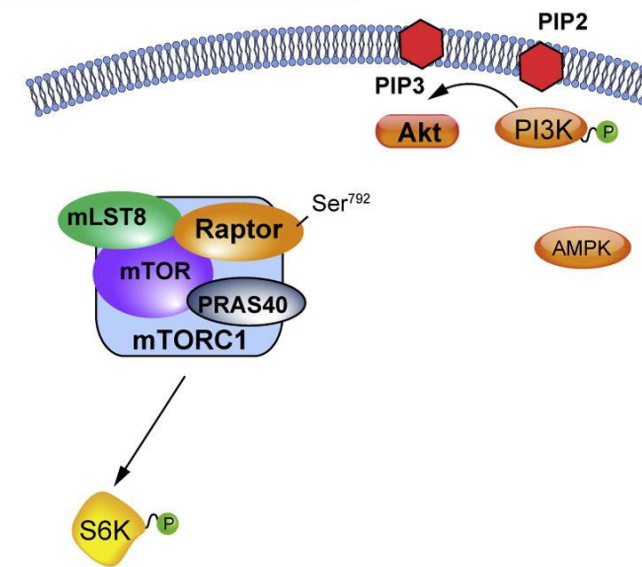
71% HCC



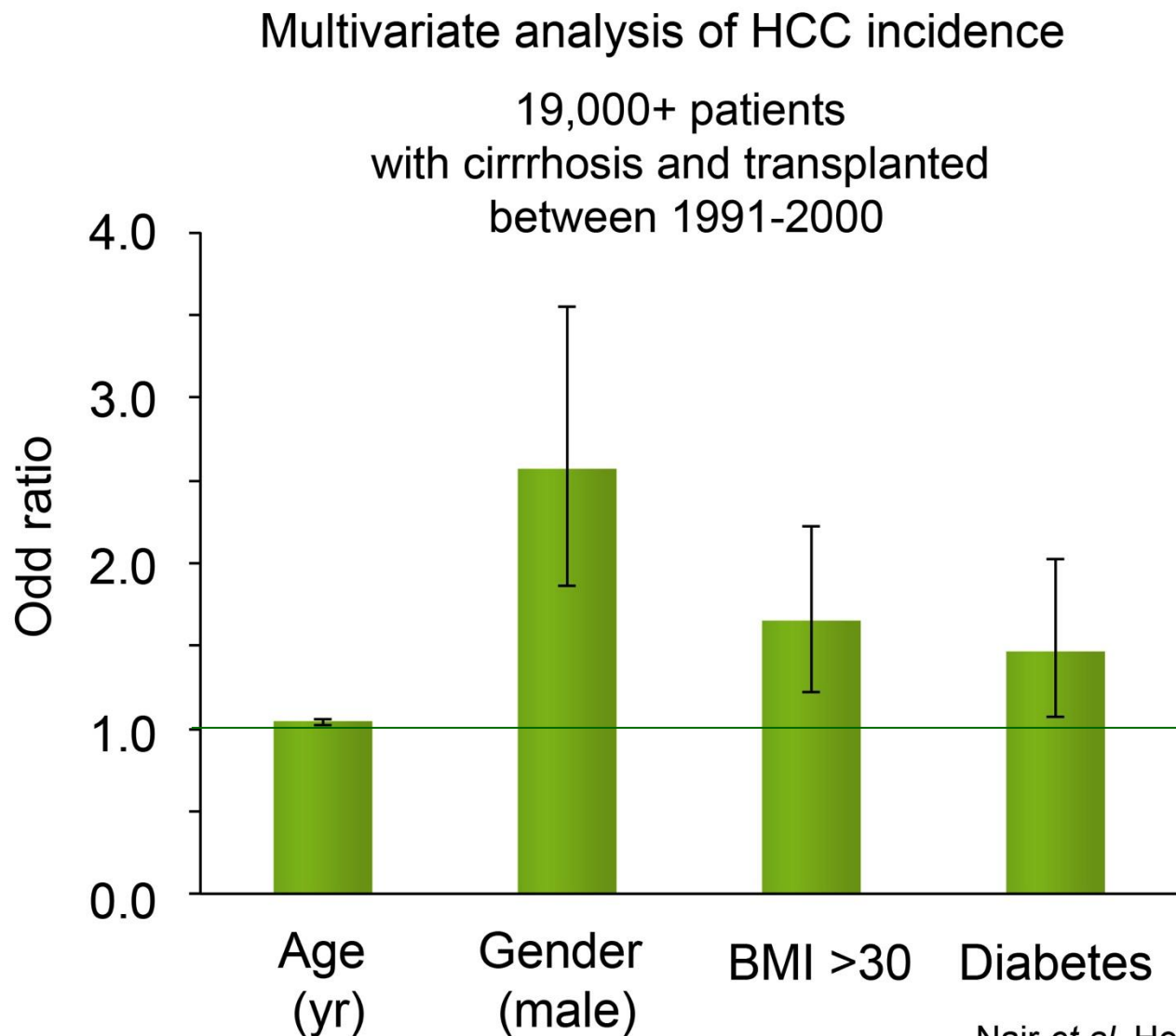
Development of NASH



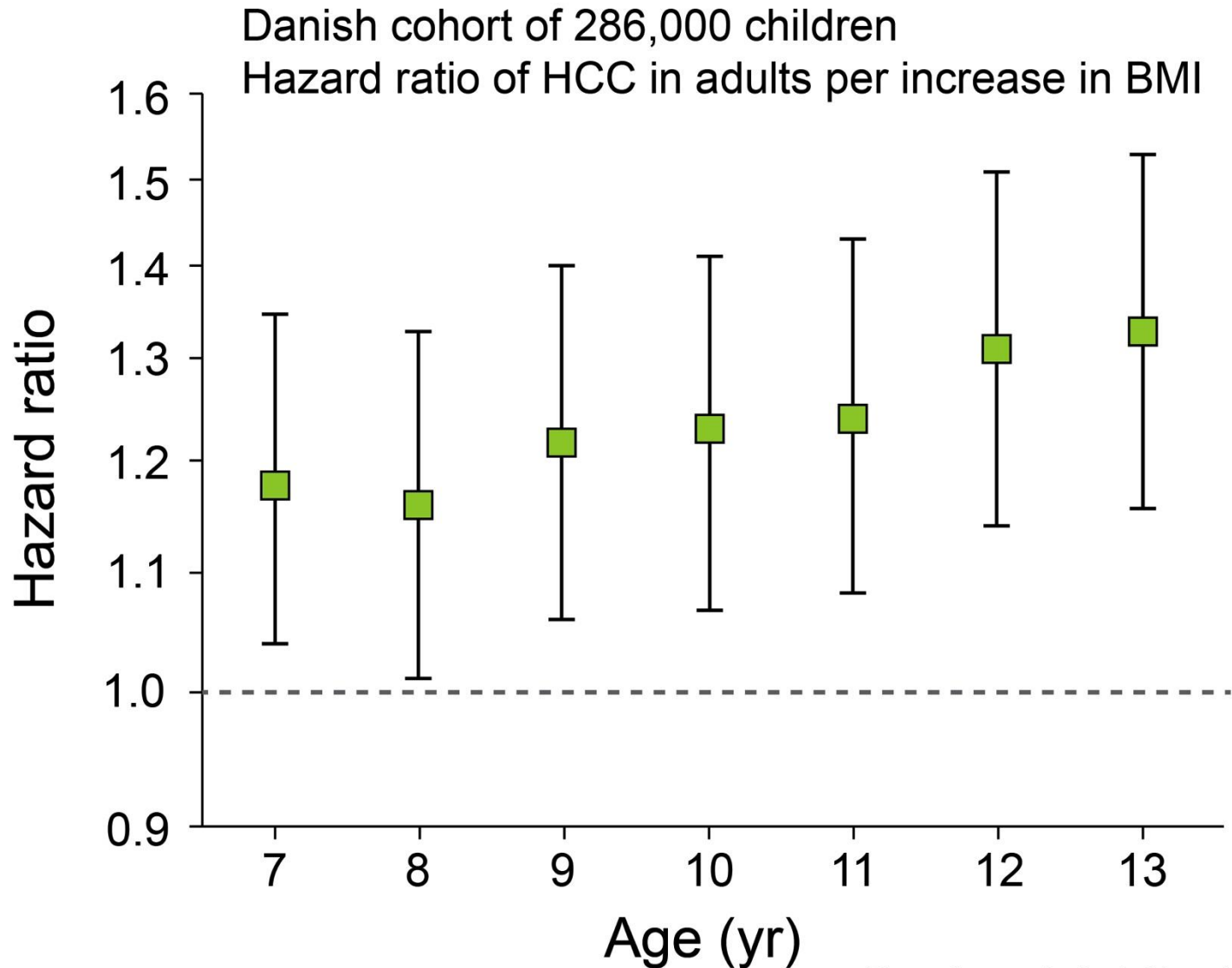
100% HCC



# Association of obesity & diabetes with HCC



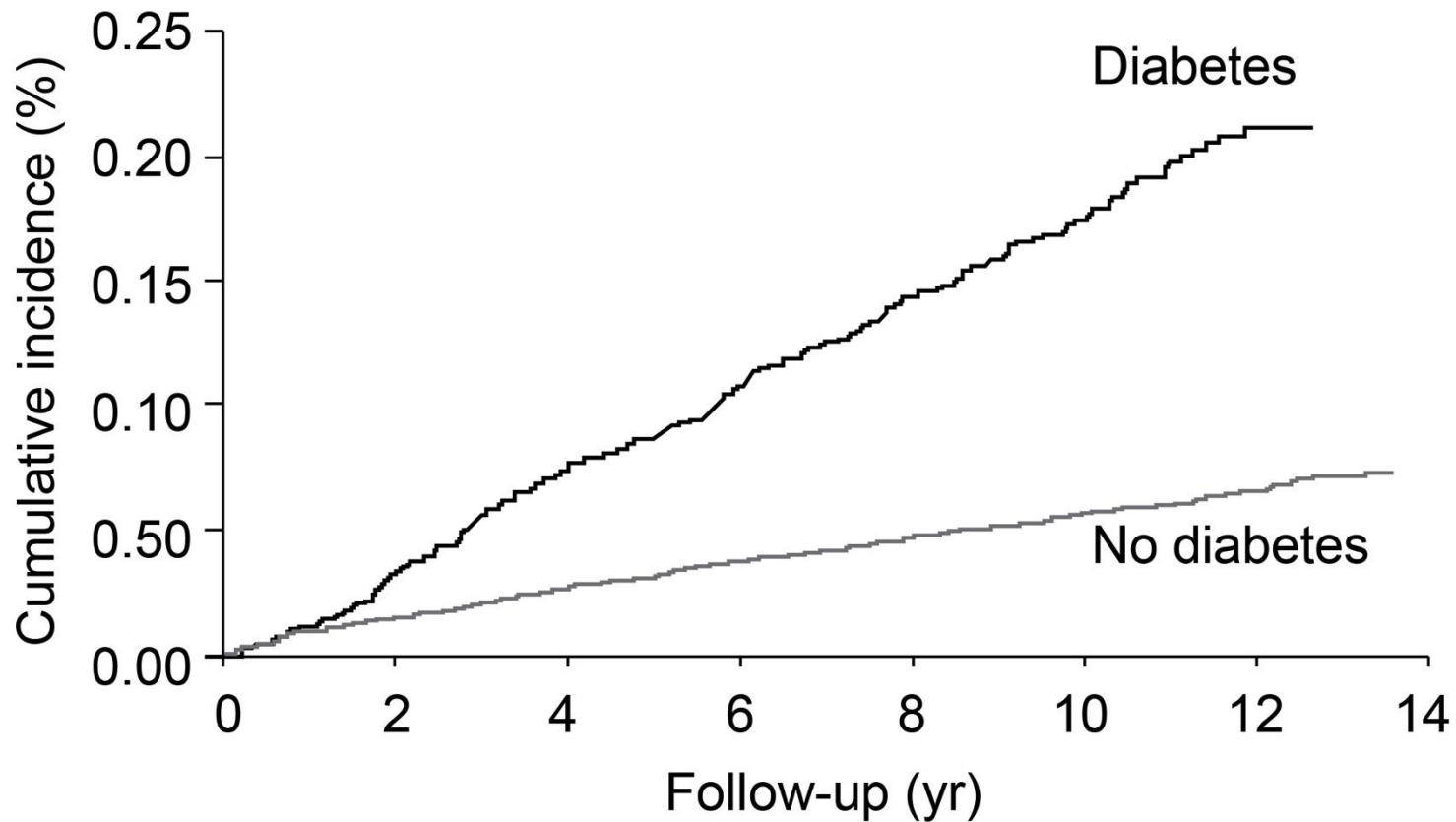
# Association of obesity with HCC





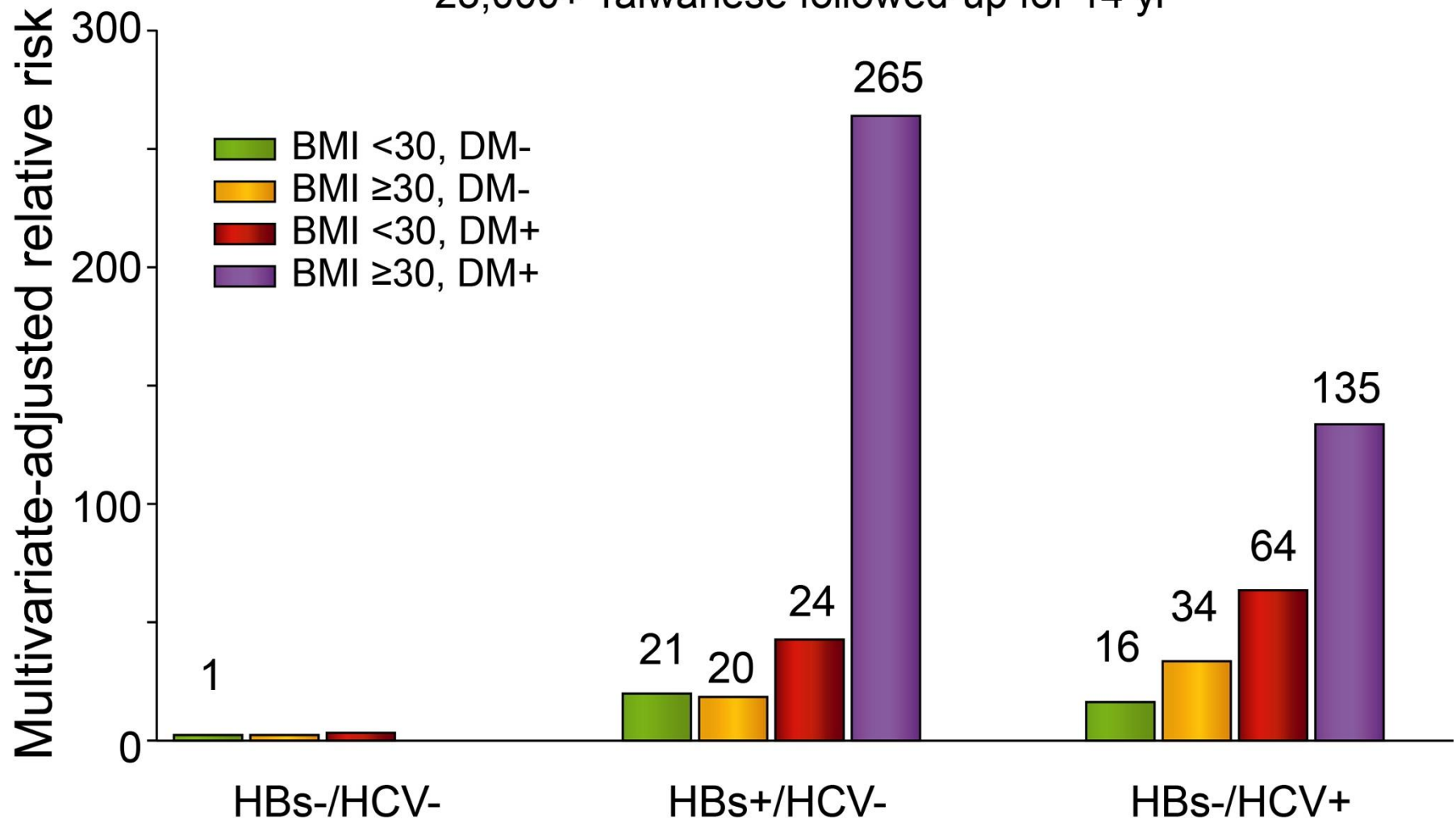
# Association of diabetes with HCC

173'643 veterans with diabetes mellitus matched with 3 veterans without diabetes



# Synergism of obesity & diabetes with HBV & HCV for HCC

23,000+ Taiwanese followed-up for 14 yr



# Effect of Metformin vs. Insulin on HCC risk

---

Nationwide case-control study in Taiwan

Multivariate analysis in 47 820 diabetic patients

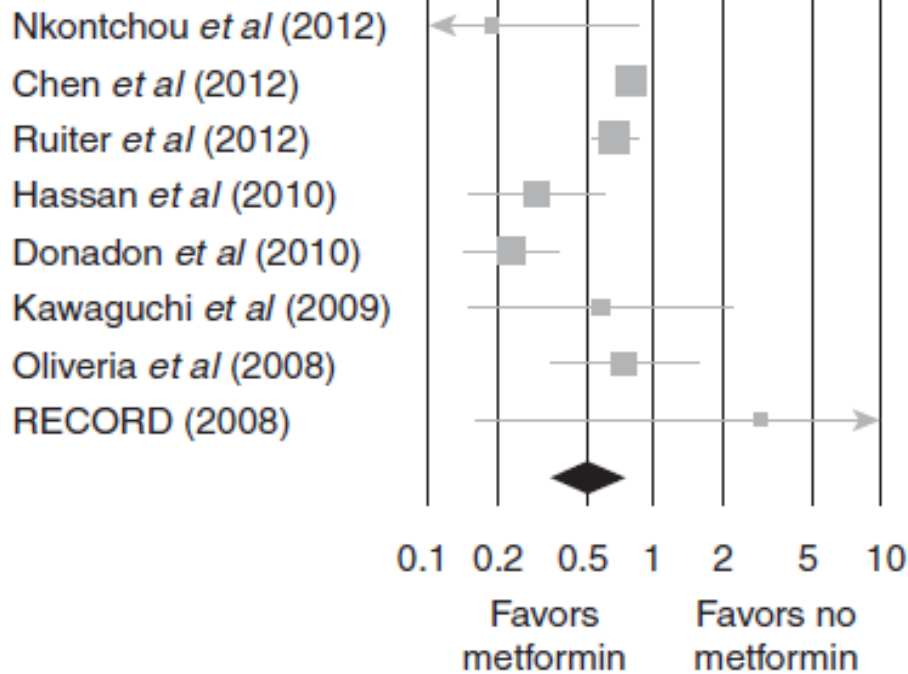
	<b>ORs (95% CI)</b>	<b>P Value</b>
<b>Hepatitis C</b>	18 (16 – 20)	<0.0001
<b>Hepatitis B</b>	15 (13 – 16)	<0.0001
<b>Insulin use</b>	4.37 (4.17 – 4.59)	<0.0001
<b>Cirrhosis</b>	3.14 (2.62 – 3.75)	<0.0001
<b>Metformin use</b>	0.79 (0.75 – 0.83)	<0.0001

Each incremental year increase in metformin use reduces HCC risk approximately 7% in diabetic patients.

# Metformin, Insulin and HCC risk

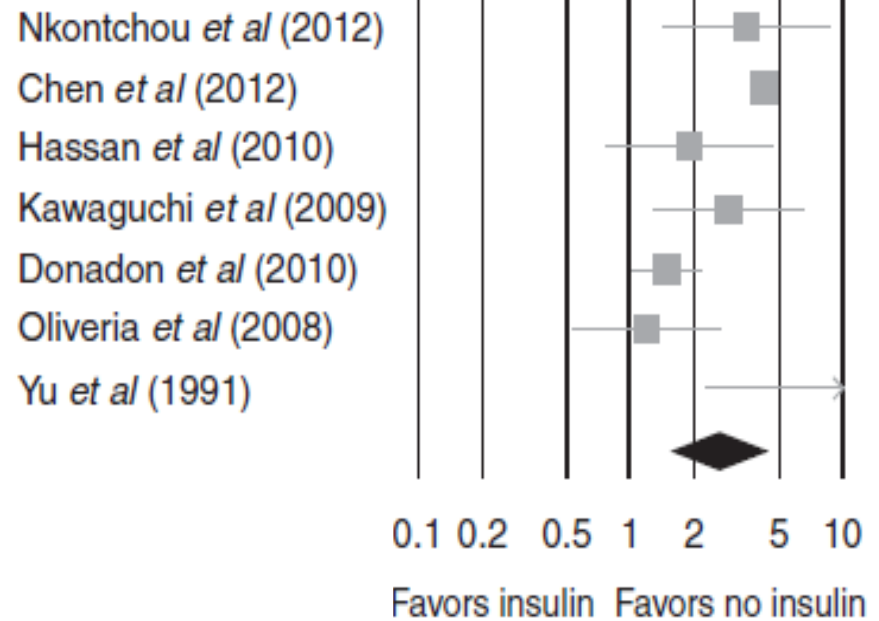
Study name

Odds ratio and 95% CI

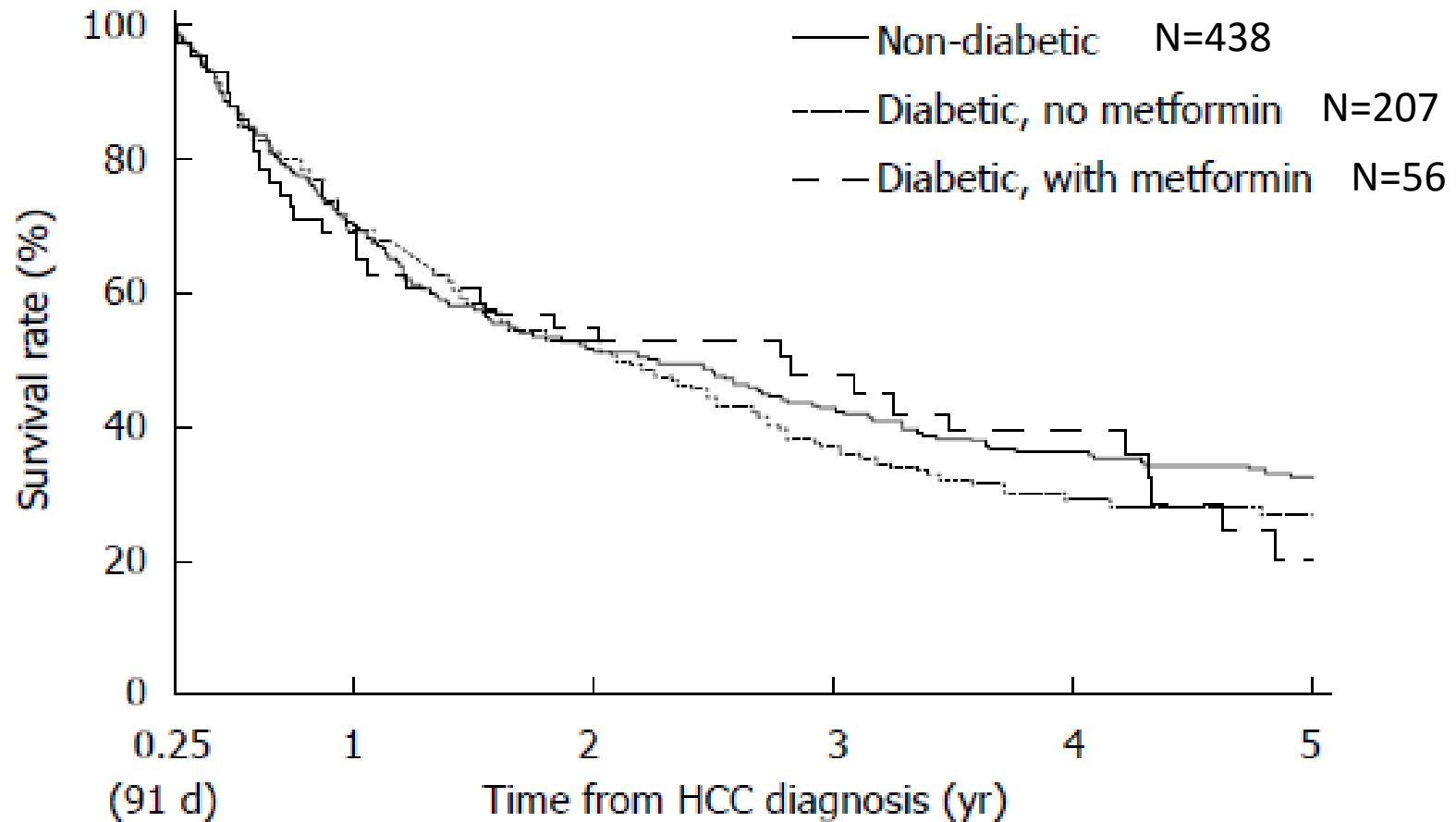


Study name

Odds ratio and 95% CI

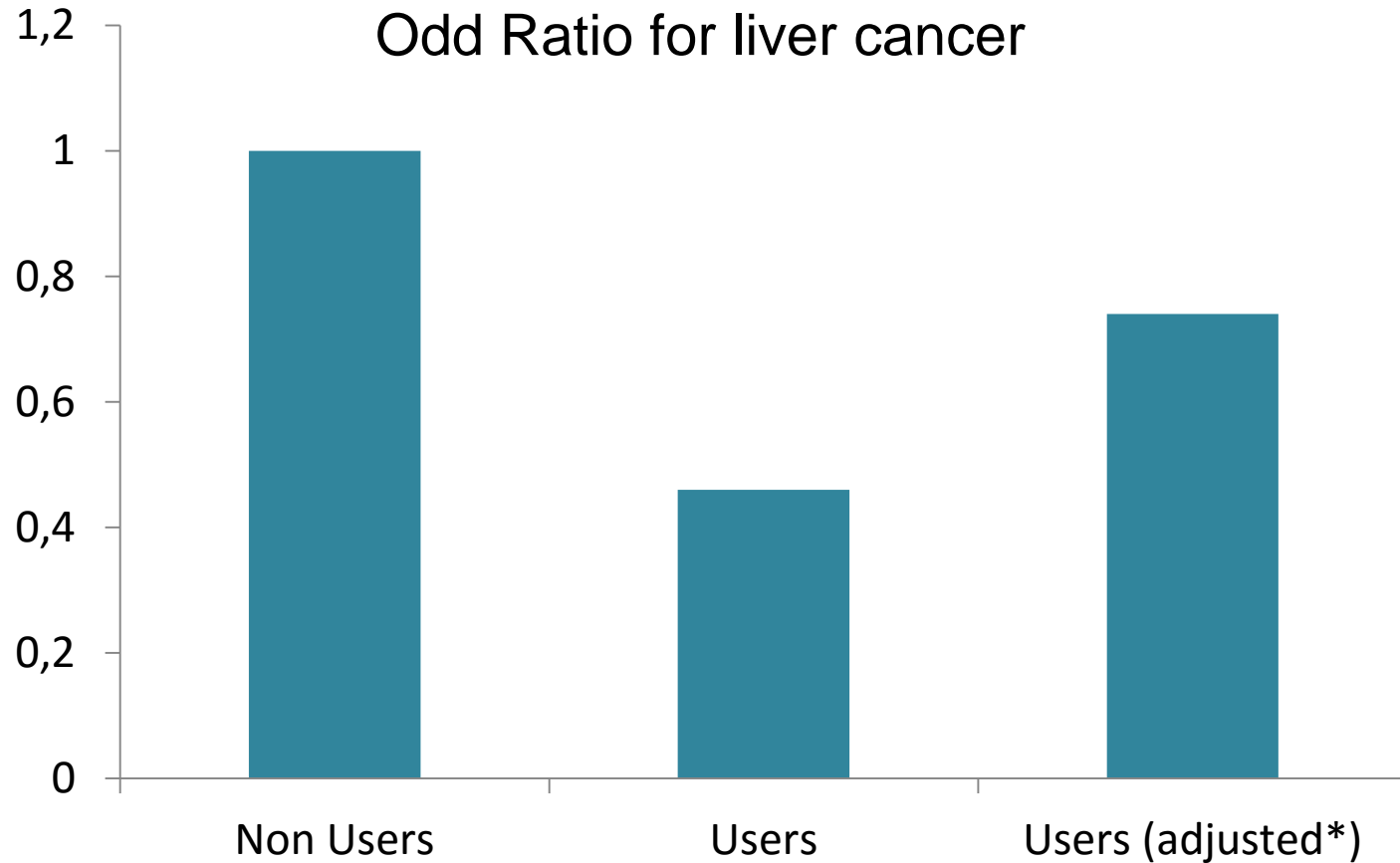


# Metformin and survival of HCC patients



# Statin and HCC risk

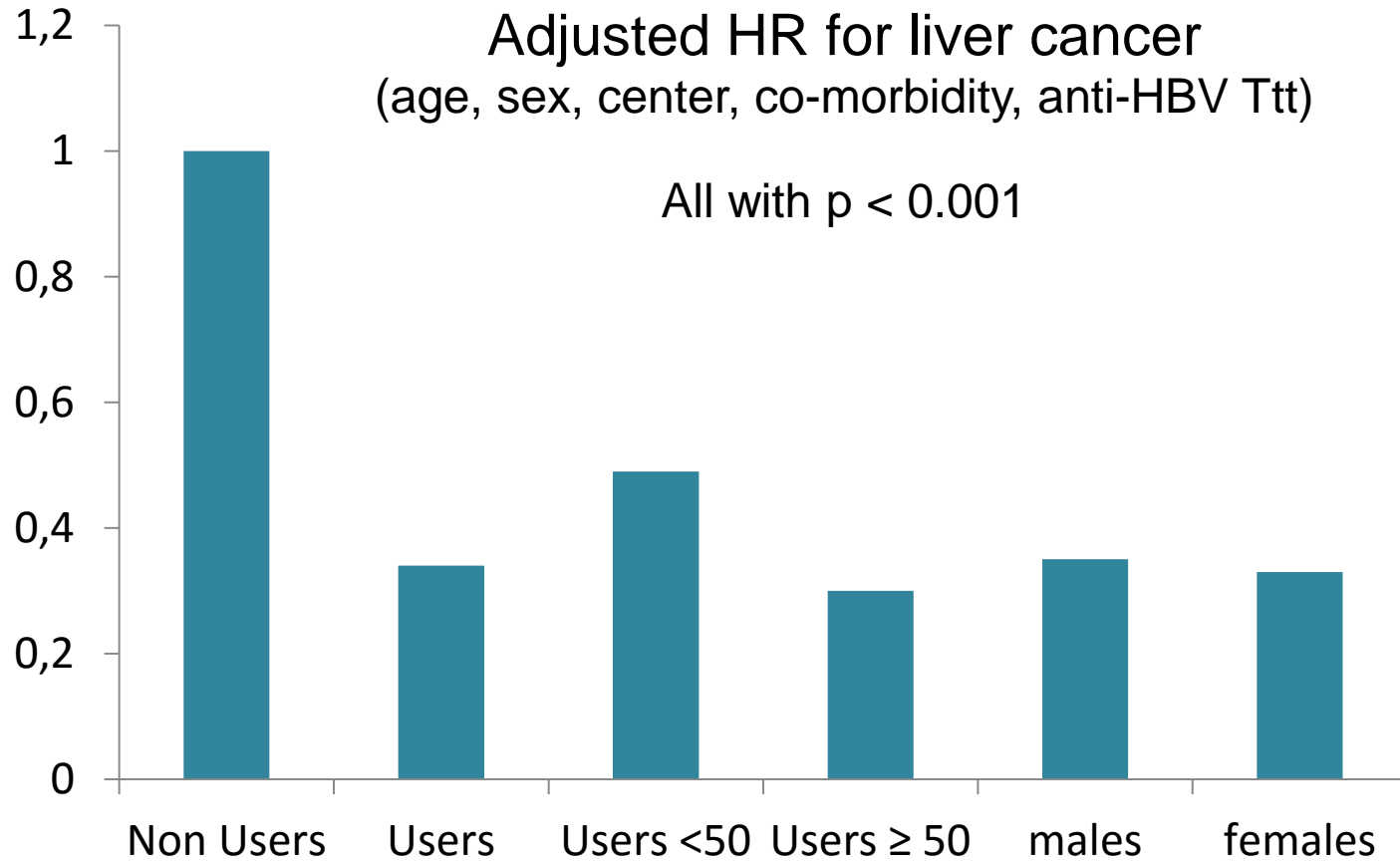
Matched case-control study nested within a cohort of diabetic patients  
(1303 cases, 5212 controls)



\* alcohol, cirrhosis, HBV, HCV, race

# Statin and HCC risk

Population-based cohort study of 71,824 HBV patients in Taiwan



Dose effect

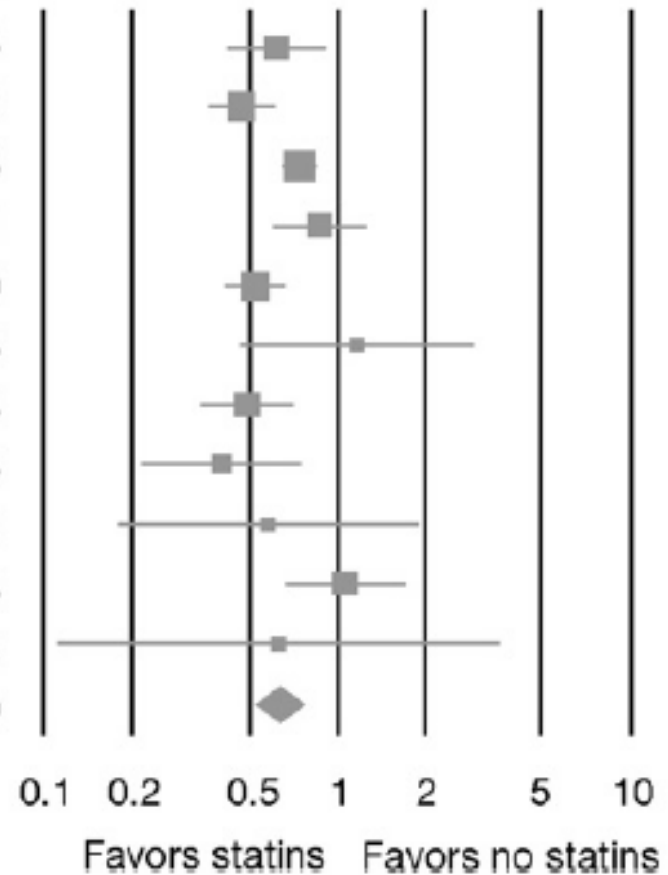
No additive effects with use of metformin

# Statin and HCC risk: Meta-analysis

**Study name**

**Odd ration and 95% CI**

	<b>Odds ratio</b>	<b>Lower limit</b>	<b>Upper limit</b>
Chiu 2011	0.620	0.419	0.918
Tsan 2012	0.470	0.361	0.612
El-Serag 2009	0.740	0.638	0.858
Marelli 2011	0.870	0.600	1.261
Khurana 2005	0.520	0.410	0.660
Friis 2005	1.160	0.460	2.928
Friedman - males - 2008	0.490	0.339	0.708
Friedman - females - 2008	0.400	0.212	0.756
Matsushita - 2010	0.580	0.180	1.869
CTT 2012	1.061	0.659	1.708
Sato - 2006	0.630	0.112	3.549
	0.630	0.523	0.760





# Lifestyles and HCC

---

No smoking

Coffee

Mediterranean diet

Exercise

No obesity

If diabetes, metformin

Statins



[www.swissliver.ch](http://www.swissliver.ch)



*Driven to care*