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Original research

Definition of age-dependent reference values for the diameter of the common bile duct and pancreatic duct on MRCP: a population-based, cross-sectional cohort study

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ABSTRACT

Objective Changes of the pancreaticobiliary ducts herald disease. Magnetic resonance cholangiopancreatography (MRCP) allows accurate duct visualisation. Data on reliable upper reference ranges are missing.

Design Cross-sectional whole body MRI data from the population-based Study of Health in Pomerania were analysed. The width of the common bile duct (CBD) and the pancreatic duct (PD) was determined. We aimed to describe the distribution of physiological duct diameters on MRCP in a population of healthy subjects and to identify factors influencing duct size.

Results After excluding pre-existing pancreaticobiliary conditions, CBD and PD diameters from 938 and 774 healthy individuals, respectively, showed a significant increase with age ($p<0.0001$) and exceeded the conventional upper reference limit of normal in 10.9% and 18.2%, respectively. Age-dependent upper reference limits of duct diameters were delineated with non-parametric quantile regression, defined as 95th percentile: for CBD up to 8 mm in subjects <65 years and up to 11 mm in subjects ≥65 years. For the PD reference diameters were up to 3 mm in subjects <65 years and up to 4 mm in subjects ≥65 years.

Conclusions This is the first population-based study delineating age-adjusted upper reference limits of CBD and PD on MRCP. We showed that up to 18.2% of healthy volunteers would have needed diagnostic workup, if the conventional reference values were used. The utilisation of the adapted reference levels may help to avoid unnecessary investigations and thus to reduce healthcare expenditure and test-related adverse events.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ An increasing diameter of the common bile duct (CBD) or pancreatic duct (PD) heralds disease.
⇒ Previous reference levels for CBD and PD rely on transabdominal ultrasound and endoscopic retrograde pancreatography (ERP) and are mainly derived from patients' cohorts. Modern imaging technology with increasing sensitivity and specificity warrants adaptation of previous reference levels.
⇒ Systematic evaluation of CBD and PD diameters employing modern non-invasive imaging technology such as MRCP (magnetic resonance cholangiopancreatography) in population-based cohorts corrected for age and relevant confounders are lacking.

WHAT THIS STUDY ADDS

⇒ Employing conventional reference levels for the diameters of CBD and PD would have resulted in additional diagnostic workup to exclude potentially life-threatening disease in up to 18.2% of healthy volunteers.
⇒ In a population-based and thus relevant setting, we established and quantified age dependency of CBD and PD diameters resulting in novel evidence-based reference levels for subjects below and above the age of 65 years as well as after gallbladder surgery. Follow-up and sensitivity analysis excluded relevant pathologies missed at first imaging.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Adaptation of reference values to modern imaging technology in a population-based setting is being suggested.
⇒ Our study will set new reference levels to improve standard of care and thus may avoid unnecessary investigations, reduce health care expenditure and test related adverse events.

INTRODUCTION

Changes in the diameters of the pancreaticobiliary ducts point to disease ranging from benign conditions like chronic pancreatitis or bile duct stones to worrisome mucinous cystic neoplasms and pancreaticobiliary cancers. Magnetic resonance cholangiopancreatography (MRCP) is the first-line, non-invasive imaging modality for full duct visualisation, with broad availability and ever-increasing accuracy.[1] However, reference ranges of duct diameters in asymptomatic individuals and their change with age and after medical procedures have only been studied in small cohorts with short follow-up and population-based data are missing.[2 3]

Discussions about the physiological upper limit of the diameter of the extrahepatic bile duct and the pancreatic duct (PD) have been ongoing in the medical literature ever since their first non-invasive visualisation, but surprisingly, no definitive answer to this seemingly simple question has been agreed on.[4] The studies defining the conventionally used upper reference limits of either 6 mm[5] or 7 mm[6 7] for the common bile duct (CBD) date back almost 40 years and were established by ultrasound at a time when simply finding the non-dilated bile duct was a challenge. For the PD, the standard of 3 mm was set by pancreatography studies in the 1970s[8] and is still in use, although it was later discovered that non-invasive imaging and endoscopic-retrograde pancreatography do not correlate well.[9 10] Thus, revisiting the question of what are the upper reference limits for both, the diameters of the PD as well as the CBD, and adopting it for increase in age has been suggested by a number of authors.[11 12] An increase in the duct diameters with advanced age has been discussed as early as 1983.[7] However, this has not be investigated in 'healthy individuals' beyond the age of 65 years. Moreover, the question whether the CBD diameter changes after cholecystectomy has been debated,[5 13 14] yet an MRI based and population-based study is not available. Therefore, we investigated the normal distribution of CBD and PD diameters in healthy volunteers from the general population who underwent MRCP. We aimed to describe the distribution of physiological diameters of pancreaticobiliary ducts on MRCP in a population of healthy subjects and to identify factors influencing duct size.

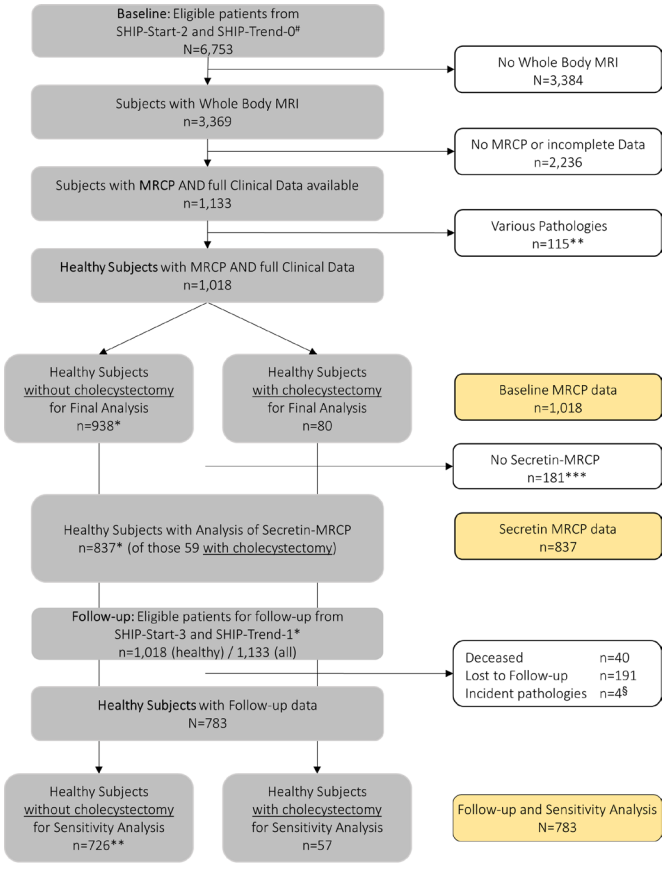
METHODS

Study population

Subjects were recruited from the Study of Health in Pomerania (SHIP).[15 16] SHIP is a prospective, population-based cohort project in Northeast Germany with the objective to study the prevalence and incidence of diseases, as well as to analyse associations between risk factors, subclinical disorders and manifest affliction. Representative samples of the 20–79 year old Caucasian inhabitants of the study region were drawn from local population registries. Further details on sampling methods and recruiting are given elsewhere.[16 17]

SHIP consists of two cohorts: SHIP-Start and SHIP-Trend. Timeline and recruitment are illustrated in online supplemental figure 1. The data for our study population, that is baseline analyses presented here, were derived from SHIP-Start-2 and SHIP-Trend-0, both acquired between 2008 and 2012. In these two study waves, whole body MRI including MRCP was first offered as part of the investigational protocol to all participants.[18 19] Follow-up periods were different for both subgroups, namely 2014–2016 for SHIP-Start and 2016–2019 for SHIP-Trend (online supplemental figure 1).

An overview over the selection of the study participants for the cross-sectional analysis is given in figure 1. In detail, among the 6753 SHIP-Start-2 and SHIP-Trend-0 participants, 3369 agreed to whole-body MRI. In 1133 subjects, MRCPs as well as full clinical data were available. These cases were subsequently screened for eligibility in the present analyses. One hundred and fifteen subjects were excluded for presence of pathologies of the pancreaticobiliary system detected either on MRI, in other study related examinations, or according to self-reported medical history. To define pancreaticobiliary health at baseline of our study, the following items were taken into consideration. MRI-related: cholelithiasis (gallbladder or duct), acute or chronic cholecystitis, parenchymal or ductal signs of acute or chronic pancreatitis, cystic pancreatic lesions, intrahepatic cholestasis,



see suppl. Figure 1, *at least one measurement taken, ** excluded were: cholecystolithiasis, choledocholithiasis, chronic pancreatitis, pancreatic fluid collections or cystic lesions including pseudocysts, cholestatic liver disease, liver cirrhosis , previous acute or chronic hepatitis , primary or metastatic malignancy of the abdomen. For details see suppl. Table 1, ***includes 5 cases with unreadable secretin-MRCP, § see text.

Figure 1 Flow chart representing the selection of the study populations. MRCP, magnetic resonance cholangiopancreatography.

cirrhosis, previous pancreatic or liver resection, tumours of upper abdomen and previous cholecystectomy. Furthermore, the following reported illnesses were screened: acute or chronic pancreatitis, pancreatic cancer, liver cancer or other cancers, gallstones or gallstone-related symptoms, cirrhosis and acute or chronic hepatitis.

Of the remaining 1018 subjects who fulfilled all inclusion criteria (figure 1), 80 had undergone cholecystectomy and were analysed as a separate subgroup. In a secondary analysis, all patients with secretin MRCP were analysed (n=837, 778 without and 59 with cholecystectomy) and compared with the baseline group previously. For this analysis, 176 without secretin-MRCP and 5 unreadable cases had to be excluded (figure 1).

A morbidity and mortality follow-up was attempted in 1018 individuals (938 healthy+80 with cholecystectomy) as part of SHIP-Start-3 and SHIP-Trend-1 as outlined previously (figure 1 and online supplemental figure 1). The median follow-up period was 65.2 months, ±5.6 months.

Follow-up data analysed included newly diagnosed pancreaticobiliary disease detected in study related examinations (including whole body MRI, liver ultrasound and blood examination) or according to self-reported medical history, as reported elsewhere.[17] Medical records not related to SHIP were not available as the identity of the subjects was kept confidential. All subjects who died, were lost to follow-up or had incident pathologies (ie, pancreatic cancer or newly diagnosed liver disease) during follow-up and were excluded secondarily from

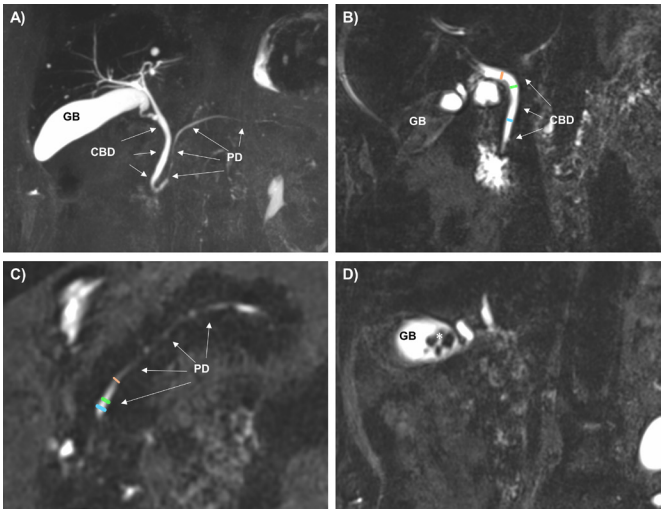


Figure 2 Representative pictures from magnetic resonance cholangiopancreatography (MRCP) of study subjects. (A) Maximum intensity projection in the coronal orientation for orientation of the reader. (B) Single section of coronal MRCP for identification of the largest diameter of the CBD. The gallbladder is partially displayed. (C) Single section of coronal MRCP for identification of the largest diameter of the PD. (D) Single section of coronal MRCP for analysis of the gallbladder. It contains round structures with no T2-signal indicating gallstone disease (asterisk). CBD, common bile duct; GB, gallbladder; PD, pancreatic duct.

the group of 'healthy' subjects for a sensitivity analysis, leaving a sample sizes of 783 of which 57 had cholecystectomy. (figure 1).

Reading of MRCP imaging and assessment of duct diameters

Duct diameters were measured by a single trained investigator (FK) blinded to any other individual data on MRCP coronal sequence using OsiriX software for Mac.[20] Training was overseen by J-PK, who has more than 10 years of professional experience in abdominal cross-sectional imaging. PT, who has more than 3 years of professional experience in diagnostic imaging, validated a subset of reads (see further). At first, the presence or absence of the gallbladder and any evidence of gallstones was recorded (figure 2A,D). Next, all abnormalities or pathological signs of the CBD and PD were recorded, including obstructing stones, strictures, irregularities or masses. The CBD was assessed at the largest diameter distal to the cystic duct, and the PD was assessed at its largest diameter in the pancreatic head. The diameters of CBD and PD were measured perpendicular to the long axis (figure 2B,C). Median differences of 1 mm and more were deemed of clinical relevance when interpreting the data, with regard to known limits of spatial resolution of MRCP and common practice in clinical decision making.[21–23]

Further information on MR technique, study medication and protocol for incidental findings, laboratory analyses and statistical analysis can be found in the online supplemental methods section.

RESULTS

Study cohort

An overview on the selection of the study participants for the cross-sectional analysis is shown in figure 1 and is outlined in detail in Methods and in the online supplemental appendix 1.

Characteristics of healthy subjects and those with cholecystectomy

Among the 938 healthy subjects eligible for the study with MRCP and clinical information available, men were slightly over-represented, accounting for 52.7% of the study population (table 1). In contrast, among the subjects with cholecystectomy, women were over-represented with 57.5%. Healthy subjects had a median age of 51 years, while cholecystectomy subjects were older with a median age of 62 years. Median body mass index (BMI) was in the overweight range (27 kg/m²) in healthy and in the cholecystectomy subjects (29 kg/m²). Moreover, median ALAT, ASAT and GGT activities were in the normal range of healthy and cholecystectomy subjects. There were no differences between the primary group and the subgroups with secretin MRCP and the subgroup with available follow-up (table 1). Characteristics of excluded subjects can be found in online supplemental table 1.

Findings and upper reference limits for duct diameters estimated by quantile regression

In the group of healthy subjects with clinical data and MRCP (n=938), the diameters of the CBD and PD increased with age. For instance, subjects in the third decade of their life had a median (IQR) native CBD diameter of 4.5 mm (1.30 mm) compared with 6.1 mm (3.05 mm) in subjects aged 70 years or older. Similarly, for the PD, subjects aged 20–29 years had median (IQR) native diameter of 1.4 mm (0.37 mm). The median native PD diameter increased to 2.6 mm (1.32 mm) in subjects aged 70 years or older. Full data are presented in table 2. In the entire cohort of healthy subjects, 18.2% of native CBD measurements exceeded the mark of 7 mm and 11.0% of native PD measurements exceeded 3 mm. These findings indicate that a large proportion of asymptomatic, healthy volunteers recruited from the general population exceeds the conventional upper reference limits for

Table 1 Characteristics of the selected healthy participants and those with cholecystectomy

	Healthy			Cholecystectomy		
Characteristics	Native (n=938)	Secretin (n=778)	With follow-up (n=726)	Native (n=80)	Secretin (n=59)	With follow-up (n=57)
Male, %	52.7	56.6	52.9	42.5	37.3	45.6
Age, years	51.0 (41.0–62.0)	50.0 (40.0–61.0)	50.0 (41.0–61.0)	62.5 (55.0–70.5)	62.0 (55.0–69.0)	62.0 (54.0–68.0)
BMI, kg/m²	27.0 (24.5–30.2)	26.9 (24.3–30.0)	27.0 (24.5–30.0)	29.3 (25.6–32.3)	30.0 (25.6–32.2)	29.0 (25.6–32.3)
ALAT, µkat/L	0.37 (0.27–0.52)	0.38 (0.27–0.52)	0.38 (0.27–0.53)	0.34 (0.28–0.51)	0.34 (0.28–0.54)	0.33 (0.28–0.51)
ASAT, µkat/L	0.30 (0.24–0.37)	0.29 (0.24–0.37)	0.30 (0.24–0.37)	0.29 (0.24–0.38)	0.30 (0.25–0.39)	0.30 (0.25–0.39)
GGT, µkat/L	0.49 (0.38–0.70)	0.49 (0.38–0.71)	0.49 (0.38–0.70)	0.48 (0.36–0.69)	0.46 (0.36–0.73)	0.49 (0.36–0.68)

Data are proportions or median (first to third quartile).
Subgroup with secretin scans is displayed separately.
ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; BMI, body mass index; CBD, common bile duct; PD, pancreatic duct.

Table 2 Median duct diameters in healthy individuals

	Healthy native	Healthy secretin	Cholecystectomy native	Cholecystectomy secretin
CBD				
Median (IQR), mm	5.3 (1.13)	5.2 (2.15)	8.2 (4.21)	8.0 (3.48)
>7 mm, %	18.2	15.9	63.8	69.5
PD				
Median (IQR), mm	1.8 (0.96)	2.0 (1.09)	2.1 (1.09)	2.3 (1.46)
>3 mm, %	11.0	17.3	22.4	32.8

Data are propotions or median (IQR).
CBD, common bile duct; PD, pancreatic duct.

the diameter of the proximal CBD and the PD. In multivariable adjusted quantile regression models age demonstrated consistent and highly significant (all models p<0.001) positive associations with CBD and PD diameters (online supplemental table 2).

Therefore, an adaption of the upper reference limits is indicated to guide clinical decision making in the future. We applied quantile regression analysis to determine age-dependent upper reference limits of duct diameters. We found that the median as well as the 95th percentile of CBD and PD diameters increased with age. Yet, the slope of the regression curve was steeper for the 95th percentile than for the median (figure 3). In the following, we derived upper reference limits for the whole cohort and distinct age groups (<65 years and ≥65 years) as displayed in table 3. In summary, for subjects younger than 65 years, a CBD diameter up to 8 mm and a PD diameter up to 3 mm can be considered within the reference range, whereas in subjects aged 65 years or older, a CBD diameter up to 11 mm and a PD diameter up to 4 mm is within the upper reference limit. We further observed that cholecystectomy leads to an enlarged CBD diameter, and upper reference limits according to quantile regression analysis are included in table 3. A online supplemental table 3 summarises upper reference limits of CBD and PD diameters in healthy subjects according to age decade of subjects.

Effect of cholecystectomy

These data refer to 80 subjects with cholecystectomy and available MRCP at baseline (without and with secretin). In subjects aged 50 years and above who had their gallbladder removed but had no evidence of remaining pancreaticobiliary pathology, the native CBD diameter was enlarged compared with healthy subjects (p<0.001 for all comparisons, online supplemental figure 2). Median native PD diameters were similar between healthy individuals and those with cholecystectomy.

In cholecystectomised subjects, CBDs exceeded the upper reference limit of 7 mm in more than 60% of cases (table 2). The effect of cholecystectomy on duct diameters was considered when determining new upper reference limits (table 3).

Effect of secretin administration

Secretin data were available from 837 subjects, 59 of those with cholecystectomy (table 1 and figure 1). Application of secretin led to an increase in the median PD diameter from 1.8 mm (IQR 0.96 mm) to 2.0 mm (IQR 1.09 mm) (p<0.01) and to a decrease in the CBD diameter (median (IQR) native 5.3 (2.12) and with secretin 5.2 (2.15), p<0.01)(table 2). The effect of secretin on duct diameters was taken into account and corrected for when determining new upper reference limits (table 3 and online supplemental table 3).

Effects of gender, liver function test and BMI on duct diameters in healthy subjects

Multivariable adjusted quantile regression models were used to analyse the relation between duct diameters, gender, liver function tests and BMI. MRCP data from subjects without cholecystectomy before (n=938) and after secretin (n=837) stimulation were analysed separately. It revealed associations between gender and CBD but not PD diameters (online supplemental table 2). The magnitude of the difference in CBD diameters between men and women was, however, marginal. Therefore, we decided not to pursue gender differences as part of this study. In further analyses, associations of alanine-aminotransferase (ALAT) activity

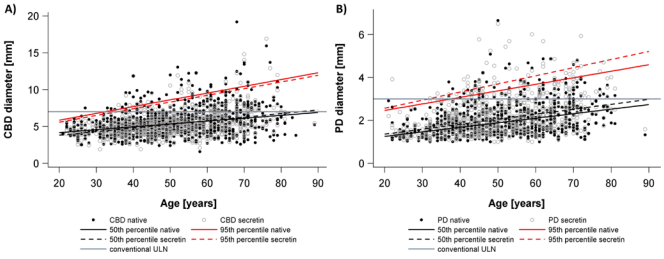


Figure 3 Scatterplot of the largest perpendicular diameter of (A) the common bile duct (CBD) and (B) the pancreatic duct (PD) according to age in healthy subjects before and after secretin administration on magnetic resonance cholangiopancreatography. Red lines represent the 95th percentile and black lines represent the 50th percentile as estimated from quantile regression models. Solid lines represent results without secretin and the dashed lines results with secretin. The horizontal dotted lines represent the conventional upper limit of normal (ULN) of 7 mm and 3 mm for the respective duct.

Table 3 Upper reference limits for common bile duct (CBD) and pancreatic duct (PD) diameters according to age, administration of secretin and cholecystectomy status

		Upper reference limits of normal		
		All ages	<65 years	≥65 years
CBD				
Native	Healthy	9.1	7.9	11.1
	Cholecystectomy	13.5	13.3	14.0
Secretin	Healthy	8.8	7.6	10.8
	Cholecystectomy	13.0	13.0	12.6
PD				
Native	Healthy	3.5	3.1	4.2
	Cholecystectomy	3.8	3.8	3.5
Secretin	Healthy	3.9	3.4	4.7
	Cholecystectomy	4.0	3.9	4.0

CBD, common bile duct; PD, pancreatic duct.

and BMI with duct diameters were assessed to exclude an influence of subclinical liver disease and obesity on the CBD or PD diameters. ALAT activity was neither associated with native or secretin-stimulated CBD diameter nor with secretin-stimulated PD diameter but with native PD diameter (online supplemental table 2 and online supplemental figure 3). Regarding BMI, we observed inverse associations with native CBD diameter as well as native and secretin-stimulated PD diameters (online supplemental table 2 and online supplemental figure 4). Again, due to the small effect sizes of the previous associations, a further evaluation of the effects was not pursued. Moreover, it demonstrated that an increase in CBD diameters is not associated with underlying liver or bile duct disease. This finding cannot be extended to the PD group since subjects with pre-existing hyperlipasaemia were excluded before secretin MRCP.

Follow-up of study subjects

Among the 1018 included subjects with MRCP (938 healthy and 80 with cholecystectomy), 40 had died during follow-up, 191 were lost to follow-up and 4 developed incident pathologies after the index examination. The respective numbers are given in figure 1. The pathologies were: two cases of pancreatic ductal adenocarcinoma, one case with liver metastases of unknown primary and one case with cirrhosis, all of which were not evident at baseline examinations (for details see online supplemental file).

Reference limits for the CBD and PD diameters after exclusion of these subjects are presented in online supplemental table 4, thus representing a cohort of subjects with sustained health. Overall, differences in upper reference limits of CBD and PD diameters in the main and the sensitivity analysis were small and well below 1 mm and thus considered not clinically relevant.

Reliability analysis

Certification of reader (FK) was achieved by randomly selecting 98 of the available 1018 (9.6%) readings for a second measurement by an independent expert reader (PT) blinded to previous results. Analysis showed excellent intraclass correlation (ICC)=0.912 (95% CI 0.846 to 0.950; p<0.0001) for CBD and ICC=0.967 (95% CI 0.943 to 0.981; p<0.0001) for PD. Cronbach's alpha was >0.8 in all sets. Intrareader reliability was very good with ICC=0.884 (95% CI 0.805 to 0.933, p<0.0001) and Cronbach's alpha >0.8 on randomly selected 104 repeated reads from the available 894 MRCPs (10.2%). Full results can be found in online supplemental table 5.

DISCUSSION

Justification of the study

MRCP is a commonly used non-invasive imaging modality in the evaluation of the pancreaticobiliary ductal system, and the availability and accuracy is increasing. Unfortunately, the physiological distribution of CBD and PD diameters among the general population as visualised on MRI has not been studied. Previous studies were restricted to patients who either had symptoms of or presented with already overt diseases of the pancreaticobiliary system.[13 24 25] Knowledge concerning the physiological diameter of CBD and PD is of clinical importance, since dilated ducts can indicate obstruction caused by inflammatory conditions, intraductal stones or tumours. The question whether conventional reference values for CBD and PD need updating has been raised by different authors. Some suggest an age dependency of the diameters with relevant physiological increase in duct diameters above the age of 50 years,[11] 65 years[2 26] or 70 years.[24]

What is new?

Here we describe the age-dependent distribution of CBD and PD diameters in a large, prospectively recruited, extensively characterised, population-based cohort of volunteers undergoing standardised whole body MRI with MRCP. Age-dependent upper reference values were calculated using quantile regression analysis. When considering all ages, in 95% of healthy subjects the diameter of the CBD measured up to 9 mm and must therefore be considered physiological. However, since the CBD diameter increases significantly with age, an age-dependent adaption is warranted. Quantile regression on the 95th quantile indicated that a CBD diameter of up to 11 mm is physiological in subjects aged 65 years or above. We conclude that the incidental finding of a CBD diameter of 8 mm in otherwise asymptomatic persons with no laboratory abnormalities should not be worrisome. In this study, we can also confirm that previous gallbladder removal leads to a postoperative CBD enlargement, leaving 95% of these subjects with a CBD diameter of 13 mm or less, not corrected for age or time interval since the operation.

Similarly, the PD diameter is increasing with age and exceeds the conventional upper reference value of 3 mm in a significant percentage of healthy subjects, even in those younger than 65 years. This effect is more pronounced when the duct diameter is assessed after secretin administration as previously described.[27] We therefore adapted the suggested reference values for MRCP with and without secretin stimulation.

The relevance and clinical importance of our findings are further supported by the fact that during the 5-year survival follow-up none of the subjects who exceeded the conventional reference values died of pancreaticobiliary malignancies.

Comparison with other cohorts

Studies on the diameter of the CBD in the healthy population are contradictory in general and scarce when it comes to MRI. Early studies suggested that the CBD in persons with no overt biliary or pancreatic disease should not exceed 4–7 mm measured on ultrasound.[5–7] Later, with better instruments available, studies described a CBD of 8.5–10 mm on ultrasound to be physiological.[28 29] A recent MRCP-based study from China suggested an age-independent upper reference limit of 6 mm for asymptomatic hospital patients.[30] Despite methodological weaknesses and small study populations, a correlation between age and diameter was seen, with an increase of 0.04–0.07 mm per year.[29 31] Kaim *et al*[12] described an increase of the CBD in asymptomatic patients older than 75 years on ultrasound and suggested the upper reference limit of 10 mm. In patients who had undergone cholecystectomy, the mean diameter was further increased and an upper reference limit of 14 mm was suggested.[12] An age-dependent increase and additional effect of cholecystectomy was confirmed by studies from various countries including more than 10 000 patients using transabdominal ultrasound,[13 14 29 32 33] endoscopic ultrasound,[24] CT[11 34] and one small study with MRCP[2]; however, the validity for the general population and for MRCP remained unclear. This gap is closed by our data.

The 3 mm upper limit of normal for the PD was defined in an endoscopic retrograde cholangiopancreatography (ERCP) study from 1976[8] in 35 patients without pancreatic disease. In two studies, including a clinical MRCP cohort from China, the mean diameter rarely exceeded 3 mm as confirmed by us and others,[35–37] but the variation in asymptomatic individuals is significant and up to 10.9% of measurements are above the 3 mm limit. None of the studies provided upper reference limits. We therefore suggest new age-dependent upper limits based on

quantile regression in contrast to mean values. In patients >70 years of age undergoing ERCP, Hastier *et al*[38] showed the PD diameter increases in 44.8% of the patients. 21 of 136 subjects had a PD dilatation greater than two SD above the mean with a maximum of 6.9 mm and five subjects had a massive dilatation over 3 SD with a maximum diameter of 8 mm.[38] Similar findings were observed in an Indian cohort.[39] Recently, a MRI-based study from Japan debated these finding, but the study population was small and the span of the age groups covered was wide, which is why the effect was most likely missed.[40]

The effect and PD diameter and duodenal filling as well as safety of secretin for PD assessment on MRI is well described.[27 41 42] It is noteworthy, however, that there is a difference between ERCP and MRCP when assessing the PD. According to Tamura *et al*, ERCP measurements yield significantly higher diameters than MRCP (ratio 1.5) in patients with chronic pancreatitis,[9] which highlights the relevance of the data presented in the current study. In contrast, a study comparing measurements of the CBD diameter between ultrasound and MRI reported comparable results,[3] suggesting a generalisability of our findings to ultrasound of the extrahepatic bile duct as well.

A number of studies dispute the relation between age, gallbladder removal and CBD, but methodological aspects might explain these differences. The studies by Karamanos *et al* and Horrow *et al*,[25 43] for example, had non-representative age distribution especially among the elderly, since subjects were recruited in hospital. Another ultrasound and one MRI study were underpowered due to small number of subjects,[3 44] and in a further, study the follow-up period after cholecystectomy was too short.[5] Online supplemental table 6 gives on overview on previously published cohorts.

Strengths and limitations

Due to the study design, our findings describe the upper reference limits for CBD and PD diameters. To test its prognostic accuracy and to define a clinical cut-off, a controlled study in patients with specific pancreaticobiliary conditions is needed. Concerning the CBD increase associated with previous cholecystectomy, it would be interesting to understand dynamics of this change with regard to time from surgery. Since information on the exact date of cholecystectomy in our study participants was not collected, we were unable to analyse this aspect in more detail. Ideally, this question should be answered in a prospective setting requiring long follow-up. Overall, the estimated upper reference limits for subjects analysed after gallbladder removal need to be interpreted with caution, as this subcohort was small. Although recruited from a distinct geographical area, due to the balanced composition and large size of the cohort, we are confident that the data are generalisable to Caucasian populations elsewhere; however, external validation studies, also including other ethnicities, are needed. The retrospective nature of the study leads to the fact that only a fraction of 34% of those undergoing MRI as part of SHIP were analysed. Thus, a selection bias cannot be excluded.

CONCLUSIONS

This is, to our knowledge, the first population-based study investigating the diameter of pancreaticobiliary ducts on MRCP. We showed that up to 18.2% of healthy volunteers would have needed diagnostic workup for enlarged CBD or PD, if the conventional reference values were to be used. We therefore suggest a new set of age-adjusted upper reference limits for the proximal CBD and PD in asymptomatic persons with normal liver function and lipase levels. Further validation and comparison with patients with proven pathology are needed. Our findings can help to avoid unnecessary investigations and thus reduce healthcare expenditure and test-related adverse events.

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Ethics approval SHIP was approved by the institutional review board, and 'written informed consent was secured from each participant. In addition, the associated project 'CBD and PD duct diameter on MRCP' was approved by the SHIP scientific advisory board on 1 April 2015 (2015/48/D). The study was conducted in accordance with national legal requirements, the WMA's Declaration of Helsinki and all participating researchers followed Good Clinical Practice (ICH GCP) guidelines. All authors had access to the study data and reviewed and approved the final manuscript. Participants gave informed consent to participate in the study before taking part.

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Suppl. Methods and Results

Definition of age-dependent reference values for the diameter of the common bile duct and pancreatic duct on MRCP: a population-based, cross-sectional, cohort study

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Suppl. Methods

Study population

Baseline examinations in the SHIP-Start cohort (SHIP-Start-0) were conducted between 1997 and 2001 in 4,308 inhabitants of the study region West Pomerania. All participants from SHIP-Start-0 were invited to participate in four follow-ups (SHIP-Start-1 to SHIP-Start-4). Baseline examinations in the SHIP-Trend cohort (SHIP-Trend-0), an independent population-based cohort in the same study region, were conducted between 2008 and 2012 in 4,420 subjects.

Of the initial 4,308 SHIP-Start-0 participants, 2,333 subjects agreed to participate in SHIP-Start-2. SHIP-Trend-0 recruited a total of 4,420 subjects [1]. In SHIP-Start-2 and SHIP-Trend-0, that represent the baseline of the study presented here, MRI and MRCP were performed upon informed consent [2, 3] and a total of 3,369 participants eventually underwent wholebody MRI [3]. The follow-up data presented here is based on SHIP-Start-3 and SHIP-Trend-1 data. SHIP-Start-3 started in 2014 and finished in 2016, while SHIP-Trend-1 started in 2016 and finished in 2019. Of the 1,018 subjects included in the cross-sectional analyses, 40 died and 191 were lost to follow-up, leaving 787 with sufficient follow-up data available. For details, please see **Figure 1** and **suppl. Figure 1**.

MR Technique, Study Medication and Protocol for Incidental Findings

We used a 1.5-T MRI system (Magnetom Avanto, Siemens Healthcare). The MRCP (navigator-triggered T2-weighted 3D turbo spin-echo) included an automatic maximum-intensity-projection (MIP) reconstruction in the coronal orientation using the following imaging parameters: TR, approximately 900 ms; long TE, 742 ms; bandwidth, 260 Hz/pixel; matrix, 384 × 384; number of slices, 44; and slice thickness 1.5 mm. The acquisition for MRCP varied between 2 to 6 minutes depending on subject size. For those receiving secretin, an unstimulated MRCP was obtained first, followed by a scan after secretin administration (Secrelux®, Sanochemia Pharmazeutika AG) in the same orientation. Secretin was administered at 1 U/kg of body weight, slow injection over 60 seconds and was followed by a 20-mL saline flush as described previously.[2, 4, 5]

For MRI examinations an additional consent form was developed in which the study participant could opt for a full report of all findings, decline any information on the findings or only being informed about potentially life threating findings. All incidental findings were discussed by a multidisciplinary advisory board and in case follow up investigations were recommended and the study participant had opted to be informed on the findings, the participant and primary

physician were contacted to pursue further diagnostic work-up, however the results of such work-up were not available for analysis.[6] This strategy has been adopted by the German national cohort study.[7] A relevant negative effect of this strategy on mental health of the study participants has been excluded.[8] A full list of data available from SHIP cohorts including MRI-data can be found here: https://www.fvcm.med.uni-greifswald.de/dd_service/data_use_explore.php?lang=ger, a full report on study related examinations has been reported elsewhere. [9]

Laboratory Analyses

Serum activities of alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), gamma glutamyl transferase (GGT), amylase, and lipase were determined photometrically on the Dimension VISTA (Siemens Healthcare Diagnostics, Eschborn, Germany) in SHIP-Start-2 and SHIP-Trend-0.

Statistical Analysis

Data documentation and statistical analyses were performed using IBM SPSS Statistics (Versions 23 - 25 for Windows) and SAS 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Demographics of the study population are reported as medians with first and third quartiles or proportions. Duct diameters in the examined subgroups, i.e. with and without secretin and for selected age groups are given as medians with interquartile range. In multivariable quantile regression models, the relation of age, sex, BMI and alanine aminotransferase (ALAT) activity and median CBD or PD diameters was assessed. From these regression models the beta-coefficients, 95% confidence intervals and the p-values are reported. Moreover, the associations between BMI and ALAT with median CBD and PD diameters were visualized in scatterplots together with the original measured values.

Wilcoxon-Mann Whitney tests were used to inspect differences in native CBD and PD diameters between men and women and to inspect differences between healthy subjects and those with cholecystectomy. Duct diameters before and after secretin administration were compared using Wilcoxon signed rank sum tests. Statistical significance was assumed at a p value of ≤ .01 if not stated otherwise.

Age-dependent upper limits of normal duct diameters were determined with non-parametric quantile regression.[10] We defined the 95th percentile as upper limit of normal and determined respective normative values for each single year of age. Subsequently, upper limits of normal for the whole cohort, for subjects < 65 years and subjects ≥ 65 years as well as according to age decades were calculated and reported. Additionally, we illustrated the upper limits of

normal for the CBD and PD diameter together with the median, the original measured values and the conventional upper limit of normal in scatterplots. In a sensitivity analysis upper limits of normal were recalculated after exclusion of subjects who died, were lost-to-follow-up or who had developed incident pancreatic cancer or liver lesions.

Reliability of MRI readings was assured by analyzing intra-class correlation (ICC) using two-way mixed effect models testing for consistency for inter-rater reliability and absolute agreement for intra-rater reliability. ICC and Cronbach´s alpha above .8 were considered acceptable [11].

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Suppl. Table 1: Characteristics of the excluded subjects

Characteristics	Exclusions n=115
Male, %	47.8
Reason for exclusion*	
Cholecystolithiasis or choledocholithiasis	47
Chronic pancreatitis	14
Cystic pancreatic lesions	52
Acute/chronic liver disease**	14
Previous pancreatic or liver resection	0
Tumors of upper abdomen	0
Age, years	63.0 (55.0 - 70.0)
BMI, kg/m²	27.5 (25.2 - 30.2)
ALAT, µktatal/l	0.38 (0.29 - 0.55)
ASAT, µktatal/l	0.32 (0.27 - 0.41)
GGT, µktatal/l	0.52 (0.38 - 0.79)

Data are proportions or median (1^{st}-3^{rd} quartile). ALAT: alanine aminotransferase, ASAT: aspartate aminotransferase, BMI: body mass index, GGT: gamma-glutamyltransferase. *Some subjects harbored multiple multiple pathologies leading to exclusion. **defined as either intrahepatic cholestasis, liver cirrhosis or previous acute or chronic hepatitis

Suppl. Table 2: Results from multivariable quantile regression models assessing the effects of sex, age, BMI and ALAT on median native and secretin-stimulated CBD and PD diameters. ß-coefficients with 95% confidence intervals (CI) and p-values for an increase in one year (age), one kg/m² (BMI) and 0.1 µkatal/l are given.

Outcome	Exposure	ß (95% CI)	p
CBD native	sex (male vs female)	0.691 (0.438; 0.943)	< .001
	age (increase 1 year)	0.042 (0.034; 0.050)	< .001
	BMI (increase 1 kg/m²)	-0.023 (-0.044; -0.003)	.028
	ALAT (increase 0.1 µkatal/l)	0.015 (-0.040; 0.069)	.602
CBD secretin	sex (male vs female)	0.791 (0.545; 1.036)	< .001
	age (increase 1 year)	0.046 (0.038; 0.055)	< .001
	BMI (increase 1 kg/m²)	-0.017 (-0.044; 0.009)	.195
	ALAT (increase 0.1 µkatal/l)	0.021 (-0.033; 0.075)	.451
PD native	sex (male vs female)	-0.042 (-0.146; 0.062)	.425
	age (increase 1 year)	0.022 (0.018; 0.026)	< .001
	BMI (increase 1 kg/m²)	-0.018 (-0.029; -0.006)	< .01
	ALAT (increase 0.1 µkatal/l)	0.033 (0.011; 0.055)	< .01
PD secretin	sex (male vs female)	0.094 (-0.039; 0.226)	.167
	age (increase 1 year)	0.024 (0.020; 0.029)	< .001
	BMI (increase 1 kg/m²)	-0.019 (-0.033; -0.005)	< .01
	ALAT (increase 0.1 µkatal/l)	0.018 (-0.019; 0.054)	.348

CBD, common bile duct; PD, pancreatic duct; BMI, body mass index, ALAT, alanin aminotransferase

Suppl. Table 3: Upper reference limits for common bile duct (CBD) and pancreatic duct (PD) diameters in healthy subjects according to age in decades and administration of secretin

Age group, years	CBD		PD	
	native	secretin	native	secretin
<30	6.3	6.0	2.6	2.7
30-39	7.2	6.9	2.9	3.1
40-49	8.1	7.8	3.2	3.5
50-59	9.0	8.7	3.5	3.9
60-69	9.9	9.6	3.8	4.3
≥70	11.4	11.0	4.3	4.8

CBD: common bile duct, CCE: cholecystectomy, PD: pancreatic duct.

Suppl. Table 4: Sensitivity analysis - upper reference limits for common bile duct (CBD) and pancreatic duct (PD) diameters according to age, administration of secretin and cholecystectomy status (CCE).

CBD		**Upper limits of normal**		
		All ages	< 65 years	≥ 65 years
native	Healthy	9.1	8.0	10.9
	CCE	13.5	13.3	14.0
secretin	Healthy	8.8	7.6	10.8
	CCE	13.0	13.0	12.6
PD				
native	Healthy	3.6	3.2	4.2
	CCE	3.8	3.8	3.9
secretin	Healthy	3.8	3.4	4.5
	CCE	4.0	3.5	4.0

CBD: common bile duct, CCE: cholecystectomy, PD: pancreatic duct.

Suppl. Table 5: Inter- and intra-rater reliability

Reliability statistics	Inter-rater reliability of FK and PT		Intra-reader reliability of FK
	CBD	PD	
Cronbach's Alpha	0.954	0.983	0.939
Cronbach's Alpha for standardized items	0.954	0.984	0.939
Number of items	2	2	2
Intra-class correlation (95 % CI)			
single	0.912 (0.846 - 0.950)	0.967 (0.943 - 0.981)	0.884 (0.805 - 0.933)
mean	0.954 (0.917 - 0.975)	0.983 (0.970 - 0.990)	0.939 (0.892 - 0.965)

CI: confidence interval; CBD; common bile duct; PD: pancreatic duct

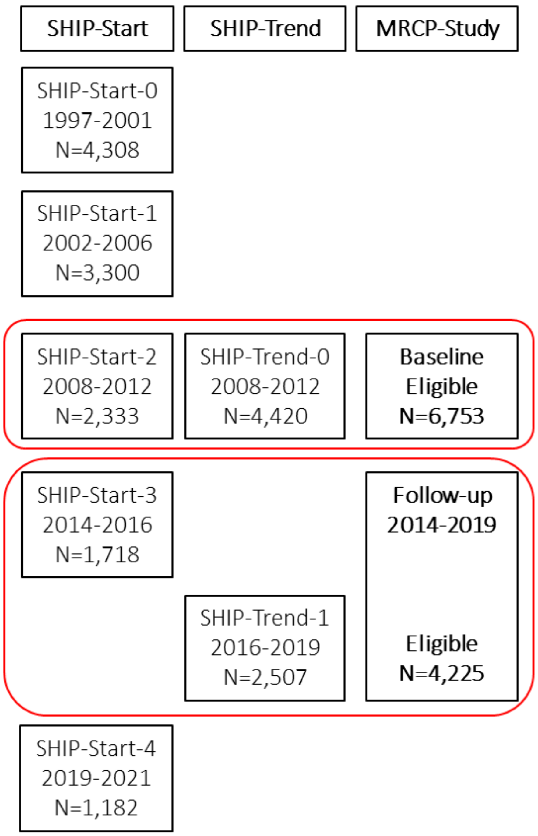
Suppl. Table 6: Overview on previous cohort studies

Study author	Modality	N	Median Age	CBD in mm	PD in mm	Increase with age	Increase with CCE	New reference limit
Govindan et al (2021) [12]	MRCP	517	54.6	5.4±1.4	/			8 mm
Karamanos et al. (2016) [13]	MRCP/ERCP	1.000	40.7	1.5-16.4	/			/
Peng et al. (2015) [14]	MRCP	862	46.10	4.13±1.11	/		/	/
McArthur et al. (2014) [15]	CT	304	51.9	5.07	/			/
Benjaminov et al. (2013) [16]	EUS	647	60.8	4.4-6.0	/			/
Chen et al. (2012) [17]	MRCP	187	51	4.6±1.8	/		/	/
Itoi et al. (2012) [18]	US	8840	51.6	4.5 ±1.4	/		/	2.83 + 0.03 x age
Senturk et al. (2012) [19]	CT	604	49.2	4.77±1.81	/			8mm for age > 50 years, 10 mm post-CCE
McArthur et al. (2012) [20]	US	720	50.9	3.5, post-CCE 4.5	/			
Park et al. (2009) [21]	CT	398	54.4	6.70±2.41	/		/	7mm for age > 50 years
Chawla et al. (2009) [22]	CT	80	53	5.2, post-CCE 6.9	/			/
Bachar et al. (2003) [23]	US	251	52.5	4.28±1.18	/		/	8,5 mm in elderly
Horrow et al. (2001) [24]	US	258	55	3.5±1.2	/		/	/
Kaim et al. (1998) [25]	US	92	84.7	6.2, post-CCE 8.7	/			10mm for age > 75 years, post-CCE 14mm
Feng und Song	US	234	/	5.9, post-CCE 6.1	/	/		/

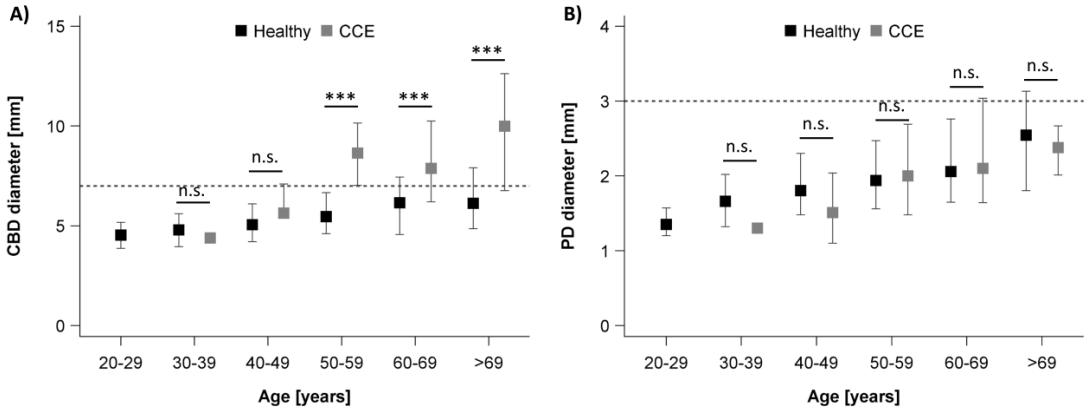
(1994) [26]								
Wu, Ho und Chen (1984) [27]	US	203	21 to 60	3.3 – 6.8	/		/	/
Niederau et al. (1983) [28]	US	830	/	2.8 ±2	/			/
Frøkjær et al. (2020) [29]	MRCP	262	52.7		2 – 3 mm		/	2.7 mm for age > 60 years
Wang et al. (2019) [30]	MRCP	280	54.4		1.99±0.53		/	/
Testoni et al. (2009) [31]	MRCP	25	57.8	/	1.1±0.6	/	/	/
Glaser und Stienecker (1999) [32]	US	131	52	/	1.9		/	/
Hastier et al. (1998) [33]	ERCP	155	>70 vs <50	/	5.3 vs. 3.3		/	/
Anand et al. (1989) [34]	ERCP	55	36.9	/	3.3±0.91		/	/
Bolondi et al. (1984) [35]	US	18	26	/	1.2±0.4		/	/
Sivak und Sullivan (1976) [36]	ERCP	35		/	3.2±0.1		/	/

positive association / not assessed

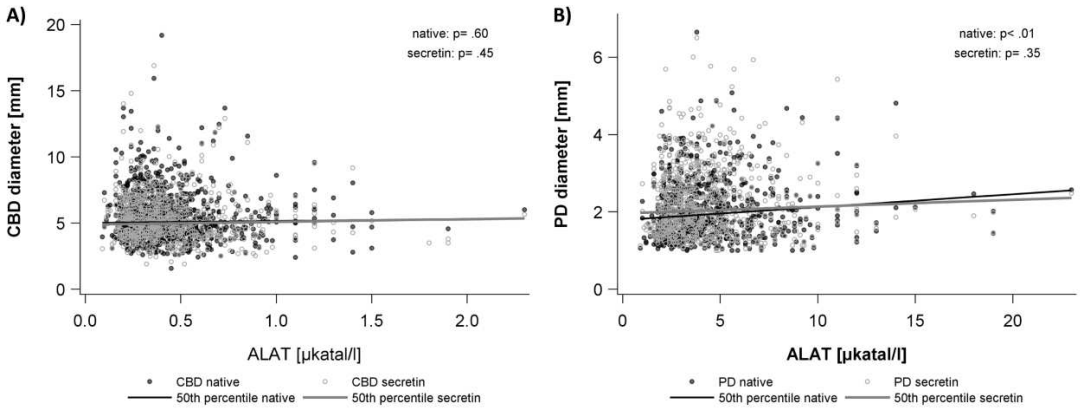
no association



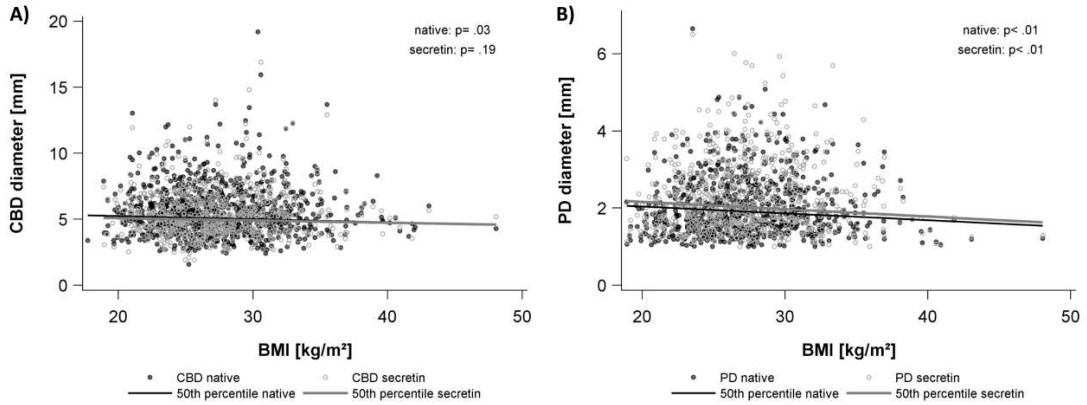
Suppl. Figure 1. Flow-chart and time line of the SHIP study cohorts from which the data included in the current analysis has been extracted.



Suppl. Figure 2. Median native duct diameters with 1.-3. quartile by age decade in healthy subjects and in subjects with cholecystectomy (CCE). The horizontal dotted line represents the conventional upper limit of normal of 7 mm and 3 mm for the respective duct. A) The diameter of the common bile duct (CBD) increases with age. CCE leads to a further increase in the diameter of the CBD. B) The diameter of the pancreatic duct (PD) increases with age. CCE has no impact on the diameter of the PD. Group differences between healthy subjects and those with CCE were tested with Wilcoxon-Mann Whitney tests. *** $p < .001$



Suppl. Figure 3. Scatterplot of the largest perpendicular diameter of (A) the common bile duct (CBD) and (B) the pancreatic duct (PD) according to alanine aminotransferase (ALAT) in healthy subjects. Solid lines represent the estimated 50th percentile as estimated from quantile regression models adjusted for sex, age and body mass index. Black dots and lines represent native duct diameters, grey dots and lines represent duct diameters after secretin administration on magnetic resonance cholangiopancreatography.



Suppl. Figure 4. Scatterplot of the largest perpendicular diameter of (A) the common bile duct (CBD) and (B) the pancreatic duct (PD) according to body mass index (BMI) in healthy subjects. Solid lines represent the estimated 50th percentile as estimated from quantile regression models adjusted for sex, age and alanine aminotransferase. Black dots and lines represent native duct diameters, grey dots and lines represent duct diameters after secretin administration on magnetic resonance cholangiopancreatography.